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Scientists extract H2 gas from oil and bitumen, giving potential pollution-free energy

Economical method to extract hydrogen from oil sands and oil fields

Scientists have developed a large-scale economical method to extract hydrogen (H2) from oil sands (natural bitumen) and oil fields. This can be used to power hydrogen-powered vehicles, which are already marketed in some countries, as well as to generate electricity; hydrogen is regarded as an efficient transport fuel, similar to petrol and diesel, but with no pollution problems. The process can extract hydrogen from existing oil sands reservoirs, with huge existing supplies found in Canada and Venezuela. Interestingly, this process can be applied to mainstream oil fields, causing them to produce hydrogen instead of oil.

Hydrogen powered vehicles, including cars, buses, and trains, have been in development for many years. These vehicles have been acknowledged to be efficient, but the high price of extracting the Hydrogen from oil reserves has meant that the technology has not been economically viable. Now a group of Canadian engineers have developed a cheap method of extracting H2 from oil sands. They are presenting this work at the Goldschmidt Geochemistry Conference in Barcelona.

"There are vast oil sand reservoirs in several countries, with huge fields in Alberta in Canada, but also in Venezuela and other countries" said Dr Ian Gates, of the Department of Chemical Engineering at the University of Calgary, and of Proton Technologies Inc.).

Oil fields, even abandoned oil fields, still contain significant amounts of oil. The researchers have found that injecting oxygen into the fields raises the temperature and liberates H2, which can them be separated from other gases via specialist filters. Hydrogen is not pre-existing in the reservoirs, but pumping oxygen means that the reaction to form hydrogen can take place.

Grant Strem, CEO of Proton Technologies which is commercialising the process says "This technique can draw up huge quantities of hydrogen while leaving the carbon in the ground. When working at production level, we anticipate we will be able to use the existing infrastructure and distribution chains to produce H2 for between 10 and 50 cents per kilo. This means it potentially costs a fraction of gasoline for equivalent output". This compares with current H2 production costs of around $2/kilo. Around 5% of the H2produced then powers the oxygen production plant, so the system more than pays for itself.

The economics of the process is favourable according to Grant Strem "What comes out of the ground is hydrogen gas, so we don't have the huge above-ground purification costs associated with oil refining: we use the ground as our reaction vessel. Just taking Alberta as an example, we have the potential to supply Canada's entire electricity requirement for 330 years (Canada uses around 2.5% of the world's electricity - around the same amount as Germany, and more than France or the UK). Our initial aim is to scale up the production from Canadian oil sands, but in fact, we anticipate that most of the interest in this process will come from outside Canada, as the economics and the environmental implications make people look very hard at whether they want to continue conventional oil production. The only product of this process is hydrogen, meaning that it the technology is effectively pollution and emission free. All the other gases remain in the ground because they cannot go through the hydrogen filter and up to the surface".

The technology was developed by Ian Gates and Jacky Wang as the result of an agreement between the University of Calgary and Proton Technologies Inc., which now holds the patent.

Professor Brian Horsfield (GFZ German Research Centre for Geosciences, Potsdam) said: "The research is highly innovative and exciting. It's an adaptation of some 1970's fire-flood production concepts, but tuned to a modern day perspective. Declining oil field production infrastructures now stand to get a new lease of life. Extensive field testing will be crucial in assessing how the system works on industrial scales and over time"

This is an independent comment; Professor Horsfield was not involved in this work
Conference website: https://goldschmidt.info/2019/

http://bit.ly/2TTJZqO

Research shows why there's a 'sweet spot' depth for underground magma chambers

Reason why magma chambers feeding volcanic eruptions tend to reside in a very narrow depth range in the Earth's crust

PROVIDENCE, R.I. [Brown University] -- A new study reveals why the magma chambers that feed recurrent and often explosive volcanic eruptions tend to reside in a very narrow depth range within the Earth's crust. The findings, published in Nature Geoscience, could help scientists to better understand volcanic processes the world over.

The research makes use of computer models that capture the physics of how magma chambers, reservoirs in the crust that contain partially molten rock, evolve over time. The models showed that two factors -- the ability of water vapor to bubble out of the magma, and the ability of the crust to expand to accommodate chamber growth -- are the key factors constraining the depth of magma chambers, which are generally found between six and 10 kilometers deep.

"We know from observations that there seems to be a sweet spot in terms of depth for magma chambers that erupt repeatedly," said Christian Huber, a geologist at Brown University and the study's lead author. "Why that sweet spot exists has been an open question for a long time, and this is the first study that explains the processes that control it."

Depths of six to 10 kilometers generally correspond to pressures of about 1.5 kilobars on the shallow side and 2.5 kilobars on deep side. The models showed that at pressures less than 1.5 kilobars, water trapped within the magma forms bubbles readily, leading to violent volcanic explosions that blast more magma out of a chamber than can be replaced. These chambers quickly cease to exist. At pressures more than 2.5 kilobars, warm temperatures deep inside the Earth make the rocks surrounding the magma chamber soft and pliable, which enables the chamber to grow comfortably without erupting to the surface. These systems cool and solidify over time without ever erupting.

"Between 1.5 and 2.5, the systems are happy," Huber said. "They can erupt, recharge and keep going."

The key to the models, Huber said, is that they capture the dynamics of both the host crust and of the magma in the chamber itself. The ability of deep magma chamber to grow without erupting was fairly well understood, but the limit that water vapor exerts on shallow magma chambers hadn't been appreciated.

"There hadn't been a good explanation for why this habitable zone should end at 1.5 kilobars," Huber said. "We show that the behavior of the gas is really important. It simply causes more mass to erupt out than can be recharged."

Huber says the findings will be helpful in understanding the global magma budget. "The ratio of magma that stays in the crust versus how much is erupted to the surface is a huge question," Huber said. "Magma supplies CO2 and other gases to the atmosphere, which influences the climate. So having a guide to understand what comes out and what stays in is important."

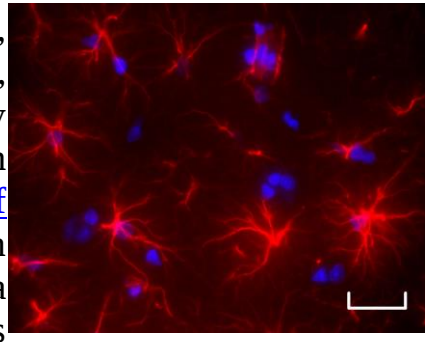
Coauthors on the paper Meredith Townsend, Wim Degruyter and Olivier Bachmann. The work was supported by the National Science Foundation (NSF-EAR 1760004) and the Swiss National Fund (200021_178928).

http://bit.ly/2L4oRR0

When a diseased liver disrupts the brain

Researchers from UNIGE, CHUV, EPFL, CIBM, HUG and UNIL have demonstrated how chronic liver diseases cause molecular changes in the brain.

The liver plays a vital role as a filter in the human body. But what happens when it malfunctions? Researchers from the Universities of Geneva (UNIGE) and Lausanne (UNIL), the Vaud University Hospital Centre (CHUV), the Centre for Biomedical Imaging (CIBM), the Federal Polytechnic School of Lausanne (EPFL) and the University Hospitals of Geneva (HUG), Switzerland, teamed up to perform a detailed analysis of hepatic encephalopathy, a type of brain damage caused by chronic liver disease. The scientists were able to observe for the first time in a mouse model that a dysfunction of the liver provokes cerebral molecular disturbances in two weeks, even though no physical symptoms are apparent. Moreover, several molecules are concerned, including two that were previously unknown. The research results, which you can read about in the Journal of Hepatology, might help detect brain damage linked to liver diseases via a brain analysis before an individual's state of health deteriorates.



Four weeks after the onset of liver disease, astrocytic cells (red) in the brains of diseased rats show altered morphology with shortening and reduction in the number of their extensions (scale bar: 25 µm). Credit: © Katarzyna Pierzchala et Dario Sessa

When the liver is diseased, as is the case with cirrhosis, a number of substances are no longer filtered, which can cause psychological, motor and neurocognitive disorders in adults. This disease, called hepatic encephalopathy, may manifest itself in a wide spectrum of symptoms, even including a coma. It is known that one of the actors in hepatic encephalopathy is ammonium. As Valérie McLin, professor in the Department of Paediatrics, Gynaecology and Obstetrics at UNIGE's Faculty of Medicine and Geneva University Hospitals (HUG), explains: "Ammonium is a substance produced when proteins break down, some of which is directed to the brain where it is transformed into glutamine - used for the production of neurotransmitters - while the other part is filtered by the liver and excreted in the urine." However, if the liver malfunctions, it causes an excess amount of ammonium in the brain, and therefore glutamine production, which can trigger cerebral edema and, in some cases, hepatic encephalopathy. There are still two unknown factors: are there other molecular actors responsible for hepatic encephalopathy? How long does it take for the brain to be affected by liver malfunction ?

Impact much earlier than anticipated

In an attempt to answer these questions, the researchers observed rats with chronic liver disease for eight weeks. "We tracked each animal individually by putting it in a high magnetic field MRI (9.4 Tesla) every two weeks so we could carry out high resolution spectroscopy (MRS). This meant we could observe the molecular alterations very precisely from the onset of the liver disease," says Dr Cristina Cudalbu, a research staff scientist and operational manager of the 9.4T MRI, Center for Biomedical Imaging at EPFL. "And we discovered hitherto unseen observations!"

The scientists found that molecular changes affect the brain as early as the second week of liver disease. And yet, the rats have minimal symptoms of the disease. "Based on earlier studies, we thought it will take about six weeks to see an impact, i.e. at the beginning of the deterioration of the animal's health," says Dr Cudalbu.

The external signs of the disease appear between the fourth and eighth week: jaundice, malnutrition or water in the belly. "From that moment, we observed that in addition to there being an excess of ammonium in the brain, the concentration of the two other molecules drops: vitamin C, an antioxidant, and creatine, which fulfils many functions, including energy-related functions," says Olivier Braissant, a professor in the Clinical Chemistry Department at CHUV and the Faculty of Biology and Medicine at the University of Lausanne (UNIL). This is the first time that the role these two new actors play in the disease has been visibly demonstrated. "These appear in a second phase after the ammonium in the blood rises," says Professor Braissant.

Should the brain be analysed to detect liver diseases?

The results suggest that an MRS brain scan might detect the neurological manifestations of chronic liver disease long before the appearance of the first symptoms. But the researchers also aim to know whether it would be possible to protect the brain from this type of deterioration - or at least reduce the damage - by compensating for the lack of creatine and vitamin C using supplements or through the use of probiotics. "We are also carrying out similar observations in humans to see whether the brain damage is similar to that in rats," concludes Professor McLin.

https://bbc.in/2KMXcoB

The little-known spinal injury 'costing the NHS millions'

Failure to identify and treat a little-known spinal condition probably costs the NHS hundreds of millions a year, according to a leading consultant.

By Clive Coleman Legal correspondent, BBC News

Cauda equina syndrome requires surgery within hours to avoid damage to the bowel, bladder, sexual organs and legs. And it can be triggered by the most seemingly innocuous of body movements.

The Royal College of GPs says the condition is rare but every doctor should be on alert for it because of how serious it can be.

Red flag signs, include nerve pain down both legs as well as pins and needles or numbness around the bottom and inner thighs.

Catrina Farnell, of Skipton, Yorkshire, was 23 and a talented dancer with dreams of becoming a choreographer, when it happened to her. She was in London, for an American football game, when she bent to pick up a bag. "Something happened to my back," she says.

"It was excruciatingly painful. I didn't know what to do. I'd never even heard of cauda equina syndrome, so I didn't know there was a ticking clock above my head. I woke up a couple of hours later unable to move my legs, with numbness and pins and needles, and eventually unable to urinate."

Now 31 and reliant on crutches and a wheelchair, Catrina's legs, bowel, bladder and sexual organs are all severely damaged.

Her frail mother Margaret, 74, has become her carer.

Catrina says: "I want to have children and I want to meet someone to be with but it feels now that they'd be more of a carer, you know because being with me, people instinctively take on the role of looking after me. "So, it just completely took that element of my life away."

'A matter of hours'

Cauda equina means "horse's tail" in Latin and describes the spray of nerves that come off the bottom of the spinal cord and activate the bladder, bowel, sexual organs and legs.

If a slipped disc hits these nerves, urgent medical treatment to remove the pressure is critical.

"Ideally you want to catch this condition in a matter of hours, do an MRI scan and do decompressive surgery," says John Reynard, a consultant urological surgeon at Oxford University Hospitals NHS Trust.

But there is a widespread belief that a shortage of resources and a lack of awareness among medical professionals is exacerbating the problem. "CES requires a clinical and radiological diagnosis, so it is critical that patients get an MRI scan, which is the only way to confirm the condition," says Nisaharan Srikandarajah, a trainee neurosurgeon with a PhD in cauda equina syndrome.

"Sadly there is a shortage of MRI radiographers working out of hours, which causes delays in getting the critical diagnosis."

After 24 hours, the damage to the cauda equina is such that outcomes for patients become significantly worse.

Martin Brown, a former champion weightlifter, injured his cauda equina in the gym. "They don't see me at home crying every night, or struggling trying to get the energy to get up, put my brave face on and pretend that everything's all right," he says.

"My masculinity went with having trouble with sexual dysfunction. "I still have to have a strict regime to manage my bowels, my bladder. "It's demoralising and dehumanising. It really knocked my self-confidence."

Catrina and Martin are supported by the Cauda Equina Syndrome Association, set up by Claire Thornber, who also has the condition, and based at Broughton Hall, in Skipton, where it offers emotional and psychological rehabilitation. Assessing how many people have the condition is difficult as some hospitals do not log case numbers.

However, the last NHS figures available, for 2010-11, show 981 surgical decompressions for CES in England alone.

And the NHS projects the cost of CES compensation claims for the period 2014-16 to be £68m, with two-thirds of this for delay or failure of diagnosis or treatment.

These figures do not include claims against GPs - and John Reynard believes the true cost is far higher. "It's difficult to get a precise figure from all the various information sources about the frequency of delays in diagnosis of cauda equina syndrome," he says. "I would estimate that it is something in the order of £150m to £200m a year in terms of compensation payments, covering legal costs."

Prof Helen Stokes-Lampard, chairwoman of the Royal College of GPs, compared the condition to meningitis.

"Cauda equina syndrome is a rare condition but, like meningitis, one that every doctor will be on alert for because of how serious it can be if not detected and managed swiftly," she said.

"The vast majority of acute back pain and back problems will not be serious and can be safely managed through careful exercises or over-the-counter painkillers, but if a patient experiences any of the red-flag symptoms for cauda equina syndrome, they should seek medical attention as soon as they can."

Specialist lawyers have little doubt that medical professionals too often act too slowly or fail to recognise the key signs of the syndrome.

Sally Leonards, a partner at JMW Solicitors, said: "My concern as a lawyer, having done this work for over 20 years, is that I'm still seeing the same cases coming through. I'm still seeing the same themes arising and the NHS don't seem to be learning from the mistakes."

Compensation payments can reach £4m, excluding legal fees.

They are high partly because many of those who get cauda equina syndrome are young, may not be able to work again and need lifetime care.

NHS Resolution, formerly the NHS Litigation Authority, said it was "committed to sharing information with our NHS trust members to highlight some of the red flags related to cauda equina syndrome".

"We are working closely with trusts and the wider NHS system to reduce avoidable harm to patients," it said.

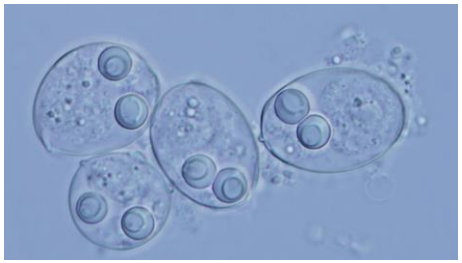
http://bit.ly/2Zqf80A

Can New Species Evolve From Cancers? Maybe. Here's How.

Researchers agree it's a long shot, but transmissible cancers could theoretically evolve into independent species. Certain weird parasites might be living proof.

Christie Wilcox

Aggressive cancers can spread so fiercely that they seem less like tissues gone wrong and more like invasive parasites looking to consume and then break free of their host. If a wild theory recently floated in *Biology Direct* is correct, something like that might indeed happen on rare occasions: Cancers that learn how to roam between hosts may gradually evolve into their own multicellular species. Researchers are now scrutinizing a peculiar group of marine parasites called myxosporeans to see whether they might be the first known example.



The parasites called myxosporeans live in fish during one stage of their life and in aquatic worms during another. If a new theory is right, they had a bizarre origin: as a form of transmissible cancer that evolved into its own species of animal. ***Ivan Fiala***

Even among microscopic parasites, myxosporeans are enigmatic. They were first discovered nearly two centuries ago, and more than 2,000 species are recognized today. Their complex life cycles make study particularly difficult: It wasn't until the 1980s that scientists realized the ones found in fish were the same species as those found in worms, and not completely different classes of parasite. And while most parasites are content merely to snuggle into their animal host's tissues, myxosporeans often take up residence inside a host's own cells.

Until fairly recently, myxosporeans were considered to be protists, offshoots of the eukaryotic line that are neither plants, animals nor fungi. In 1995, however, Mark Siddall, then at the Virginia Institute of Marine Science, and his colleagues argued that myxosporeans are weird members of the cnidarians, the group that includes jellyfish and corals. Since then, genetic studies have bolstered that position.

But their location on the tree of life doesn't explain how myxosporeans ended up with such strange traits. Myxosporeans boast some of the smallest known animal genomes. The genome of *Kudoa iwatai*, for example, is estimated to be a mere 22.5 megabases, considerably smaller than that of any other cnidarian genome. It's less than one-twentieth the size of the genome of *Polypodium hydriforme*, a closely related cnidarian parasite.

Moreover, their genomes have not just been catastrophically reduced. They specifically lack certain genes thought to be essential for multicellular life. It's not clear how or why a complex multicellular creature discarded these seemingly necessary genes along with huge chunks of its DNA.

Yet Alexander Panchin, a senior researcher at the Russian Academy of Sciences, and his colleagues have an intriguing if controversial hypothesis to explain it. Early this year, they proposed that myxosporeans initially branched off from their cnidarian kin not as independent animals but as tumors.

Evolutionary Scandals

Panchin knows the idea of cancer-derived animals sounds far-fetched — so much so that, in the paper, he and his co-authors refer to them as Scandals (an acronym for "speciated by *can*cer *d*evelopment anim*als*").

At first, Scandals were just a thought experiment. While Panchin was writing about transmissible cancers, he heard his colleagues express surprise at the genes for complex tissues that were turning

up in certain unusual but simple parasitic animals. Further conversations led to what Panchin calls the "fantastic" idea that such simple parasites could have cancerous origins. "So we took all the data and we proposed this hypothesis," he said.

According to Panchin's three-step scenario, a Scandal would start off as a cancer, but not just any cancer. It would have to be transmissible, so that it wouldn't die when its host did. Then the cancer would have to spread to other species, and then independently evolve multicellularity. Those steps might seem to present insurmountable barriers, and yet there's reason to believe each one could have happened.

The first step, the emergence of the transmissible cancer, is the most straightforward because we know it happens, although it is rare. Devil facial tumor disease (DFTD) has become notorious as a transmissible cancer devastating Tasmanian devils, who transmit it to one another in their bites.

The Tasmanian devil (left) and the Pacific blue mussel (*Mytilus trossulus*, right) are two of the species affected by transmissible cancers. Mathias Appel (tasmanian devil); NOAA (mussels)

More common but perhaps less famous is canine transmissible venereal tumor (CTVT), a sexually transmitted disease among dogs that, according to a recent analysis by Elizabeth Murchison of the University of Cambridge and her colleagues, has been evolving as a transmissible cancer for as long as 8,500 years. (In a 2014 report, Murchison and her co-authors described CTVT as perhaps "the oldest and most widely disseminated cancer in the natural world.")

Transmissible cancers are not confined to mammals; they have also been found in mollusks. There's no reason to think it would be impossible for transmissible tumors to arise in a cnidarian too. Cnidarians certainly aren't immune to cancers in general. If myxosporeans are Scandals, they most likely began as tumors of other cnidarian parasites — such as their *Polypodium* cousins, for instance.

Although the spread of a cancer to other species might seem unlikely, "it's not unheard of," said Athena Aktipis, an assistant professor at Arizona State University. Aktipis, who specializes in the evolution of cancer, points to cases such as that of a man with HIV who was discovered to be infected with tumor cells from a tapeworm. Such worm cancers have turned up repeatedly among people with compromised immune systems, and the known cases likely represent only the small minority of occurrences in which the source of a strange growth was tracked down. If this kind of species hopping happens right before our eyes, "maybe we should also consider the possibility that things that were cancer or cancerlike sometimes, in the right conditions, could become parasites on other species," she said.

"I think that the field has been way too cautious about talking about when cancer becomes its own species, or its own kind of organism," Aktipis said. In her view, researchers have seen too many examples of transmissible tumors like CTVT and DFTD. "It's a parasite. It's a parasitic organism."

Perhaps the least likely step in the Scandal hypothesis is the one where the cancerous parasite evolves from a unicellular existence to a multicellular one with distinct hosts and stages. Myxosporeans are simple animals but truly multicellular — so if they arose from a

transmissible tumor, that tumor would have had to evolve distinct cell types.

Multicellularity is thought to have evolved at least 25 times in eukaryotes, the domain of life that includes complex single-celled creatures as well as plants, animals and fungi. In animals, though, it's believed to have arisen just once at the very base of our lineage. Some multicellular branches of the eukaryotes have reverted to unicellularity, but no animals have been known to do so (unless, like some scientists, you consider cancer itself to be a kind of reversion). As yet, there don't seem to be lineages of any kind in which multicellularity was gained, lost and then gained again, in keeping with the Scandal hypothesis. "We understand that this is a very improbable scenario," Panchin said.

But that doesn't mean it couldn't have happened. "I think it's certainly possible that clusters of cancer cells that are transmissible could evolve to have something like a life cycle," Aktipis said. "There's nothing special about the evolutionary process that says you can only evolve a life cycle if you are a branch of the evolutionary tree that didn't derive from [a part of] another organism."

Following the Evidence

In the hope of finding more substantive evidence for the Scandal theory, Panchin and his team compared the genomes of a variety of simple species (most of them parasitic) with those of five myxosporeans, three single-celled creatures and 29 other animals. They looked for hints of a cancerous past by checking for the absence of genes that are often lost when cells turn malignant. These include genes involved in apoptosis, the regulated self-sacrifice that purges abnormal cells from the body. Any organism evolving from a transmissible tumor would presumably lack such genes.

Although the scientists had expected other parasites to be the most likely Scandal candidates, only the myxosporeans had lost key tumor-suppressing genes. So they drilled deeper and found that the myxosporeans have lost so many genes related to apoptosis that they probably can't trigger that death pathway at all. That deficiency stood out: "Even if you look at very simplified parasites which are animals, we don't see this degree of lack of cancer-related genes," Panchin said.

Aktipis thinks that Panchin and his co-authors have presented some intriguing reasons why "we should at least consider the possibility that some of the parasitic organisms that we see today might have evolved from transmissible cancers." But it's not case closed, she said. "This paper is a beginning for this work, not a decisive proof of it by any means."

Juliana Naldoni, a parasitologist and myxosporean specialist with the Federal University of São Paulo, isn't convinced that myxosporeans are Scandals at all. "They are actually much more complex than initially thought and evolve quite intricate [and specific] mechanisms of interaction with their hosts," she said. Some species also have complex features, such as cells organized into structures resembling muscles for movement, for example. She just doesn't find it plausible that such complexity arose from a cancer.

Adrian Baez-Ortega, a doctoral student and bioinformatician with Murchison's Transmissible Cancer Group at the University of Cambridge, agrees with Naldoni. "It is a thought-provoking paper, if not a very convincing one," he wrote in an email to *Quanta*. He isn't terribly impressed by the loss of apoptosis genes, for example. "In the context of such a dramatic genome reduction, the claim that the lack of genes specifically related to apoptosis points to a cancerous origin seems rather cherry-picked," he explained.

But mostly he's skeptical that a transmissible cancer could last long enough to evolve multicellularity. Cancer cells have incredibly unstable genomes. Although this allows them to mutate rapidly and elude their host's defenses, Baez-Ortega pointed out that on an evolutionary timescale, "this is a very detrimental strategy. As time goes on, a good portion of a cancer's genome becomes nonfunctional or abnormal, and this might impede not just survival, but also the development of sophisticated traits like multicellularity." The way he sees it, "even if a transmissible cancer could have survived for millions of years, it would be much more likely to remain a unicellular parasite."

That said, he thinks the Scandal hypothesis is worth further investigation. "There is almost nothing evolution cannot do," he said. Rather than focusing on specific missing genes, he would like researchers to scan candidate species for the diverse genomic changes that occur in cancers, from point mutations to large-scale chromosome rearrangements. "If a cancer were to become a long-lived species, all these modifications would be preserved in its genome," he said.

Even Panchin and his colleagues aren't going all-in on the hypothesis that myxosporeans are Scandals. "I think that's fair to say it's probably not true," he said. It's just that, with the work they've done so far, they can't rule it out. "We've been trying to refute it with the means that we have."

He added, "We are going to try to falsify the hypothesis through looking at the Malacosporea genome." Malacosporeans are cnidarian parasites and the closest known relatives of myxosporeans, but they are so much more complex that they are clearly not cancer derived. If they, too, turn out to lack apoptosis genes, it would suggest that the myxosporean loss doesn't stem from a cancerous past.

Even if, in the end, the data suggest myxosporeans aren't evolved cancers, Panchin noted that Scandals could still be out there waiting to be discovered. "We are hoping that maybe some zoologists who have been investigating some other peculiar kind of animal at some point will say, 'Probably those guys are wrong about Myxosporea, but this [animal], he's obviously a cancer.'"

http://bit.ly/30puwHu

Neanderthal tool-making process may have been simpler than previously thought

Neanderthals may have found that there is a very simple way to make this useful glue

by New York University

Neanderthals and other early humans produced a tarry glue from birch bark; this was long considered proof of a high level of cognitive and cultural development. Researchers had long believed that birch tar—used by the Neanderthals to make tools—could only be created through a complex process in which the bark had to be heated in the absence of air.

However, an international team led by researchers at the University of Tübingen and including faculty from New York University's Department of Anthropology and the NYU Tandon School of Engineering found that there is a very simple way to make this useful glue. The study was published August 19 in *Proceedings of the National Academy of Sciences* (*PNAS*).

"Our paper challenges common beliefs that the presence of birch tar in Neanderthal archaeological assemblages means they had sophisticated cognitive abilities," said co-author Radu Iovita, a paleoanthropologist and Paleolithic archaeologist in the Department of Anthropology at NYU and a member of the faculty of the Department of Early Prehistory and Quaternary Ecology at the University of Tübingen.

Prior researchers had experimented with pits, clay structures, ash mounds, and metal and ceramic vessels as means to heat the bark in the absence of oxygen. Instead, this research team experimented with ordinary materials available in the Stone Age. They collected cut fresh birch bark or dead bark in the forest and burned it near flat river stones. After three hours, the process yielded a usable amount of a black sticky material.

The tar could easily be scraped off the surface of the stones. Its molecular characteristics were similar to archaeological samples from Neanderthal sites and, more important, it formed a stronger glue than tar produced in more complex oxygen-free processes.

After burning the birch bark on stone, the stone is covered with tar. **University of Tübingen, Claudio Tennie**

The team used their adhesive to make a wood-scraping tool and turned to a robot that used force-control technology developed by Ludovic Righetti and Johannes Pfleging.

Righetti is an associate professor in the Electrical and Computer Engineering and the Mechanical and Aerospace Engineering Departments at NYU Tandon and a senior researcher at the Max-Planck Institute for Intelligent Systems in Tübingen. Pfleging is a visiting scholar of anthropology at NYU and a doctoral student in robotics at the Federal Institute of Technology (ETH) in Zürich, Switzerland.

Their robot arm dragged the tool with a precision that humans cannot emulate over 170 strokes. The approach also allowed the researchers to measure the effects with precision: The tool showed no weakening of the adhesive bond. In another test, the researchers used the adhesive to stick a stone scraper to a wooden handle, as the Neanderthals had done. Iovita was able to scrape the tough outer membrane from the thigh bone of a calf.

The researchers say this method of making birch tar is so simple that early humans could have easily discovered it by accident in the course of their everyday activities. The production and use of birch tar can therefore no longer serve as an indicator of modern or complex behavior.

Researchers used birch pitch to attach flint to wood, as Neanderthals would have done, but the wood was fashioned into a type of drill bit so their force-controlled robotic arm could precisely test the adhesion. **NYU Tandon, Johannes Pfleging**

"Birch tar extraction does not prove Neanderthal behavioral complexity," appears in PNAS – Proceedings of the National Academy of Sciences, week of August 19, 2019.

More information: *Patrick Schmidt et al. Birch tar production does not prove Neanderthal behavioral complexity, Proceedings of the National Academy of Sciences (2019). DOI: 10.1073/pnas.1911137116*

http://bit.ly/2KKIPBq

Scientists discover new way to reconstruct what extinct animals looked like

New way to reconstruct anatomy of ancient vertebrate animals by analyzing the chemistry from internal organs

by University College Cork

Scientists could be set to reveal the most accurate depictions of ancient vertebrates ever made after a world-first discovery at University College Cork (UCC) in Ireland.

UCC palaeontologists have discovered a new way to reconstruct the anatomy of ancient vertebrate animals, analyzing the chemistry of fossilized melanosomes from internal organs.

The study, published today in the journal *Proceedings of the National Academy of Sciences* of the United States of America, was led by UCC's Valentina Rossi and her supervisor Dr. Maria McNamara in collaboration with an international team of chemists from the US and Japan.

The team used cutting-edge synchrotron techniques to analyze the chemistry of the fossil and modern melanosomes using X-rays, allowing them to peer inside the anatomy of fossils and uncover hidden features.

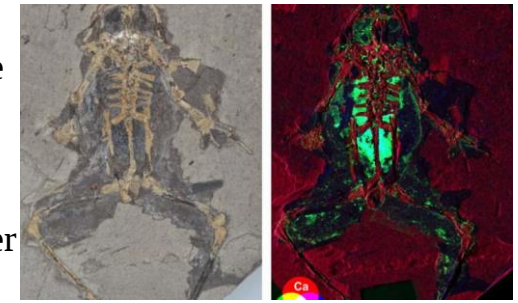


Fig. 1. 10 million-year-old fossil frog from Libros, Spain and X-ray map showing elevated levels of copper and zinc in the internal organs. Fossil photograph copyright the Natural History Museum, London. X-ray fluorescence map. **Valentina Rossi**

Until recently, most studies on fossil melanin have focused on the skin and feathers, whereas here the pigment is linked to visible color. Unexpectedly, the new study also showed that melanin is abundant in internal organs of modern amphibians, reptiles, birds and mammals, and their fossil counterparts.

"This discovery is remarkable in that it opens up a new avenue for reconstructing the anatomy of ancient animals. In some of our fossils we can identify skin, lungs, the liver, the gut, the heart, and even connective tissue," said senior author Dr. Maria McNamara.

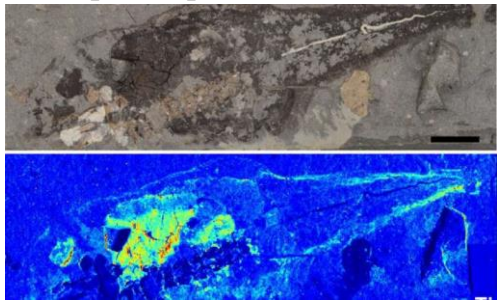


Fig. 2: 10 million-year-old fossil tadpole from Libros, Spain and X-ray map showing elevated levels of titanium in the skin, eye and especially the liver. X-ray fluorescence map. **Credit: Valentina Rossi.**

"What's more, this suggests that melanin had very ancient functions in regulating metal chemistry in the body going back tens, if not hundreds, of millions of years."

The team made the initial discovery of internal melanosomes last year on fossil frogs. "After the pilot study, we had a hunch that these features would turn out to be more widespread across vertebrates. But we never guessed that the chemistry would be different in different organs," Rossi said.

The advent of new synchrotron X-ray analysis techniques "allows us to harness the energy of really fast-moving electrons to detect minute quantities of different metals in the melanosomes."

The fossils are so well-preserved that even the melanin molecule can be detected.

More information: *Valentina Rossi et al. Tissue-specific geometry and chemistry of modern and fossilized melanosomes reveal internal anatomy of extinct vertebrates, Proceedings of the National Academy of Sciences (2019).* *DOI: 10.1073/pnas.1820285116*

http://bit.ly/2MtvoYw

Centuries-old Japanese family firms make history relevant to today's business world

Strategy-makers in long-lived Japanese firms face a challenge to match generations of history and guidance with modern-day corporate challenges and change.

日本のニュース

A study by researchers from Lancaster University, Politecnico di Milano, UCL and Aaalto University, published in the Strategic Management Journal, reveals that in many Japanese firms, foundational ka-kun - loosely translated as family mottos - remain relevant for decades, or even centuries.

Revered founders and leaders laid out the statements, such as family lessons, testaments and open letters, for their successors, articulating values for personal and business conduct and expressing principles that ensured past prosperity.

The researchers found strategy-makers grapple with this history to turn them from a potential source of inertia into a resource for change. Some ka-kun - in amended form - are still formally adhered to, despite changes within companies and their environments, while others are radically altered or no longer mentioned, reflecting the challenge of keeping them relevant many years after they were set

down. Only one company - which had preserved the same core business, ownership within the family and scale - honoured the ancient motto in its original form.

"The ka-kun tend to become emotionally-laded symbols of historical commitments for these firms. When they are used effectively, they can create a shared sense of purpose, mobilise collective action and responsiveness to changing competitive conditions, and lay the groundwork for sustainable competitive advantages," said co-author Dr Innan Sasaki, of Lancaster University Management School.

"When they were first forged, these statements were future-oriented - looking at where the firms wanted to be, and channeling energy, effort and resource in that direction. However, the passage of time means many are no longer relevant, even though they have acquired symbolic status, charged with emotion and inextricably tied to the firms' collective sense of self and legacy.

"This creates a tension between looking to the future and recognising the past of the statements, a struggle which is likely to become more pronounced over time, presenting the challenge if what to do regarding the ka-kun."

Professor Davide Ravasi, of the UCL Management School, added: "Corporate leaders are using a variety of strategies to deal with the revered past when going through strategic change, which both address the need to maintain continuity with the past and strategic relevance now."

The researchers found three differing strategies in the usage of the ka-kun in the face of strategic change in modern Japan to establish a sense of continuity: elaborating, recovering and decoupling.

Elaborating sees the transfer of part of the content of the historical statement into a new one. This was seen with sake manufacturer Gekkeikan, who adapted ka-kun set out in 1933 both in 1955 and 1997.

Recovering forges a new statement based on the retrieval and re-use of historical references, such as with Tokyo Keizai University, who looked back to their 1902 foundation in new mottos in 1992 and 2006.

Decoupling allows the co-existence of the historical statement and a contemporary one with different values, as seen with Yamanaka Hyoemon Shouten, founded in 1718 to commercialize food and sake, and adapting a new motto with a newly-appointed CEO in 2016.

Firms in Japan use all three methods to recognise their past while looking to the future, with recovering and decoupling often triggered by significant changes to the organization and/or its strategy.

"Elaborating helps maintain a sense of continuity by explicitly linking part of the revised statement with the original," said Dr Sasaki. "Revised statements are often presented as a development or an update of previous iterations, highlighting continuity while also refocusing attention on values managers view as important to keep the organisation viable in the present.

"The recovering strategy rests on the search of written, oral or even material memory. References to legendary leaders or a glorious past are used to emotionally energise and rally the organisation around a new strategy.

"Managers redirect attention to values they consider relevant to inspire and legitimise strategic change. At the same time, they claim continuity by reusing texts produced in the distant past. The new statement focuses on emerging issues and justifies changes, while the historical statement maintains a reassuring anchor in the past.

"Decoupling allows the maintenance of historical statements as a reassuring anchor with the past, maintaining a sense of stability and continuity in times of change. Like in the case of recovering, the

new statement is associated with organisational or strategic, however, decoupling is more frequently associated with emerging issues not addressed by historical statements."

Professor Eero Varra, of Aalto University Business School and Lancaster University Management School added: "All three strategies involve selective remembering and forgetting to varying degrees to bring the mottos into the modern business world. Change needs to be accommodated, but without threatening the integrity of the historical identity of companies, with values passed on from generation to generation through the ka-kun."

https://wb.md/2ZkiIVQ

Vaping Harms Vasculature, Even Without Nicotine

Vaping even one nicotine-free e-cigarette produced transient changes in blood vessels

Marlene Busko

In a small group of healthy young people who did not smoke or vape, vaping one nicotine-free electronic cigarette (e-cigarette) produced transient changes in blood vessels similar to those seen in early atherosclerosis, a study found.

The acute changes seen after one-time vaping — inhaling and exhaling the vaporized aerosol mist from the heated liquid in a battery-operated e-cigarette — suggest that repeated vaping would lead to chronic vascular endothelial dysfunction, the authors of this MRI study say.

The study, by Alessandra Caporale, PhD, a postdoctoral researcher from the Laboratory for Structural, Physiologic and Functional Imaging, Department of Radiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, and colleagues, was published online August 20 in *Radiology*.

The study used nicotine-free e-cigarettes; therefore, the findings shatter any mistaken belief that it is only the nicotine in e-cigarettes that is harmful to health.

"Endothelial dysfunction — the inability or reduced ability of the vasculature to expand to allow for increase in blood flow when needed — is the earliest stage of atherosclerosis pathogenesis," senior study author Felix W. Wehrli, PhD, director of the Laboratory for Structural, Physiologic and Functional Imaging and professor at the University of Pennsylvania, told *Medscape Medical News* in a joint interview with Caporale.

"The harms of cigarettes are obviously well known," Wehrli summarized, "but what was not well known [and what was shown in this study] was that e-cigarettes — even though advertised as comparatively unharmful — may actually ultimately cause harm similar to cigarettes and unrelated to nicotine."

Parents of middle school and high school students, whose e-cigarette use has increased dramatically, should be aware of these harms, Wehrli and Caporale stressed.

The many flavors that e-cigarettes come in "attract young people and potentially attract them to potential life-long addiction," Caporale said. She noted that some e-cigarettes contain more nicotine than what is stated on the label.

Not as Benign as Some Believe

Similarly, Karen M. Wilson, MD, MPH, a pediatrician at Icahn School of Medicine at Mount Sinai, New York City, who was not involved with the study, told *Medscape Medical News* that "there has been this narrative that electronic cigarettes create this harmless 'water vapor,' " thereby making them useful for adults who want to quit smoking.

But "what we're really starting to understand" is that in addition to nicotine, the aerosol contains other potentially toxic particles, she said.

According to Wilson, although it is unknown what the effects will be after 20 or 30 years, this study suggests that, as with smoking,

"we are likely to see an increase in cardiovascular disease" from vaping.

Importantly, "some of these vascular changes in the lungs or the direct irritation from those toxins and particulates in the aerosol [may be] what's precipitating" the recently seen cluster of cases of severe lung disease in young people who had been vaping, Wilson said.

As recently reported, from July through August 8, there were 12 confirmed cases and 13 cases under investigation of teens and young adults in Wisconsin who were hospitalized for severe lung problems after vaping.

Newer e-cigarette models, such as the Juul (Juul Labs), that have nicotine salt make it easier to inhale higher concentrations of nicotine, Wilson pointed out. "By the time [young people] recognize that it's dangerous, they're already addicted."

Importantly, the current study shows that "even without the nicotine, [e-cigarettes are] still harmful," she stressed, adding that there is no need to inhale anything except air or, if needed, a medication, such as albuterol for asthma.

Similarly, Deepak L. Bhatt, MD, MPH, a cardiologist at Brigham and Women's Hospital and a professor at Harvard Medical School in Boston, Massachusetts, told *Medscape Medical News*, "Vaping is growing among young people at an alarming rate, and the widespread belief among them is that this is safe for health." Bhatt was not involved with the study.

However, "this study demonstrates that these aerosols do negatively impact markers of endothelial function as assessed by MRI and adds to the growing literature that vaping is bad for cardiovascular health.

"Unfortunately, the full clinical impact of vaping will not be known for several years," he noted.

Effect of Aerosols on Blood Vessels

The e-liquid in e-cigarettes contains propylene glycol, glycerin, flavorings, and different amounts of nicotine. When heated, the aerosol that is formed contains formaldehyde and acetaldehyde (probable carcinogens) and tiny metal particles (likely from the heating element).

Once inhaled, these substances reach the lung alveoli, where they are taken up by blood vessels and can cause systemic oxidative stress and inflammation, as reported in studies of e-cigarettes that contain nicotine, the researchers write.

To investigate this in e-cigarettes without nicotine, Caporale and colleagues performed an MRI study in 17 men and 14 women who were 18 to 35 years old.

The participants had never smoked or vaped. Their body mass index was 18 to 35 kg/m^2, and they had no overt cardiovascular or neurovascular disease.

Under supervision, the participants took part in a "vaping challenge" in which they inhaled for 3 seconds (with no coughing or swallowing of the vapor) 16 times, using a disposable e-cigarette (Eco series; Epuffer) that contained propylene glycol, glycerol, and flavor but no nicotine.A 3.7-volt battery operated the e-cigarettes.

The participants underwent MRI scanning of the superficial femoral artery and vein, the superior sagittal sinus, and the aorta before and after the vaping challenge.

The researchers determined flow-mediated femoral artery dilation and femoral vein oxygen saturation by constricting the blood vessels of the upper leg using a cuff, and then releasing the cuff.

"The blood flow is completely disrupted for the femoral artery and vein for a few minutes, and then it is released, and then blood will shoot through the artery and return to the heart through the veins," Wehrli explained.

The researchers also assessed the cerebrovascular reactivity of the sagittal sinus using a breath-hold test, in which the participants held their breath for 30 seconds and breathed normally for 2 minutes three times.

MRI imaging was used to determine aortic pulse wave velocity.

A comparison of pre- and post-vaping MRI data after a single vaping challenge yielded the following results:

- ***a 34% reduction in femoral artery flow–mediated dilation and a 25.8% reduction in blood flow acceleration (P <. 001 for both), indicating endothelial dysfunction;***
- ***a 20% reduction in oxygen saturation of the femoral vein (P < .001), indicating microvascular impairment; and***
- ***a 3% increase in aortic pulse-wave velocity (P = .05), suggesting aortic stiffening.***

There were no statistically significant differences in the cerebrovascular reactivity of the sagittal sinus (*P* = .0

"Even though 31 is not a very big number [of participants], the effects we observed [were] highly statistically significant," Wehrli emphasized.

Related Studies Support Current Findings

It would be unethical to perform this experiment using tobacco cigarettes in nonsmokers, Wehrli noted.

However, the team previously conducted a study that showed similar harmful vascular effects in long-term cigarette smokers.

In addition, another study they recently conducted demonstrated that nicotine-free e-cigarette vaping caused a transient increase in serum markers of inflammation (C-reactive protein) and oxidative stress, which peaked 1 to 2 hours after vaping and returned to baseline within 6 hours.

These results support the imaging findings in the current study.

The research was funded by the National Heart, Lung, and Blood Institute. The authors have disclosed no relevant financial relationships.

Radiology. Published online August 20, 2019. Full text

http://bit.ly/2ZfowVz

A single change at telomeres controls the ability of cells to generate a complete organism

The TRF1 protein is only present at telomeres, but it has an effect on the entire genome that is essential for the pluripotency state

Pluripotent cells can give rise to all cells of the body, a power that researchers are eager to control because it opens the door to regenerative medicine and organ culture for transplants.

But pluripotency is still a black box for science, controlled by unknown genetic (expression of genes) and epigenetic signals (biochemical marks that control gene expression like on/off switches).

The Telomeres and Telomerase Group, led by Maria Blasco at the Spanish National Cancer Research Centre (CNIO), now uncovers one of those epigenetic signals, after a detective quest that started almost a decade ago.

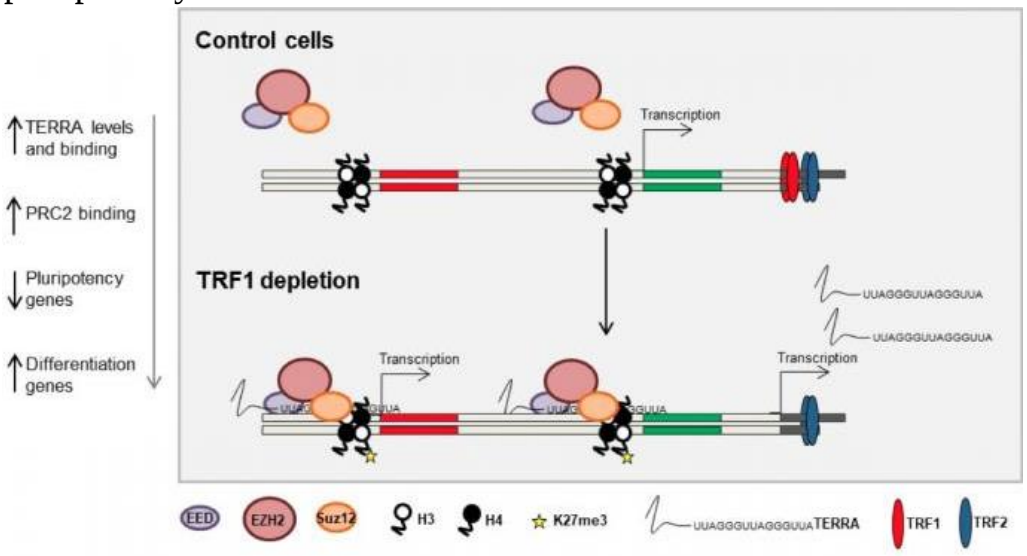
It is a piece of the puzzle that explains the observed powerful connection between the phenomenon of pluripotency and telomeres -protective structures at the ends of chromosomes-, a kind of butterfly effect in which a protein that is only present in telomeres shows a global action on the genome. This butterfly effect is essential to initiate and maintain pluripotency.

The DNA of telomeres directs the production of long RNA molecules called TERRAs. What the CNIO researchers found is that TERRAs act on key genes for pluripotency through the Polycomb proteins, which control the programs that determine the fate of cells in the early embryo by depositing a biochemical mark on the genes.

The on/off switch that regulates TERRAs, in turn, is a protein that is only present in telomeres; this protein is TRF1, one of the components of the telomere-protecting complex called shelterin. The new result is published this week in the journal *eLife*.

Why is a telomere gene required for pluripotency?

It has been known for about fifteen years how to return the power of pluripotency to cells by acting on certain genes. However, the researchers noticed that this recipe did not work if the TRF1 gene was turned off. Moreover, TRF1 was one of the most activated genes when pluripotency was induced. These facts intrigued the researchers. Why was TRF1, a gene whose product is only found in telomeres, activated so much, and how could this be essential for pluripotency?



In normal iPS cells (induced pluripotent stem cells) TRF1 is highly expressed, the Polycomb (PRC2) complex (encompassing EDD, EZH2 and Suz12) is weakly bound to the genome and pluripotency genes are expressed. After TRF1 depletion, TERRA increases its expression, this event results in PRC2 recruitment to genes involved in the control of pluripotency and differentiation and establishment of the K27me3 epigenetic mark, altering their expression **CNIO**

"We could not understand how a gene that deals with telomere maintenance has such a profound effect on a global process like pluripotency," says Maria Blasco, Head of the Telomeres and Telomerase Group at CNIO.

To find an explanation, they decided to carry out a random search by analyzing the changes in the expression of the entire genome when the expression of TRF1 was prevented - something like blindly casting a large net into the sea to see what is in it. "We saw that TRF1 had an enormous, but very organized, effect," explains Blasco.

The expression of many genes was altered, and more than 80% of them were directly related to the phenomenon of pluripotency. The researchers also noted that many of these genes were regulated by Polycomb, a protein complex that is very important in the early stages of embryonic development and that directs cells to specialize into the different cell types of the adult body.

The link is TERRA

But they still did not understand what the link between Polycomb and TRF1 was. Last year, however, Blasco's Group discovered that the TERRA molecules that are produced in telomeres communicate with Polycomb and that together they are involved in building the telomere structure.

The researchers decided to analyze the interaction between TERRA and the entire genome, and sure enough, they found that TERRA stuck to the same genes that were regulated by Polycomb. This suggested that TERRA was the link between TRF1 and pluripotency.

TRF1 "exerts a butterfly effect on the transcription of pluripotent cells, by altering the epigenetic landscape of these cells through a novel mechanism, which involves TERRA-mediated changes in the action of Polycomb," the researchers write in *eLife*.

As Rosa Marión, first author of the study, explains, "these findings tell us that TRF1 is essential for reprogramming specialized cells and for maintaining pluripotency."

The study has been funded by the Spanish Ministry of Science, Innovation and Universities, the National Institute of Health Carlos III, the Community of Madrid, World Cancer Research and the Botín Foundation and Banco Santander through Santander Universities.

*Reference article: TERRA regulate the transcriptional landscape of pluripotent cells through TRF1-dependent recruitment of PRC2. Rosa M. Marión et al (*eLife, *2019). DOI: https://doi.org/10.7554/eLife.44656*

http://bit.ly/30rZmPK

Metabolic Biomarker "Score" May Predict Death in Next 5–10 Years

The researchers intend for the tool to eventually help doctors make treatment decisions.

Emma Yasinski

One day, doctors may be able to use the metabolites in blood samples to predict the likelihood of a person surviving another five to 10 years, according to a newly developed tool described today (August 20) in *Nature Communications*. The authors of the report say the information may be useful in helping decide whether or not to do surgery on patients who are frail or could serve as endpoints in new clinical trials.

The study "shows the potential usefulness of metabolomic biomarkers," says Paola Sebastiani, a biostatistician at Boston University who was not involved in the study. She adds that the field will need longitudinal studies in the future to assess the biomarkers' clinical usefulness.

The team's goal was to find blood-based biomarkers that can "indicate risk of vulnerability, especially if that information provides opportunities for an improvement in lifestyle or better treatment," says Eline Slagboom, a molecular epidemiologist at Leiden University and the senior author on the study.

Doctors often use functionality measures such as grip strength and gait to determine an elderly patient's health status, but these measures are imprecise. Other traditional biomarkers don't necessarily apply to patients who hit a certain age. "For example, a somewhat higher weight, blood pressure, or cholesterol level is not as bad for individuals over 80 years of age as compared to younger individuals," says Slagboom. So her group undertook the largest study of its kind to detect blood-based biomarkers of metabolism. "We have worked with biobanks from all over the world for three years to come to these results."

The team used data from 12 cohorts of individuals of European descent, a total of 44,168 people aged 18–109, to identify 14 metabolites that they could use to develop a "score" to evaluate a person's risk for mortality at five and 10 years out. During the study's follow up, which ranged from around three years to nearly 17, depending on the cohort, 5,512 of the participants died.

Most of the biomarkers, which are involved in a variety of physiological processes such fatty acid metabolism, fluid balance, and inflammation, have previously been associated with mortality on their own, but never combined to form a single predictive score. And what's more is, unlike traditional measures of weight and cholesterol, the biomarkers consistently predicted mortality in all participants rather than only among the younger ones.

A single point added to the score was associated with a 2.73-fold increased risk of mortality during the course of the study. In one of the cohorts of 7,603 individuals (including 1,213 who died), the team compared the accuracy of the metabolic score and of traditional biomarkers in predicting mortality. The metabolic score was about 83 percent accurate, whereas the traditional scores were about 78 percent accurate.

"We were surprised that the association of our biomarker score with mortality was so strong, given that it is only based on 14 metabolic markers in blood measured at a single point in the life of individuals," says the study's lead author, Joris Deelen, a researcher at the Max Planck Institute for the Biology of Ageing and the lead author of the study.

Despite the study's impressive size, the authors caution that the information can't yet be used to estimate an individual person's risk

of mortality. And outside experts also warned about over-interpreting the study's results.

The study "proposes a hypothesis," says Leo Cheng, a pathologist at Massachusetts General Hospital, but it doesn't "prove anything." That will require an independent cohort of participants. However, he adds that using a score that combines the information from all 14 biomarkers is "the correct thing [to do]" to provide a holistic look at metabolic pathways that may represent a person's health.

The scientists used nuclear magnetic resonance (NMR) to analyze the samples because it is inexpensive and allowed them to process a large number of samples, but this strategy can lead to less reliable results than newer techniques for detecting metabolites, such as mass spectrometry.

Slagboom and her team are beginning to test the validity of the biomarker score in a range of existing studies to determine when the measurement might be most useful. For example, she says, she wonders if it could be used for elderly patients who enter the hospital with hip fractures or if the score could be useful to determine if a novel medication improves the risk of mortality in older patients. But Cheng warns that the people most interested in the ability to predict the likelihood of five and 10 year mortality may not be healthcare providers and patients, but instead, their insurers.

J. Deelen, et al., "A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals," **Nature Communications**, *doi:10.1038/s41467-019-11311-9, 2019.*

http://bit.ly/2Mx08HQ

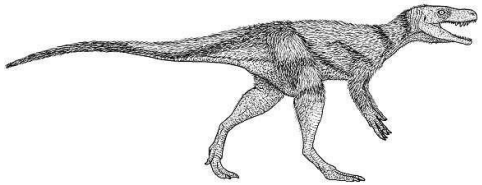
Rise of dinosaurs linked to increasing oxygen levels

Scientists have found that increasing oxygen levels are linked to the rise of North American dinosaurs around 215 M years ago.

by Goldschmidt Conference

A new technique for measuring oxygen levels in ancient rocks shows that oxygen levels in North American rocks leapt by nearly a third in just a couple of million years, possibly setting the scene for a dinosaur expansion into the tropics of North America and elsewhere. This is presented in a Keynote talk at the Goldschmidt Geochemistry conference, in Barcelona.

The US-based scientists have developed a new technique for releasing tiny amounts of gas trapped inside ancient carbonate minerals. The gases are then channelled directly into a mass spectrometer, which measures their composition.



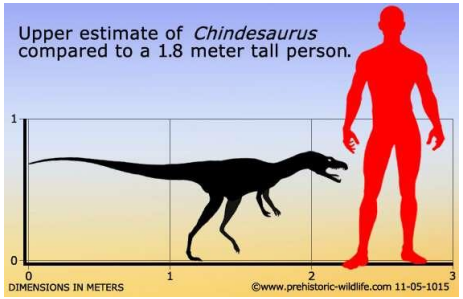
Chindesaurus. **National Park Service/Jeffrey Martz, nps.gov/pefo/learn/news/gertieday2015.htm**

Lead researcher, Professor Morgan Schaller (Rensselaer Polytechnic Institute, New York) said: "We tested rocks from the Colorado Plateau and the Newark Basin that formed at the same time about 1000 km apart on the supercontinent of Pangea. Our results show that over a period of around 3 million years—which is very rapid in geological terms—the oxygen levels in the atmosphere jumped from around 15% to around 19%. For comparison, there is 21% oxygen in today's atmosphere. We really don't know what might have caused this increase, but we also see a drop in CO_2 levels at that time."

"We expect that this change in oxygen concentration would have been global change, and in fact we found the change in samples which were 1000km apart. What is remarkable is that right at the oxygen peak we see the first dinosaurs appearing in the North American tropics, the Chindesaurus. The Sauropods followed soon afterwards. Again, we can't yet say if this was a global development, and the dinosaurs don't rise to ecological dominance in the tropics until after the End-Triassic extinction. What we can say is that this shows that the changing environment 215 M years ago was right for

their evolutionary diversification, but of course oxygen levels may not have been the only factor."

Chindesaurus was an upright carnivorous dinosaur (around 2m long and nearly 1m high). Found extensively in North America, with origins in the North American Tropics, it was a characteristic late Triassic Dinosaur of the American Southwest. It was originally discovered in the Petrified Forest National Park. The Sauropods, which appeared soon after Chindesaurus, were the largest animals ever to live on land.



Scientists have found that increasing oxygen levels are linked to the rise of North American dinosaurs around 215 M years ago. A new technique for measuring oxygen levels in ancient rocks shows that oxygen levels in North American rocks leapt by nearly a third in just a couple of million years, possibly setting the scene for a dinosaur expansion into the tropics of North America and elsewhere. From the Goldschmidt Geochemistry conference, Barcelona. **prehistoric-wildlife.com/Darren Pepper, prehistoric-wildlife.com/species/c/chindesaurus.html**

Commenting, Professor Mike Benton (University of Bristol) said:"The first dinosaurs were quite small, but higher oxygen levels in the atmosphere are often associated with a trend to larger size. This new result is interesting as the timing of oxygen rise and dinosaur appearance is good, although dinosaurs had become abundant in South America rather earlier, about 232 million years ago."Professor Benton was not involved in this work; this is an independent comment.

At the time the gases were trapped, the Colorado Plateau and the Newark Basin were part of the giant supercontinent, Pangea. Both were located near the equator. The rocks containing the oxygen and carbon dioxide were dated by measuring the radioactive decay of Uranium which was found in the samples.

More information: *New constraints on ancient atmospheric oxygen concentrations and the Late Triassic rise of the first North American dinosaurs, goldschmidt.info/2019/*

http://bit.ly/2zd7oA8

Women more likely to have 'typical' heart attack symptoms than men

BHF-funded research also shows no difference in key heart attack symptoms between men and women, with both sexes needing to know the most common warning signs

Women who have heart attacks experience the same key symptoms as men, quashing one of the reasons given for women receiving unequal care.

The British Heart Foundation-funded research puts into question a long-held medical myth that women tend to suffer unusual or 'atypical' heart attack symptoms, and emphasises the need for both sexes to recognise and act on the warning signs.

Incorrectly assuming that women having a heart attack suffer different symptoms to men could lead to misdiagnosis, delayed treatment and less intensive medical interventions being offered. Previous BHF-funded research has shown the resulting differences in care for women were estimated to have contributed to at least 8,200 avoidable deaths in England and Wales in the last decade.

In this latest study, published in the *Journal of the American Heart Association*, researchers at the University of Edinburgh recorded the symptoms of people attending the Emergency Department (ED) at Edinburgh Royal Infirmary who had a blood test called a troponin test. This test is used when doctors suspect a person is having a heart attack, and measures a protein released by damaged heart cells during a heart attack.

Between 1st June 2013 and 3rd March 2017, doctors in the ED ordered the troponin test for 1,941 people. Of these people, 274 were diagnosed as having a type of heart attack known as an NSTEMI (90 women and 184 men). This is the most common type

of heart attack, and occurs when the coronary artery is partially blocked.

Chest pain was the most common symptom for both men and women, with 93 per cent of both sexes reporting this symptom. A similar percentage of men and women reported pain that radiated to their left arm (48 percent of men and 49 per cent of women).

More women had pain that radiated to their jaw or back and women were also more likely to experience nausea in addition to chest pain (33 per cent vs 19 per cent).

Less typical symptoms, such as epigastric pain (heartburn), back pain, or pain that was burning, stabbing or similar to that of indigestion, were more common in men than women (41 per cent in men vs 23 per cent in women).

Previous research has suggested that women and men report different heart attack symptoms. However, the symptoms were often recorded after a heart attack diagnosis was confirmed, which may introduce bias. This study aimed to avoid this by asking an independent research nurse to interview and record the symptoms of all patients arriving at the ED with a possible heart attack before they were given a diagnosis.

The authors now say that further research is needed in larger and more diverse populations to confirm their findings.

Early diagnosis of a heart attack is essential for treatment and survival. BHF-funded research has previously shown that women having a heart attack are up to 50 per cent more likely than men to receive the wrong initial diagnosis and are less likely to get a pre-hospital ECG.

Amy Ferry, cardiology research nurse at the University of Edinburgh and first author, said: "Our concern is that by incorrectly labelling women as having atypical symptoms, we may be encouraging doctors and nurses not to investigate or start treatment for coronary heart disease in women.

"Both men and women present with an array of symptoms, but our study shows that so-called typical symptoms in women should always be seen as a red flag for a potential heart attack."

Professor Jeremy Pearson, Associate Medical Director at the British Heart Foundation, said: "Heart attacks are often seen as a male health issue, but more women die from coronary heart disease than breast cancer in the UK. We need to change this harmful misconception because it is leading to avoidable suffering and loss of life.

"In the UK, three women die of coronary heart disease every hour, many of them due to a heart attack. We know that women tend to wait longer before calling 999 after first experiencing heart attack symptoms. But that delay can dramatically reduce your chance of survival." The BHF is calling for everyone to be more aware of the most common symptoms of a heart attack:

- ***pain or discomfort in your chest that occurs suddenly and doesn't go away***
- ***pain that may spread to your left or right arm, or to your neck, jaw, back or stomach. For some people the pain or tightness is severe, while other people just feel uncomfortable***
- ***feeling sick, sweaty, light-headed or short of breath.***

A heart attack is a medical emergency and can be life threatening. People experiencing any of these symptoms should phone 999 immediately for an ambulance, regardless of their sex.

http://bit.ly/2L5dqAP

Unprecedented therapy found effective for blood cancer patients with no treatment options

New type of therapy to be effective for patients with a particular resistant type of bone marrow cancer

New York, NY - Mount Sinai researchers have found a new type of therapy to be effective for patients with a particular type of bone marrow cancer that is resistant to several standard therapies,

according to results of a clinical trial published in The New England Journal of Medicine in August.

This trial tested selinexor with dexamethasone, a combination that significantly knocked down the cancer in more than a quarter of patients, including two patients who went into complete remission. Proteins and messenger RNAs play an important part of cancer cell growth, and selinexor has an unprecedented mechanism that blocks the export of protein and messenger RNAs from the nucleus of the cancer cell to the cytoplasm, causing the cancer cell to die. This therapy caused at least a minimal response in almost 40 percent of patients who had multiple myeloma, a cancer of a type of white blood cell called a plasma cell.

"This study proved that a novel, first-in-class drug with a new mechanism of action can kill a patient's cancer cells," said the study's senior author, Sundar Jagannath, MBBS, Director of the Multiple Myeloma Program and Professor of Medicine (Hematology and Medical Oncology) at The Tisch Cancer Institute at Mount Sinai. "This proved that the drug worked in patients who had exhausted every other treatment and who would have been placed on hospice care otherwise."

The clinical trial, called the STORM Part 2 Study, studied the response of 122 patients taking selinexor and dexamethasone, both oral drugs, in trials across the United States and Europe. Mount Sinai enrolled a quarter of the patients in the international study.

Patients generally saw a response to the drugs within one or two months. While there was no organ toxicity, side effects included low blood count without bleeding, nausea, vomiting, lack of appetite or fatigue.

"This study is meaningful for patients with multiple myeloma who haven't had success on multiple other therapies," said the study's first author Ajai Chari, MD, Director of Clinical Research in the Multiple Myeloma Program at The Tisch Cancer Institute at Mount Sinai. "An increasing number of patients have resistance to the standard drugs used in the treatment of multiple myeloma, and the overall survival in these patients is short, sometimes less than three months."

Selinexor was approved by the FDA for patients resistant to multiple therapies in early July. This study was funded by Karyopharm, the manufacturer of selinexor.

Selinexor is also being investigated in multiple myeloma in combination with other approved multiple myeloma drugs as well as in other malignancies such lymphoma and ovarian cancer.

This study is a major milestone in myeloma research for the team at The Tisch Cancer Institute at Mount Sinai, which recently launched a new Center of Excellence for Multiple Myeloma. The new Center brings together internationally recognized physicians to provide comprehensive, compassionate care for patients with multiple myeloma and related diseases and to advance innovative research and personalized treatments that lead to cures. Dr. Jagannath will serve as Director of the Center which treats the largest number of myeloma patients in the country.

"The Center of Excellence for Multiple Myeloma is part of The Tisch Cancer Institute and uses the most advanced diagnostic and treatment approaches within state-of-the-art facilities of a National Cancer Institute-designated cancer center," said Ramon Parsons, MD, PhD, Director of The Tisch Cancer Institute, Chair of Oncological Sciences, and Ward-Coleman Professor in Cancer Research of the Icahn School of Medicine at Mount Sinai. "Coordinated care teams include experts from the Bone Marrow Transplant Program, pathology, radiology, immunology, genomics, infectious diseases, orthopedic surgery, cardiology, and nephrology, and patients will have broad access to comprehensive supportive services, including from social workers, financial counselors, and clergy."

http://bit.ly/33Tn4Xu

Lower back pain? Self-administered acupressure could help

A recent study finds that a traditional Chinese medicine technique, can improve chronic pain symptoms in the lower back.

ANN ARBOR, Mich. - "Acupressure is similar to acupuncture, but instead of needles, pressure is applied with a finger, thumb or device to specific points on the body," says Susan Murphy, ScD, OTR, an associate professor of physical medicine and rehabilitation at Michigan Medicine and lead author of the study.

Murphy says that while acupressure has been previously studied -- and found to be beneficial -- in people with cancer-related or osteoarthritis pain, there are few studies that have examined acupressure in people with back pain.

In the study, published in *Pain Medicine*, the research team randomly assigned 67 participants with chronic low back pain into three groups: relaxing acupressure, stimulating acupressure or usual care. "Relaxing acupressure is thought to be effective in reducing insomnia, while stimulating acupressure is thought to be effective in fatigue reduction," Murphy says.

Participants in the acupressure groups were trained to administer acupressure on certain points of the body, and spent between 27 and 30 minutes daily, over the course of six weeks, performing the technique.

Participants in the usual care group were asked to continue whatever treatments they were currently receiving from their care providers to manage their back pain and fatigue.

"Compared to the usual care group, we found that people who performed stimulating acupressure experienced pain and fatigue improvement and those that performed relaxing acupressure felt their pain had improved after six weeks," Murphy says.

"We found no differences among the groups in terms of sleep quality or disability after the six weeks."

Potential treatment option

Murphy notes that chronic pain is difficult to manage and people with the condition tend to have additional symptoms such as fatigue, sleep disturbance and depression.

"Better treatments are needed for chronic pain," Murphy says. "Most treatments offered are medications, which have side effects, and in some cases, may increase the risk of abuse and addiction."

She says this study highlights the benefits of a non-pharmacological treatment option that patients could perform easily on their own and see positive results.

"Although larger studies are needed, acupressure may be a useful pain management strategy given that it is low risk, low cost and easy to administer," Murphy says. "We also recommend additional studies into the different types of acupressure and how they could more specifically be targeted to patients based on their symptoms."

http://bit.ly/2KZOVN3

UC San Diego researchers convert pro-tumor macrophages into cancer killers

Monoclonal antibody that induces the immune system to seek and kill αvβ3-expressing cancer cells

Epithelial cancers, such as cancers of the lung and pancreas, use the αvβ3 *(alpha* v *beta* 3) molecule to gain drug resistance to standard cancer therapies and to become highly metastatic. In a paper published in *Cancer Research*, University of California San Diego School of Medicine researchers identified a new therapeutic approach in mouse models that halts drug resistance and progression by using a monoclonal antibody that induces the immune system to seek and kill αvβ3-expressing cancer cells.

"This antibody is designed to seek and destroy the most stem-like, drug-resistant, aggressive tumor cells. It does this by building a

bridge between tumor-associated macrophages and these highly aggressive tumor cells," said David Cheresh, PhD, Distinguished Professor and vice chair of Pathology. "What we have been able to observe in mice is that when we give this drug to drug-resistant tumors, it prolongs their response to standard of care and prevents their capacity to enter the blood stream."

Using the αvβ3 antibody LM609, Cheresh and his team exploited the appearance of αvβ3 receptors on tumor cells to redirect tumor-associated macrophages (TAMs) into recognizing and killing αvβ3 expressing tumor cells.

During the study period, no tumor progression or drug resistance was detected while untreated animals developed tumor growth and metastasis. The research in mouse models focused on pancreatic and lung cancer cells treated in combination with LM609 and the EGFR inhibitor erlotinib. But, the antibody is expected to work in combination with various drugs currently used to treat cancer patients, said Cheresh.

"We have observed a highly significant link between the appearance of αvβ3 expressing tumors and the appearance of tumor-associated macrophages," said Cheresh, associate director of innovation and industry alliances at UC San Diego Moores Cancer Center. "Normally, the appearance of tumor-associated macrophages promotes tumor growth and metastasis. However, our antibody arms these macrophages to join our fight against the cancer."

Macrophages are specialized immune cells that promote tissue inflammation, stimulate the immune system and rid the body of foreign debris, including cancer cells. TAMs instead create a pro-tumor environment that accelerates tumor growth, angiogenesis (the development of new blood vessels to support the tumor) and suppresses immune recognition of the tumor by the host immune response.

As tumors progress, the abundance of TAMs increases, allowing the cancer to become more aggressive and spread. As tumors become drug-resistant, αvβ3 appears on cell surfaces.

The Cheresh lab previously discovered that αvβ3 is upregulated on various cells during normal wound repair and in cancer cells as cancer becomes invasive. In both cases, this molecule triggers cells to enter a stress-tolerant state. In normal epithelial cells, this state enables them to initiate tissue remodeling, such as healing. In cancer, it allows cells to become drug-resistant and highly metastatic.

The current study revealed a new approach to induce TAMs to reverse course, killing cancer cells rather than supporting them. The antibody prompts these macrophages to begin killing tumor cells through a mechanism known as antibody-dependent cytotoxicity (ADCC).

"These results were initially unexpected since macrophages usually destroy cells via phagocytosis, a process that involves them literally devouring the foreign or target cell," said Cheresh, a faculty member of the Sanford Consortium for Regenerative Medicine. "Also, ADCC is typically known to be induced by natural killer cells, but we saw very few of these NK cells in the late-stage, drug-resistant cancers we have examined."

"We believe that the effectiveness of this antibody is based on three things: Its capacity to recognize drug-resistant cancers. Its ability to bind to a particular receptor on tumor-associated macrophages. And its capacity to induce ADCC of these highly aggressive tumor cells."

The protein CD47, which is found on many cells in the body and is often hijacked by cancer cells, tells macrophages not to eat these cells. The αvβ3 antibody bypasses the CD47 "don't eat me signal" by inducing ADCC as opposed to phagocytosis.

"In our studies, macrophages are not killing through phagocytosis which would be blocked by the appearance of CD47 on the tumor cell target. Rather, we're inducing macrophage to kill its tumor cell target by its ability to mediate ADCC. The therapeutic antibody we are utilizing is bridging the macrophage to the αvβ3-expressing tumor cell as a target. When this occurs it releases a cytotoxic substance that kills the tumor cell."

The team is currently producing a humanized version of this antibody, which Cheresh hopes will do in humans what LM609 does in mice.

Co-authors include: Hiromi I. Wettersten, Sara M. Weis, Paulina Pathria, Tami Von Schalscha, Toshiyuki Minami, and Judith A. Varner, all at UC San Diego.

Disclosure: David Cheresh is founder and Judith Varner is an adviser to Alpha Beta Therapeutics, the company which will be developing a drug based on this technology.

http://bit.ly/2HyFQtN

Once considered rare, an itchy dermatologic skin disorder is more common than thought

Data provides first estimate on prurigo nodularis prevalence in United States

Johns Hopkins researchers report that prurigo nodularis (PN), a skin disease characterized by severely itchy, firm bumps on the skin, may be associated with other inflammatory skin disorders as well as systemic and mental health disorders. Compared with other skin diseases, however, not much is known about PN. While symptoms of PN can be managed, no cures exist. Researchers were looking to determine associated conditions that are more common in patients with PN, compared with similar patients without PN.

A report on the findings was published in the *Journal of Investigative Dermatology*.

"A lot of patients who have prurigo nodularis also have associated severe health conditions that need more immediate attention, and many of these PN patients may fall through the cracks," says dermatologist Shawn Kwatra, M.D., assistant professor of dermatology at the Johns Hopkins University School of Medicine.

While skin conditions such as psoriasis and eczema are known to be caused by an overactive immune system, the underlying molecular cause of PN remains unknown because the disease has been understudied. Kwatra and colleagues then sought to learn more by first estimating how prevalent PN is in the United States.

As a starting point, Kwatra and team analyzed one of the largest national databases of insurance data in the U.S. (IBM MarketScan Commercial Claims and Encounters) between October 2015 and December 2016. They identified patients 18-64 years old with medical insurance who presented two or more insurance claims relating to PN, maintained for three months or more, and compared them with patients without PN, patients with atopic dermatitis and patients with psoriasis.

In their study, they identified 7,095 people with PN, 23,882 with atopic dermatitis without PN and 38,283 with psoriasis without PN. Based on these numbers, they calculated that more than 72 per 100,000 people are affected with PN, primarily females with an average age of 50 years.

"The real numbers may be higher than this because our data only included people with health insurance and between the ages of 18 and 64," says Johns Hopkins University School of Medicine fourth-year medical student Amy Huang.

According to The National Institutes of Health, PN may develop from other skin diseases or other health issues that may be common in families, and even environmental factors may place one at an increased risk of developing PN. Analyzing the data further, the team found that those with PN have increased risk of other conditions compared with people without PN, including HIV, kidney disease, non-Hodgkin's lymphoma and mental health disorders.

"We are eager to better understand PN because that will help in the management of our patients," says Kwatra. "Our goal is to inform other physicians about the frequency of PN-related associated conditions to guide an evidence-based, targeted diagnostic workup. Enhanced disease recognition and ongoing translational studies will provide further clues to the development of PN."

While there is no cure for PN, current treatment includes phototherapy, topical steroids and off-label management with immune suppressants and anticonvulsants. Kwatra says it's important for physicians to be well-informed about related conditions so PN can be properly diagnosed and managed.

Ongoing research initiatives include examining the patterns of PN in children and adults age 65 and over and how PN treatment affects these populations. Additional studies are ongoing by Kwatra's group to understand the molecular explanation of PN.

Further research is needed to clarify how chronic conditions such as atopic dermatitis, HIV, renal impairment and mental health conditions may contribute to the development of PN.

"With such a large population of people who have this neglected disease, we've only scratched the surface and are happy to take the lead with investigating this understudied condition," Kwatra says.

Co-authors were Joseph K. Canner, M.H.S., Raveena Khanna and Sewon Kang, M.D., of the Johns Hopkins University School of Medicine.

The authors report no conflicts of interest for this study.

The study was supported by a grant from the Skin of Color Society and the Dermatology Foundation Medical Dermatology Career Development Award.

http://bit.ly/2MxT6Tg

Researchers suggest amount of practice is not what differentiates great musicians from the merely good

Evidence contradicts findings of a study reporting that practice time differentiated great musicians from the merely good

by Bob Yirka, Science X Network, Phys.org

A pair of researchers with Case Western Reserve University has found evidence that contradicts the findings of an earlier study reporting that practice time differentiated great violin and piano players from the merely good. In their paper published in the journal *Royal Society Open Science*, Brooke Macnamara and Megha Maitra describe their attempts to reproduce the results of a 1993 study and what they found.

In 2008, author Malcolm Gladwell published a book called *Outliers* that outlined the results of a study carried out in 1993. In that study, a team of researchers had looked at the practice habits of a group of accomplished violinists and pianists. After analysis, they concluded that greatness in players was not attributable to genes or talent, but to the number of hours that musicians had practiced before reaching the age of 20. They found that 10,000 hours of practice was all that it took to master either instrument.

Since that time, others have cited the number to make a point about success in any given field. Now, in this new effort, the researchers suggest that the findings by the team were in error—they report that genes, environment and a host of other factors account for violin mastery. In short, they suggest that the 10,000 rule is not based on reality.

The researchers came to their conclusions by attempting to replicate the results of the earlier team. They interviewed three groups of aspiring violinists—those who were deemed the best, those who were rated as good, and those who were politely described as less accomplished. They also asked the volunteers to keep diaries to track how much they practiced.

The researchers report that they found that less-accomplished players had practiced on average only 6,000 hours before reaching the age of 20. But both the best and the good averaged 11,000 hours of practice before reaching age 20—a finding that suggested practice alone could not account for master-level violinists. They

also found that other factors such as genetics played a role. They also noted that the earlier team did not differentiate types of practice. The volunteers in the new effort reported that practicing alone was more fruitful than with an instructor, but they varied in how many hours were spent with each.

More information: *Brooke N. Macnamara et al. The role of deliberate practice in expert performance: revisiting Ericsson, Krampe & Tesch-Römer (1993), Royal Society Open Science (2019). DOI: 10.1098/rsos.190327*

http://bit.ly/2NlnWhL

The Dinner Party That Served Up 50,000-Year-Old Bison Stew

When life gives you frozen bison, make dinner.

by Paula Mejia

One night in 1984, a handful of lucky guests gathered at the Alaska home of paleontologist Dale Guthrie to eat stew crafted from a once-in-a-lifetime delicacy: the neck meat of an ancient, recently-discovered bison nicknamed Blue Babe.

The dinner party fit Alaska tradition: Since state law bans the buying, bartering, and selling of game meats, you can't find local favorites such as caribou stew at restaurants. Those dishes are enjoyed when hunters host a gathering. But their meat source is usually the moose population—not a preserved piece of biological history.

Blue Babe, in all its glory. **UA Museum of the North**

Blue Babe had been discovered just five years earlier by gold miners, who noticed that a hydraulic mining hose melted part of the gunk that had kept the bison frozen. They reported their findings to the nearby University of Alaska Fairbanks. Concerned that it would decompose, Guthrie—then a professor and researcher at the university—opted to dig out Blue Babe immediately. But the icy, impenetrable surroundings made that challenging. So he cut off what he could, refroze it, and waited for the head and neck to thaw.

Soon, Guthrie and his team had Blue Babe on campus and started learning more about the ancient animal. They knew that it had perished about 36,000 years ago, thanks to radiocarbon dating. (Though new research shows that Blue Babe is at least 50,000 years old, according to the university's Curator of Archaeology, Josh Reuther.) Tooth marks and claw marks also suggested that the bison was killed by an ancestor of the lion, the *Panthera leoatrox*.

Blue Babe froze rapidly following its death—perhaps the result of a wintertime demise. Researchers were amazed to find that Blue Babe had frozen so well that its muscle tissue retained a texture not unlike beef jerky. Its fatty skin and bone marrow remained intact, too, even after thousands of years. So why not try eating part of it?

It had been done before. "All of us working on this thing had heard the tales of the Russians [who] excavated things like bison and mammoth in the Far North [that] were frozen enough to eat," Guthrie says of several infamous meals. "So we decided, 'You know what we can do? Make a meal using this bison.'"

Guthrie decided to host the special dinner when taxidermist Eirik Granqvist completed his work on Blue Babe and the late Björn Kurtén was in town to give a guest lecture.

VERY OLD BISON—Eirik Granqvist, chief head taxidermist for the Zoological Museum, University of Helsinki, Finland, works to restore the remains of a bison which died 36,000 years ago. The bison was preserved in permafrost until discovered three years ago. The specimen will soon be on display at the University of Alaska museum.
(Staff photo by Eric Manning)

Eirik Granqvist working on the taxidermy of Blue Babe. **UA Museum of the North**

“Making neck steak didn’t sound like a very good idea,” Guthrie recalls. “But you know, what we could do is put a lot of vegetables and spices, and it wouldn’t be too bad.”

To make the stew for roughly eight people, Guthrie cut off a small part of the bison’s neck, where the meat had frozen while fresh. “When it thawed, it gave off an unmistakable beef aroma, not unpleasantly mixed with a faint smell of the earth in which it was found, with a touch of mushroom,” he once wrote. They then added a generous amount of garlic and onions, along with carrots and potatoes, to the aged meat. Couple that with wine, and it became a full-fledged dinner.

Guthrie, who is a hunter, says he wasn’t deterred by the thousands of years the bison had aged, nor the prospect of getting sick. “That would take a very special kind of microorganism [to make me sick],” he says. “And I eat frozen meat all the time, of animals that I kill or my neighbors kill. And they do get kind of old after three years in the freezer.”

Thankfully, everyone present lived to tell the tale (and the bison remains on display at the University of Alaska Museum of the North). The Blue Babe stew wasn’t unpalatable, either, according to Guthrie. “It tasted a little bit like what I would have expected, with a little bit of wring of mud,” he says. “But it wasn’t that bad. Not so bad that we couldn’t each have a bowl.” He can’t remember if anyone present had seconds, though.

http://bit.ly/2NpSpeE

A Man Accidentally Swallowed a Fish Bone. It Tore a Hole Through His Intestine.

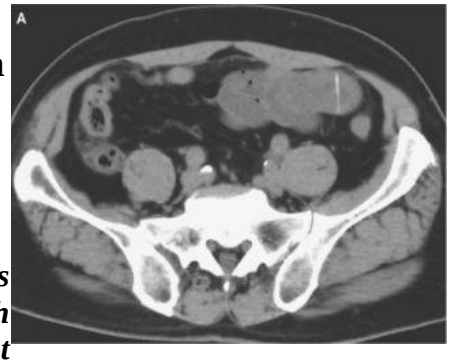
A tiny fish bone wreaked havoc on a man's gut.

By Rachael Rettner 17 hours ago Health

After a man accidentally swallowed a tiny fish bone, it tore a hole through his intestine.

The 73-year-old man, who lives in Japan, went to the emergency room after he developed sudden and severe pain in his lower abdomen, according to a report of the man's case, which is published today (Aug. 21) in The New England Journal of Medicine.

During a physical exam at the hospital, the man had tenderness across his lower abdomen, as well as a slight fever. The man told doctors that, the day before his pain started, he had eaten yellowtail. A CT scan of the man's abdomen revealed that his small intestine had been punctured by "a linear, high-density body." In other words, an object that looked a lot like a small bone was stuck in his intestine. The man underwent surgery, and doctors found that a 2-centimeter-long (0.8 inch) fish bone had pierced straight through his small intestine.



A fish bone pierced a hole through a man's intestine. Above, an X-ray showing the fish bone in the man's gut, in the upper right corner of the image. **© Shutterstock**

To treat the patient, doctors needed to remove part of his small intestine. He also received antibiotics to ward off any possible infections that could have resulted from having a hole in the bowel. The man recovered well, and he was able to leave the hospital after eight days, according to the report, from doctors at the Kochi Medical School in Nankoku, Japan.

People accidentally swallow fish bones all the time. But it's rare for a swallowed "foreign body" to cause a tear in the intestine; less than 1% of cases of an ingested foreign body result in such a tear, according to a 2014 paper published in the World Journal of Gastroenterology. Even fish bones, "despite their sharp ends and

elongated shape," typically pass through the gastrointestinal tract without causing problems, the authors of the 2014 paper said.

When an ingested fish bone does cause problems, it more commonly gets stuck in a person's throat, according to a 2011 paper published in the Indian Journal of Radiology and Imaging.

People who wear dentures are at higher risk of ingesting fish bones because they may have trouble feeling the bones in their mouth while eating, according to Healthline. (The study authors didn't report whether the patient in the current case wore dentures.) Other people who may be at higher risk of swallowing fish bones include children, older adults and people who eat fish while intoxicated.

People can lower their risk of swallowing fish bones by buying fillets, which tend to have fewer bones hiding in them than whole fish do, Healthline says. In addition, taking small bites and eating slowly can help lower the risk.

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

Cuba's untold Zika outbreak uncovered

An unreported spike in cases from 2017 is revealed through international travellers, a technique that could help with early detection in other epidemics.

By studying cases of people infected by Zika virus while travelling abroad, researchers have uncovered a previously unreported outbreak in Cuba.

Nathan Grubaugh at Yale School of Public Health in New Haven, Connecticut, and his collaborators examined a total of 153 cases of people who had visited Cuba from Florida or Europe between 2016 and 2018. The team estimates that Cuba experienced an outbreak in which somewhere between 1,000 and 20,000 people became infected, most of them in 2017 — a period when the Caribbean country reported no Zika cases to the relevant international agencies. Elsewhere in the Americas, cases had peaked a year before, but the Cuban outbreak might have been delayed by the country's aggressive mosquito-control efforts, the authors suggest.

By sequencing the Zika genome from 14 people, the team revealed that contagion had spread to Cuba mainly from other Caribbean countries. The authors say that their method could be extended to other infectious diseases, such as influenza, to unveil large outbreaks in countries where detecting or reporting of local cases is difficult.

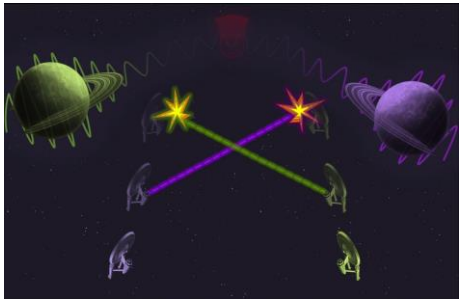
Cell (2019)

http://bit.ly/2Zo2PxF

In a quantum future, which starship destroys the other?

Quantum physicists blur the lines of cause and effect, illustrating how a sequence of events can flip and co-exist at the same time

Quantum mechanics boasts all sorts of strange features, one being quantum superposition - the peculiar circumstance in which particles seem to be in two or more places or states at once.



A starship exercise where two ships fire at each other. In a quantum future, an evil being can place planet in superposition near one ship or the other, leading to both starships simultaneously destroying each other. **Magdalena Zych, Igor Pikovski**

Now, an international group of physicists led by Stevens Institute of Technology, University of Vienna and University of Queensland flip that description on its head, showing that particles are not the only objects that can exist in a state of superposition - so can time itself.

"The sequence of events can become quantum mechanical," said co-author Igor Pikovski, a physicist at the Center for Quantum Science and Engineering at Stevens Institute of Technology. " We

looked at quantum temporal order where there is no distinction between one event causing the other or vice versa."

The work, reported in the August 22 issue of Nature Communications, is among the first to reveal the quantum properties of time, whereby the flow of time doesn't observe a straight arrow forward, but one where cause and effect can co-exist both in the forward and backward direction. In the upcoming era of quantum computers, the work holds particular promise: quantum computers that exploit the quantum order of performing operations might beat devices that operate using only fixed sequences.

To show this scenario, Pikovski and colleagues merged two seemingly conflicting theories - quantum mechanics and general relativity - to conduct a Gedanken experiment, a way of using the imagination to investigate the nature of things. The team, consisting of Pikovski, Magdalena Zych, Fabio Costa and Caslav Brukner, started by asking the question, "what would a clock measure if it was influenced by a massive object in a quantum superposition state, i.e. both near and far at the same time?"

According to general relativity, the presence of a massive object slows down the flow of time, such that a clock placed close to a massive object will run slower compared to an identical one that is farther away.

To illustrate what happens, imagine a pair of starships training for a mission. They are asked to fire at each other at a specified time and dodge the fire at another time, whereby each ship knows the exact time when to fire and when to dodge. If either ship fires too early, it will destroy the other, and this establishes an unmistakable time order between the firing events.

However, if a powerful agent could place a sufficiently massive object, say a planet, closer to one ship it would slow down its flow of time. As a result, the ship would dodge the fire too late and would be destroyed.

Quantum mechanics complicates the matter. When placing the planet in a state of superposition near one ship or the other, both can be destroyed or survive at the same time. The sequence of events exists in a state of superposition, such that each starship simultaneously destroys the other.

The authors illustrate for the first time how this quantum scenario can occur and how it can be verified. "Moving planets around is hard," said Pikovski. "But imagining it helped us examine a quantum aspect of time that was previously unknown."

http://bit.ly/31XG8ly

Adaptation to life in cattle may be driving E. coli to develop harmful features

Kyushu University-led research sheds light on an underlying origin of E. coli strains that cause food poisoning

A large-scale study of the genetic differences and similarities among *E. coli* bacteria from cattle and humans indicates that features causing food poisoning in humans may continuously be emerging in bacteria from cattle as a means to better adapt to their environment.

While *E. coli* bacteria are one of the most well-known causes of food poisoning, a wide variety of *E. coli* strains exists, many of which are harmless, permanent residents of our intestines. However, the ingestion of harmful strains of *E. coli* on contaminated food can lead to severe illness, vomiting, and diarrhea.

"To develop the most effective preventive measures, we need a deep understanding of the source and living conditions of the bacteria," says Yoshitoshi Ogura, associate professor at Kyushu University's Department of Bacteriology, who led the research.

"Although cattle have long been thought to be a main source of *E. coli* that cause food poisoning, why dangerous forms would keep appearing in cattle has been unclear."

Ogura's group, in collaboration with researchers across Japan and in France, Belgium, and the United States, set out to help answer this question by investigating the genetics of *E. coli* bacteria collected from cattle and humans in 21 countries spanning six continents.

"To date, there have been only a limited number of reports of the genome sequences of *E. coli* from cattle, so we needed to fill that gap," comments Yoko Arimizu, first author on the paper in *Genome Research* announcing the new results. While the largest number of samples was from Japan, strains from other regions exhibited characteristics that were well distributed among those from Japan, indicating a good diversity of the set of samples.

Based on the genetic features of the bacteria, the researchers could generally separate the different strains of *E. coli* into two groups, with one primarily consisting of bacteria collected from humans and the other of those from cattle. Applying the same analysis to clinically obtained *E. coli* that are known to cause illness, the researchers found that most of the strains causing intestinal problems belonged to the group associated with cattle.

Furthermore, many of the samples from cattle exhibited features similar to those causing food poisoning, such as the production of Shiga toxin. While these features generally appear not to cause illness in cattle, their prevalence in the investigated samples suggests that such characteristics are beneficial for life in a cattle's intestine. "As long as there is pressure to maintain or strengthen these illness-producing characteristics to better adapt to living in a cattle's intestine, new variants of *E. coli* that cause food poisoning are likely to continue appearing," states Ogura.

The researchers speculate that these characteristics may help *E. coli* protect itself from bacteria-eating organisms present in cattle intestines, but more work is needed to identify the exact reason.

For more information about this research, see "Large-scale genome analysis of bovine commensal Escherichia coli *revealed that bovine-adapted* E. coli *lineages are serving as evolutionary sources of the emergence of human intestinal pathogenic strains," Yoko Arimizu, Yumi Kirino, Mitsuhiko P. Sato, Koichi Uno, Toshio Sato, Yasuhiro Gotoh, Frédéric Auvray, Hubert Brugere, Eric Oswald, Jacques G. Mainil, Kelly S. Anklam, Dörte Döpfer, Shuji Yoshino, Tadasuke Ooka, Yasuhiro Tanizawa, Yasukazu Nakamura, Atsushi Iguchi, Tomoko Morita-Ishihara, Makoto Ohnishi, Koichi Akashi, Tetsuya Hayashi, and Yoshitoshi Ogura,* Genome Research *(2019),* https://doi.org/10.1101/gr.249268.119

http://bit.ly/33N7DzU

Scorpion toxin that targets 'wasabi receptor' may help solve mystery of chronic pain

May be used in studying chronic pain and inflammation, and eventually lead to development of new non-opioid pain relievers

Researchers at UC San Francisco and the University of Queensland have discovered a scorpion toxin that targets the "wasabi receptor," a chemical-sensing protein found in nerve cells that's responsible for the sinus-jolting sting of wasabi and the flood of tears associated with chopping onions. Because the toxin triggers a pain response through a previously unknown mechanism, scientists think it can be used as a tool for studying chronic pain and inflammation, and may eventually lead to the development of new kinds of non-opioid pain relievers.

The scientists isolated the toxin, a short protein (or peptide) that they dubbed the "wasabi receptor toxin" (WaTx), from the venom of the Australian Black Rock scorpion. The discovery came as the researchers were conducting a systematic search for compounds in animal venom that could activate, and therefore be used to probe and study, the wasabi receptor -- a sensory protein officially named TRPA1 (pronounced "trip A1") that's embedded in sensory nerve endings throughout the body. When activated, TRPA1 opens to reveal a channel that allows sodium and calcium ions to flow into the cell, which can induce pain and inflammation.

"Think of TRPA1 as the body's 'fire alarm' for chemical irritants in the environment," said John Lin King, a doctoral student in UCSF's Neuroscience Graduate Program and lead author of a study

published August 22, 2019 in *Cell*, which describes the toxin and its surprising mode of action. "When this receptor encounters a potentially harmful compound -- specifically, a class of chemicals known as 'reactive electrophiles,' which can cause significant damage to cells -- it is activated to let you know you're being exposed to something dangerous that you need to remove yourself from."

Cigarette smoke and environmental pollutants, for example, are rich in reactive electrophiles which can trigger TRPA1 in the cells that line the surface of the body's airway, which can induce coughing fits and sustained airway inflammation. The receptor can also be activated by chemicals in pungent foods like wasabi, onions, mustard, ginger and garlic -- compounds that, according to Lin King, may have evolved to discourage animals from eating these plants. WaTx appears to have evolved for the same reason.

Though many animals use venom to paralyze or kill their prey, WaTx seems to serve a purely defensive purpose. Virtually all animals, from worms to humans, have some form of TRPA1. But the researchers found that WaTx can only activate the version found in mammals, which aren't on the menu for Black Rock scorpions, suggesting that the toxin is mainly used to ward off mammalian predators.

"Our results provide a beautiful and striking example of convergent evolution, whereby distantly related life forms -- plants and animals -- have developed defensive strategies that target the same mammalian receptor through completely distinct strategies," said David Julius, PhD, professor and chair of UCSF's Department of Physiology, and senior author of the new study.

But what the researchers found most interesting about WaTx was its mode of action. Though it triggers TRPA1, just as the compounds found in pungent plants do -- and even targets the very same site on that receptor -- the way it activates the receptor was novel and unexpected.

First, WaTx forces its way into the cell, circumventing the standard routes that place strict limits on what's allowed in and out. Most compounds, from tiny ions to large molecules, are either ingested by the cell through a complex process known as "endocytosis," or they gain entry by passing through one of the many protein channels that stud the cell's surface and act as gatekeepers.

But WaTx contains an unusual sequence of amino acids that allows it to simply penetrate the cell's membrane and pass right through to the cell's interior. Few other proteins are capable of the same feat. The most famous example is an HIV protein called Tat, but surprisingly, WaTx contains no sequences similar to those found in Tat or in any other protein that can pass through the cell's membrane.

"It was surprising to find a toxin that can pass directly through membranes. This is unusual for peptide toxins," Lin King said. "But it's also exciting because if you understand how these peptides get across the membrane, you might be able to use them to carry things -- drugs, for example -- into the cell that can't normally get across membranes."

Once inside the cell, WaTx attaches itself to a site on TRPA1 known as the "allosteric nexus," the very same site targeted by pungent plant compounds and environmental irritants like smoke. But that's where the similarities end.

Plant and environmental irritants alter the chemistry of the allosteric nexus, which causes the TRPA1 channel to rapidly flutter open and closed. This allows positively charged sodium and calcium ions to flow into the cell, triggering pain. Though both ions are able to enter when TRPA1 is activated by these irritants, the channel exhibits a strong preference for calcium and lets much more of it into the cell, which leads to inflammation. By contrast,

WaTx wedges itself into the allosteric nexus and props the channel open. This abolishes its preference for calcium. As a result, overall ion levels are high enough to trigger a pain response, but calcium levels remain too low to initiate inflammation.

To demonstrate this, the researchers injected either mustard oil, a plant irritant known to activate the wasabi receptor, or WaTx into the paws of mice. With mustard oil, they observed acute pain, hypersensitivity to temperature and touch -- key hallmarks of chronic pain -- and inflammation, as evidenced by significant swelling. But with WaTx, they observed acute pain and pain hypersensitivities, but no swelling.

"When triggered by calcium, nerve cells can release pro-inflammatory signals that tell the immune system that something's wrong and needs to be repaired," Lin King said. "This 'neurogenic inflammation' is one of the key processes that becomes dysregulated in chronic pain. Our results suggest that you can decouple the protective acute pain response from the inflammation that establishes chronic pain. Achieving this goal, if only in principle, has been a longstanding aim in the field."

The researchers believe their findings will lead to a better understanding of acute pain, as well as the link between chronic pain and inflammation, which were previously thought to be experimentally indistinguishable. The findings may even lay the groundwork for the development of new pain drugs.

"The discovery of this toxin provides scientists with a new tool that can be used to probe the molecular mechanisms of pain, in particular, to selectively probe the processes that lead to pain hypersensitivity," Lin King said. "And for those interested in drug discovery, our findings underscore the promise of TRPA1 as a target for new classes of non-opioid analgesics to treat chronic pain."

Authors: Additional authors include Joshua J. Emrick, Mark J.S. Kelly and Katalin F. Medzihradszky of UCSF; Volker Herzig and Glenn F. King of the Institute for Molecular Bioscience at the University of Queensland.

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https://wb.md/30yxlpJ

Full Chemo Doses Early On Maximize Breast Cancer Survival

Survival is significantly better for breast cancer patients who receive the full dose of adjuvant chemotherapy, particularly in the first three cycles, compared with women whose doses are reduced, report Canadian researchers.

Liam Davenport

The results were published in the August issue of the *Journal of the National Comprehensive Cancer Network.*

"What surprised us the most was how dramatically early reductions in chemotherapy affect survival compared to later modifications," lead author Zachary Veitch, MD, Department of Oncology, University of Calgary, Tom Baker Cancer Center, Alberta, Canada, commented in a statement.

"This became even more apparent when patients were further separated based on chemotherapy dose cutoffs," he added.

"Often, the first cycle of chemotherapy can be difficult for patients, and oncologists must convey the need for maintaining initial dose intensity while using other medications to control side effects and manage comorbidities," Veitch commented.

An expert not involved in the study agreed. John Ward, MD, from the Huntsman Cancer Institute at the University of Utah, Salt Lake City, who is a member of the expert panel that drew up the National Comprehensive Cancer Network's clinical practice guidelines for breast cancer, commented in a statement: "Adjuvant therapy in

early-stage breast cancer leads to improved survival. When chemotherapy is part of the adjuvant treatment, it is important to give the prescribed doses. This study adds further support for the need to do so."

In many cases, the dose is reduced to minimize side effects or because of comorbidities, such as kidney disease or diabetes. "Balancing side effects with efficacy is always a challenge," Ward commented.

"When a treatment is palliative, quality of life factors into dosing choices," he continued. However, "When cure is the goal, as it is with adjuvant therapy, it is important to strive to give the therapy as planned. The juice is worth the squeeze," he said.

Chemotherapy Dose Reductions

For their study, Veitch and colleagues analyzed data from the Alberta Cancer Registry. They identified 1302 women with stage I–III *HER2*-negative breast cancer who were treated with an adjuvant chemotherapy regimen comprising 5-fluorouracil, epirubicin, cyclophosphamide, and docetaxel (FEC-D) during the period from 2007–2014.

Patients received at least four cycles of FEC-D, but no more than six. The total chemotherapy dose (TCD) was averaged across the treatments. A value of zero percent was assigned for any missed cycles.

The majority of the women (84%) received ≥85% of the TCD across all six cycles; 16% received reduced doses (<85% of TCD).

Women who received ≥85% of the TCD were younger than those who did not, at 54 years vs 57 years ($P < .01$), and were more likely to be premenopausal, at 44.5% vs 28.2% ($P < .001$).

They were also more likely to have a lower score on the updated Charlson comorbidity index: 84.5% had a score of 0, vs 72.8% of women who received <85% of the TCD ($P < .001$).

There were no significant differences between the two groups in terms of pathologic features, although there was a significant difference in tumor grade ($P < .014$). It is likely that the difference was driven by the fact that the women who received ≥85% of the TCD were more likely to have grade I disease, at 9.7% vs 3.5%.

As expected, women who received a larger proportion of the TCD were substantially more likely to have received six cycles of FEC-D, at 100%, vs 62.9% of those who received <85% of the TCD.

Difference in Survival

With respect to outcomes, the investigators found that the amount of chemotherapy that was received had a significant impact on survival.

The median follow-up was 59.9 months.

The analysis showed that TCD ≥85% was associated with >5-year disease-free survival (DFS), at 85.9% vs 79.2% for a lower TCD ($P = .025$), and better 5-year overall survival, at 88.8% vs 80.7% ($P < .001$).

Multivariate analysis indicated that a TCD <85% vs ≥85% was associated with significantly lower DFS, at a hazard ratio for progression of 1.45 ($P = .040$), and overall survival, at a hazard ratio for death of 1.50 ($P = .043$).

The team divided the cohort into those patients who had an early cumulative dose reduction, defined as receiving <100% of the first three FEC-D cycles, and those who received a late cumulative dose reduction, which included women who had received all of the first three cycles.

They found that outcomes were not compromised when dose reduction occurred only during the later cycles (which were the only cycles to include docetaxel). This suggests that late reductions in chemotherapy may not have as much of an impact on DFS and OS compared with early reductions, the authors comment. They note that "this finding is not completely unexpected."

Impact of Late vs Early Dose Reductions

Veitch commented that there may be several reasons for the difference in the impact of early vs late dose reductions on survival outcomes.

"First, the amount of docetaxel that was prescribed in the last three cycles may be higher than needed for the FEC-D regimen.

"Lower doses have been shown to be as effective in other standard-of-care chemotherapy regimens, and lower doses have been used in other countries with good outcomes," he said.

"Second, the majority of cancer cells that are sensitive to chemotherapy may be killed in the first few treatments, rather than in the later treatments." Hence, "reducing the dose late may not have as much of an impact," he added.

Funding for the study has not been disclosed. Coauthor Douglas A. Stewart, MD, has acted as a consultant for Apobiologix, Sandoz, and Amgen. The other authors have disclosed no relevant financial relationships.

J Natl Compr Canc Netw. 2019;17:957–967. Full text

http://bit.ly/30AydKO

Here's Why Drugs That Work So Well in Mouse Brains Often Fail Miserably in Humans

Brain cells in mice turn on genes that are very different from the ones in human brain cells.

By Yasemin Saplakoglu 3 days ago Health

Neuroscientists face a major obstacle in developing drugs to treat brain disorders — if the drugs work really well on mice, they often fall short when humans are treated. Now, a new study suggests a potential reason why: Brain cells in mice turn on genes that are very different from the ones in human brain cells.

Mice and humans have evolutionarily conserved brains, meaning they have very similar brain architectures made up of similar types of brain cells. In theory, that makes mice ideal test subjects for neuroscientists, who don't typically have the ability to peer into living human brains.

Yet for mysterious reasons, treatments that worked beautifully in the mouse brain often don't pan out when tested in humans.

To figure out why that may be, a group of scientists from the Allen Institute for Brain Science in Seattle analyzed brains donated from deceased people and brain tissue donated by epilepsy patients after brain surgery. They specifically looked at a part of the brain called the medial temporal gyrus, which is involved in language processing and deductive reasoning.

Researchers sorted through nearly 16,000 cells from this brain region and identified 75 different cell types. When they compared the human cells with a data set of mouse cells, they found that mice had counterparts that were similar to almost all of those human brain cells.

But when they looked at which genes were switched on or off inside those cells, they found stark differences between the mouse and human cells.

For example, serotonin is a neurotransmitter — or brain chemical — that regulates appetite, mood, memory and sleep. It does so by binding to brain cells via a receptor on the cell surface, which acts like a glove that is made to catch a baseball.

But a mouse's serotonin receptors are not found on the same cells that they're found in humans, the researchers discovered. So a drug that increases serotonin levels in the brain, such as those used to treat depression, might deliver it to vastly different cells in mice than in humans.

They also found differences in the expression of genes that help build connections between neurons. In essence, the cellular roadmap in our brains may look very different from what it looks like in a mouse.

"The bottom line is there are great similarities and differences between our brain and that of the mouse," co-senior author Christof Koch, the chief scientist and president of the Allen Institute for

Brain Science, said in a statement. "One of these tells us that there is great evolutionary continuity, and the other tells us that we are unique." "If you want to cure human brain diseases, you have to understand the uniqueness of the human brain," he added. The findings were published yesterday (Aug. 21) in the journal Nature.

https://nyti.ms/2MC16Tk

This Daily Pill Cut Heart Attacks by Half. Why Isn't Everyone Getting It?

"Polypills" of generic drugs may dramatically reduce heart attacks and strokes in poor countries, a new study suggests. Some experts still aren't enthusiastic.

By Donald G. McNeil Jr.

Giving people an inexpensive pill containing generic drugs that prevent heart attacks — an idea first proposed 20 years ago but rarely tested — worked quite well in a new study, slashing the rate of heart attacks by more than half among those who regularly took the pills.

A drugstore in Tehran. A study by doctors at Tehran University found that the heart attack rate fell by more than half among rural Iranian villagers between the ages of 50 and 75 who took pills containing generic drugs.
Agence France-Presse — Getty Images

If other studies now underway find similar results, such multidrug cocktails — sometimes called "polypills" — given to vast numbers of older people could radically change the way cardiologists fight the soaring rates of heart disease and strokes in poor and middle-income countries

Even if the concept is ultimately adopted, there will be battles over the ingredients. The pill in the study, which involved the participation of 6,800 rural villagers aged 50 to 75 in Iran, contained a cholesterol-lowering statin, two blood-pressure drugs and a low-dose aspirin.

But the study, called PolyIran and published Thursday by The Lancet, was designed 14 years ago. More recent research in wealthy countries has questioned the wisdom of giving some drugs — particularly aspirin — to older people with no history of disease.

The stakes are high. As more residents of poor countries survive childhood into middle age and beyond — and as rising incomes contribute to their adoption of cigarette smoking and diets high in sugar and fat — a polypill offers a way to help millions lead longer, healthier lives.

About 18 million people a year die of cardiovascular disease, and 80 percent of them are in poor and middle-income countries threatened by rising rates of obesity, diabetes, tobacco use and sedentary living. Medical experts, however, are sharply divided over the polypill concept.

Its advocates — including some prominent cardiologists — point to the study as evidence that the World Health Organization should endorse distributing such pills without a prescription to hundreds of millions of people over age 50 around the globe. Some have estimated that widespread use could cut cardiac death rates by 60 to 80 percent.

"The polypill concept is very important and it's surprising that it's taking so long for people to accept it," said Dr. Salim Yusuf, director of the Population Health Research Institute at McMaster University in Canada and an expert on cardiac health in poor countries, who was not involved in the Iran study. "This study takes us one step closer."

Other leading cardiologists consider the approach unethical and dangerous. Because aspirin, statins and blood-pressure drugs all have side effects, they argue, no one should get them without first

being assessed for risk factors like high blood pressure, high cholesterol or family history.

"I'm a skeptic of the one-size-fits-all, four-drugs-for-everyone approach," said Dr. Steven E. Nissen, head of the department of cardiovascular medicine at the Cleveland Clinic. "It runs counter to what most of us in the U.S. consider good medical practice."

Simple tests, including cholesterol tests that use only a finger prick, are available, he noted.

Dr. Thomas R. Frieden, a former director of the Centers for Disease Control and Prevention and now the president of Resolve to Save Lives, an organization that seeks to lower worldwide cardiac deaths, said he thought a four-drug pill like the one used in the study was appropriate only for people who had suffered a cardiac event.

Some blood pressure medications are safe enough to give to untested people, he said. But aspirin, which can cause bleeding in the brain, is not; and statins, which can, in rare cases, cause liver and muscle damage, may not be.

The Iran study was conducted by doctors from Tehran University, the University of Birmingham in Britain and other institutions.

It was the first study of such a multidrug pill that was large and long-lasting enough to measure "clinical outcomes" — how many people actually had heart attacks, strokes or episodes of heart failure while taking the pills, rather than just how many, for example, lowered their blood pressure or cholesterol.

Similar studies are underway in many countries.

However, since there is so much controversy about the ingredients used in the medication, each study has its own pill recipe.

Dr. Yusuf is leading the TIPS 3 trial on about 5,700 people in Bangladesh, Canada, Colombia, India, Malaysia, the Philippines, Tanzania and Tunisia; it uses a pill containing three blood-pressure drugs and a statin. (The trial's three other "arms" use low-dose aspirin, vitamin D and a placebo pill.) It is expected to end in March.

And the SECURE trial is recruiting about 3,200 patients in seven European countries who are over 65 and have already had one heart attack. Its pill contains aspirin, a statin and a single blood-pressure drug. It is expected to end in late 2021.

In the Iran trial, those assigned to take pills had a third fewer cardiac events over five years than the control group, whose participants got face-to-face advice and monthly text reminders to lose weight, stop smoking, eat healthy food and exercise.

(Because it was conducted in northern Iran, they were also advised to avoid another local habit — opium smoking.)

All participants were asked to return their used blister packs of pills. Those who appeared to have taken at least 70 percent of them had the highest protective effect — 57 percent fewer cardiac events.

The rates of serious adverse events were similar in both groups. Only a few in each trial arm suffered from bleeding in the brain, the stomach or the intestines, all of which can be caused by aspirin.

Mysteriously, although the cholesterol levels of those who got the pills dropped significantly during the trial, their blood pressure levels did not.

That puzzled several experts who looked at the results, including Dr. Frieden, who said the two anti-hypertension drugs used — a diuretic and an ACE inhibitor — should have significantly cut blood-pressure levels. "That result doesn't make sense," he said.

Dr. Tom Marshall, a cardiac disease prevention specialist at the University of Birmingham and a co-author of the study, acknowledged the anomaly, saying, "I wish I had the answer."

Baseline blood pressures in the population were not high, averaging 130 over 79, he said.

Dr. Frieden said he was also troubled that the trial did not explain whether blood pressure readings were taken by machine or by

people with stethoscopes. Some machines and some poorly trained humans get inaccurate results, he said.

The trial was conducted in the “Golestan Cohort,” a group of more than 50,000 Turkmen-speaking people currently enrolled in cancer studies administered by Iranian researchers in coordination with the W.H.O. and the National Cancer Institute.

Dr. Rekha Mankad, director of the Women’s Heart Clinic at the Mayo Clinic in Minnesota, who was not involved in the Iran study, said it had some flaws, including early problems with how clusters were chosen and the fact that each cluster inevitably included some people already on heart-disease medication.

Nonetheless, she said, the overall study was well-designed and she particularly praised the fact that half the participants were women.

“And,” she added, “the adherence rate was fantastic.”

More than 80 percent of the study participants took most of their pills. Poor adherence, she said, is one of the biggest problems that polypills are meant to fight.

Not only do poor people have little access to doctors or pharmacies, she noted, but “patients constantly say, ‘Listen, doc, I take too many pills,’ and drop something.” “This is one pill with all the major things patients need,” she added. “Now we need to see how difficult it will be to apply it to the real world.”

http://bit.ly/2KRKJjq

Exciting new vaccine targets killer disease TB

Successful development and testing of a new type of vaccine targeting tuberculosis

Australian medical researchers from the Centenary Institute and the University of Sydney have successfully developed and tested a new type of vaccine targeting tuberculosis (TB), the world's top infectious disease killer.

Reported in the '*Journal of Medicinal Chemistry*', the early-stage vaccine was shown to provide substantial protection against TB in a pre-clinical laboratory setting.

"Tuberculosis is a huge world-wide health problem. It's caused by a bacteria that infects the lungs after it's inhaled, is contagious and results in approximately 1.6 million deaths per year globally," said Dr Anneliese Ashhurst, co-lead author of the reported study and affiliated with both the Centenary Institute and the University of Sydney.

The research program targeting the deadly disease has currently taken over five years of effort to implement. During that time Dr Ashhurst and a team of scientists have created the advanced synthetic TB vaccine and have now demonstrated its effectiveness using mouse models.

"Two peptides (small proteins) which are normally found in tuberculosis bacteria were synthesized and then bound extremely tightly to an adjuvant (a stimulant) that was able to kick-start the immune response in the lungs," said Dr Ashhurst.

"We were then able to show that when this vaccine was inhaled into the lungs, it stimulated the type of T cells known to protect against TB. Importantly, we then demonstrated that this type of vaccine could successfully protect against experimental airborne TB infection," she said.

Professor Warwick Britton, Head of the Centenary Institute Tuberculosis Research Program and co-senior researcher on the project with Professor Richard Payne, School of Chemistry, University of Sydney, emphasized the importance of the work being done. "There currently exists only one lone vaccine for TB (known as BCG) and this is only effective in reducing the risk of disease for infants," said Professor Britton.

"It fails to prevent infection or provide long term protection in older individuals and it isn't considered suitable for use in individuals

with an impaired immune system. More effective vaccines are urgently required to save lives," he said. Professor Britton is excited that the team's vaccine strategy - directly generating immunity in the lungs - has proven to be the right research approach to take.

"The important thing is that the vaccine actually gets to the lungs because that's where you first see TB. Ultimately, we would love to see a form of this vaccine available for use in an easily inhaled nasal spray which would provide life-long TB protection. Although this outcome is still many years away, we are certainly heading in the right direction. Our next steps will be to determine if our synthetic vaccine can be developed into a form suitable for use in humans," said Professor Britton.

There are an estimated two billion individuals carrying TB globally and up to 10% of these individuals develop the disease in their lifetime. More than 50 per cent of TB cases occur in the Asia Pacific region.

PUBLICATION: Mucosal vaccination with a self-adjuvanted lipopeptide is immunogenic and protective against Mycobacterium tuberculosis.

URL: https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.9b00832

http://bit.ly/2MAroWh

Shingles vaccination of older adults cost-effective in Canada

Shingrix vaccine appears to provide better protection than the Zostavax vaccine

Vaccinating older adults against shingles in Canada is likely cost-effective, according to a study in *CMAJ (Canadian Medical Association Journal)*, and the Shingrix vaccine appears to provide better protection than the Zostavax vaccine. Herpes zoster, or shingles, affects about 1 in every 3 adults, causing a painful rash that can result in long-term pain in 8% to 27% of people.

The study used a model to compare the effectiveness and cost-effectiveness of the recombinant subunit (RZV, Shingrix) and live attenuated zoster (LZV, Zostavax) vaccines in adults aged 50 years and older in Canada. The LZV vaccine has been available in Canada since 2008, and RZV was approved in 2017.

The number of people needed to be vaccinated to prevent one case of shingles was lower for RZV (Shingrix) than for LZV (Zostavax) for all ages. For example, in people aged 60 years, the number needed to vaccinate was 18 for RZV and 78 for LZV.

"Our model predicted that the recombinant subunit zoster vaccine is likely cost-effective in Canada for adults 60 years or older and that it provides greater health benefits than the live attenuated zoster vaccine for all age groups," writes Dr. Marc Brisson, Centre de research du Centre hospitalier de l'Université de Québec and the Université Laval, Québec, Quebec, with coauthors.

The study results are consistent with other economic evaluations in the United States and the Netherlands.

"Effectiveness and cost-effectiveness of vaccination against herpes zoster in Canada: a modelling study" is published August 26, 2019.

http://bit.ly/2ZqQkS2

Physicians slow to use effective new antibiotics against superbugs

New, more effective antibiotics are being prescribed in only about a quarter of infections

PITTSBURGH - New, more effective antibiotics are being prescribed in only about a quarter of infections by carbapenem-resistant Enterobacteriaceae (CRE), a family of the world's most intractable drug-resistant bacteria, according to an analysis by infectious disease and pharmaceutical scientists at the University of Pittsburgh School of Medicine and published today by the journal Open Forum Infectious Diseases.

This sluggish uptake of such high-priority antibiotics prompted the researchers to call for an examination of clinical and pharmaceutical stewardship practices across U.S. hospitals, as well

as behavioral and economic factors, to see if the trend can be reversed before lackluster sales lead the pharmaceutical industry to stop developing much-needed antibiotics.

"The infectious diseases community spent the past decade saying, 'We need new antibiotics, this is a top priority,' and now we're at risk of sounding like the boy who cried wolf," said lead author Cornelius J. Clancy, M.D., associate professor of medicine and director of the mycology program and XDR Pathogen Laboratory in Pitt's Division of Infectious Diseases. "We have a responsibility to learn why it takes so long for antibiotics to be adopted into practice and figure out what we need to do to ensure the best antibiotics quickly reach the patients who desperately need them."

The U.S. Centers for Disease Control and Prevention has classified CRE as urgent threat pathogens and calls them the "nightmare bacteria." The World Health Organization and Infectious Disease Society of America have designated CRE as highest priority pathogens for development of new antibiotics. At the time of those declarations, polymyxins were the first-line antibiotics against CRE, even though they failed to work in about half the cases and carried a significant risk of damaging the kidneys.

Since 2015, five antibiotics against CRE have gained U.S. Food and Drug Administration (FDA) approval: ceftazidime-avibactam, meropenem-vaborbactam, plazomicin, eravacycline and imipenem-relebactam. Studies, including those conducted at UPMC, have shown that the first three of these antibiotics are significantly more effective at fighting CRE and less toxic than polymyxins (eravacycline and imipenem-relebactam are still too new for conclusive data).

Clancy and his colleagues surveyed hospital-based pharmacists in the U.S. to gauge their knowledge of the new antibiotics and their willingness to use them. The drugs were classified as the "first-line" choice against CRE blood infections by 90% of the pharmacists, pneumonia by 87%, intra-abdominal infections by 83% and urinary tract infections by 56%.

"Clearly hospital-based pharmacists are aware of these antibiotics and believe they are the best choice for the vast majority of CRE infections," said Clancy.

But when the team estimated the number of CRE infections nationwide and used national prescription data to calculate the proportions of old vs. new antibiotics used to treat those infections, they found that from February 2018 through January 2019, the new antibiotics were used only about 23% of the time. Their use likely started to exceed that of polymyxins only in December 2018, nearly four years after the first of the new antibiotics was approved by the FDA. Even after accounting for CRE infections in which new antibiotics might not be first-choice agents, the team found that use was only about 35% of what was expected based on positioning by hospital-based pharmacists.

Allergan and The Medicines Company, developers of two of the new antibiotics, have sought to exit the antimicrobial field since introducing their drugs because of insufficient returns on investment. Achaogen declared bankruptcy months after attaining FDA approval for a third new antibiotic.

The researchers suggest several reasons for the slow uptake of the new antibiotics, starting with cost. A 14-day course of the new antibiotics costs between $13,230 and $15,070, compared to $305 to $784 for the old drugs.

"Cost is a limitation, but I'm not convinced it is the sole cause of our findings," said Clancy. "Clinicians may not be prescribing the new drugs due to concerns about accelerating antibiotic-resistance or because initial studies on their effectiveness were relatively small. We need to get at the root causes of the disconnect between what the doctors prescribe and what the pharmacists we surveyed believe they should be prescribing, and then find a solution."

Additional authors on this study are M. Hong Nguyen, M.D., and Brian A. Potoski, Pharm.D., of Pitt; and Deanna Buehrle, Pharm.D., of the VA Pittsburgh Healthcare System. There was no funding for this study. Clancy and Nguyen report unrelated research funded by various pharmaceutical and medical device companies, detailed in the study manuscript.

http://bit.ly/323noBa

Filter-feeding pterosaurs were the flamingos of the Late Jurassic

Modern flamingoes employ filter feeding and their feces is, as a result, rich in remains of microscopically small aquatic prey.

Very similar contents are described from more than 150-million-year-old pterosaur droppings, according to a recent paper in *PeerJ*. This represents the first direct evidence of filter-feeding in Late Jurassic pterosaurs and demonstrates that their diet and feeding environments were similar to those of modern flamingoes.

Pterosaurs were a diverse group of flying reptiles that roamed the skies during the age of dinosaurs. Skeletal fossils suggest that they, just like modern birds, adapted to diverse lifestyles and feeding habits. Direct evidence on diets such as gut contents, however, are rare, and only known from a few pterosaur species.

Coprolites, fossilized droppings, are surprisingly common, and could hold valuable information on the diet of extinct animals. Unfortunately, it is often difficult to know which animal produced which dropping.

In a recent paper, researchers from Uppsala University and the Polish Academy of Sciences describe the contents of three coprolites collected from a surface with abundant pterosaur footprints in the Wierzbica Quarry in Poland. The coprolites' size, shape and association to the tracks suggest that they were produced by pterosaurs, most probably belonging to a group called Ctenochasmatidae.

The fossil droppings were scanned using synchrotron microtomography, which works in a similar way to a CT scanner in a hospital, but with much stronger X-ray beams. This makes it possible to image the contents of fossils in three dimensions. The scans of the pterosaur coprolites revealed many microscopic food remains, including foraminifera (small amoeboid protists with external shells), small shells of marine invertebrates and possible remains of polychaete worms.

"A reasonable explanation for how a pterosaur big enough to have produced the droppings ingested such small prey is through filter feeding," says Martin Qvarnström, Ph.D. student at Uppsala University and one of the authors of the article.

Some ctenochasmid pterosaurs are thought to have been filter feeders. Pterodaustro, which comes from the Cretaceous and is thus slightly younger than the Polish coprolites, possessed a sieving basket consisting of many long, thin teeth and was certainly a filter feeder. Older ctenochasmids did not possess such an obvious sieving basket, but some had elongated snouts with many slender teeth, also interpreted as adaptations for filter feeding. These pterosaurs were around at the time the droppings were made, and as the footprints from the site have also been attributed to ctenochasmids, it is likely that such pterosaurs produced both the droppings and the footprints.

The modern Chilean flamingo, which is a filter feeder, can produce droppings full of foraminifera when feeding in coastal wetlands.

"The similar contents of the droppings of these flamingos and the pterosaur coprolites could be explained by similar feeding environments and mesh sizes of the filter-feeding apparatus. It appears therefore that the pterosaurs which produced the footprints and droppings found in Poland were indeed the flamingos of the Late Jurassic," says Martin Qvarnström.

More information: *Martin Qvarnström, Erik Elgh, Krzysztof Owocki, Per E. Ahlberg & Grzegorz Niedzwiedzki (2019). Filter feeding in Late Jurassic pterosaurs supported by coprolite contents. PeerJ. In Press.*