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New blood test detects early stage pancreatic cancer

New blood test can detect pancreatic cancer in the very earliest stages of the disease

Pancreatic cancer is currently very difficult to detect while it is still resectable. A new blood test developed by researchers at Lund University in Sweden, Herlev Hospital, Knight Cancer Center and Immunovia AB, can detect pancreatic cancer in the very earliest stages of the disease. The results have been published in the Journal of Clinical Oncology.

Due to diffuse symptoms, pancreatic cancer is usually diagnosed very late in the disease progression. Therefore, despite pancreatic cancer representing less than 3% of all cancer cases, more people currently die from it than breast cancer. By 2030, pancreatic cancer is expected to be the second deadliest type of cancer in the world.

"Our test can detect pancreatic cancer with 96% accuracy at stage I and II, while there is still the possibility of successful surgical intervention. There is currently no cure and few treatment options for advanced pancreatic cancer, which is the late stage when pancreatic cancer is usually diagnosed", explains Carl Borrebaeck, professor at the department of Immunotechnology at Lund University.

The study used samples from patients in both Denmark and the US, at different stages of the disease.

The blood test is developed on a so-called antibody microarray that consists of hundreds of recombinant antibody fragments. These antibody fragments are specific for a number of immune-regulatory proteins, cancer-associated antigens, and so on.

Since the immune system is the first to respond to threats like complex diseases, such as cancer, autoimmune diseases and infections, the microarray was designed to mirror this early response. This provides information about the development of tumours long before being visible on CT or detected by ctDNA. From those hundreds of markers, 29 markers were selected to detect pancreatic cancer with 96% accuracy at stage I and II.

In the future, the screening method could be used to screen people who are at a higher risk of developing pancreatic cancer, such as those with a hereditary risk, newly onset diabetes patients and patients with chronic inflammation of the pancreas.

The next step has already been initiated, which is a large US prospective study for high risk individuals.

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Counting (on) sheep? Promising gene therapy for visually impaired sheep now safe for human trials

Gene therapy successfully treated hereditary achromatopsia

Back in 2009, a group of Israeli researchers identified a herd of Awassi sheep suffering from "day blindness". As its name implies, these sheep were blind during the day (in bright light) but could see at night, in low-light conditions.

As published in Human Gene Therapy, a team led by Hebrew University of Jerusalem Koret School of Veterinary Medicine Professor Ron Ofri, Professor Eyal Banin of Hadassah Medical Center and Professor Elisha Gootwine of the Volcani Agricultural Research Organization, found that these sheep suffered from a genetic mutation that causes "hereditary achromatopsia," the scientific term for day blindness. Achromatopsia is prevalent in human beings, as well. However, due to its hereditary nature, the rate of this disorder fluctuates from population to population, being more prevalent in places with a high rate of marriages between relatives. In Jerusalem, for example, day blindness affects 1 in every 5,000 people.

Prof. Ofri and his colleagues began gene therapy trials for the "day blind" sheep, with the help of Professor W.W. Hauswirth of the University of Florida. Affected sheep were injected with a virus that carried a normal copy of the missing gene. It was a success; the

treated sheep were regained their day vision, while those not treated remained visually impaired. (See video at: http://cowry.agri.huji.ac.il/Gootwine2016.mp4).

Based on these promising findings, the FDA has approved clinical trials for human patients and several U.S. medical centers have already begun using this therapy to treat patients with achromatopsia. Recently, Israel's Ministry of Health approved human clinical trials in Israel. They will begin later this year at Hadassah Medical Center. "Less than ten years after we first discovered the vision-impaired herd, we began human clinical trials. This marks a wonderful feat in ovine-to-human and research-to-cure efforts", shared Professor Ofri. Most promisingly, the oldest surviving sheep from the original study still have daytime vision thanks to a single dose of gene therapy administered to them six years ago.

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Woman's Liver Problems Tied to Her Turmeric Supplement

Turmeric supplement may have triggered an uncommon liver problem

By Rachael Rettner, Senior Writer | September 17, 2018 09:54am ET

Turmeric supplements are popular these days, but for one woman in Arizona, taking a turmeric supplement may have triggered an uncommon liver problem, according to a new report of the case.

What's more, the link between the woman's liver problem and her turmeric supplement use wasn't identified by her doctors — but rather by the woman herself, after she consulted the internet.

Until the woman brought it up, her doctors weren't aware that she was taking a turmeric supplement, and the case underscores the need for doctors and patients to communicate about the supplements that patients are taking, the report's authors said.

The report, by researchers at the University of Arizona, was published Sept. 10 in the journal BMJ Case Reports.

Turmeric as a supplement

Turmeric is perhaps best-known as a spice in curry powder, but some studies suggest that it has anti-inflammatory properties. Early research suggests that turmeric may help with certain conditions, such as osteoarthritis and rheumatoid arthritis, but more research is needed on its benefits, according to the National Institutes of Health (NIH).

In the new case, the 71-year-old woman started taking turmeric supplements after she read a news article about a study in animals that suggested turmeric may help prevent stroke. She was also taking 20 other medicines and supplements. Her health care providers knew about most of these medicines and supplements, but not the turmeric. About eight months after she started the turmeric supplements, a blood test showed elevated levels of liver enzymes — a sign of liver problems, the report said.

Further tests revealed the woman had a condition called autoimmune hepatitis, in which the body's immune system attacks the liver, causing inflammation and liver damage, according to the NIH.

After her diagnosis, the woman was monitored closely without receiving specific treatment. But three months later, she told her doctor she had stopped taking turmeric, after she read on the internet about a possible link to liver problems.

This was the first time the woman had told her doctors about the turmeric supplement. And her suspicion about its tie to her liver problems may have been right — after she stopped taking the turmeric supplement, her doctors noticed a rapid decrease in her levels of liver enzymes, the report said.

It's known that in about 10 to 15 percent of people with autoimmune hepatitis, the condition is triggered by drugs or supplements, the report said. In these cases, the condition is called drug-induced autoimmune hepatitis. It's unclear how drugs or supplements trigger drug-induced autoimmune hepatitis, but it's thought that in some

cases, the breakdown of drugs may lead to the formation of molecules that trigger an immune reaction, according to the NIH.

When the authors of the new report reviewed 35 previous studies of turmeric supplements in people, they found that about 5 percent of participants in those studies experienced liver problems tied to the supplements. It may be that some patients, such as older adults or those who consume alcohol, are more prone to these problems tied to supplements.

Still, the authors said that it's unclear whether turmeric compounds were indeed responsible for the liver problems in the woman's case. A sample of the product was not available to test, but it could be that contaminants in the product, rather than the turmeric itself, triggered the condition, the report said. Or, it may be that the combination of turmeric and other medicines and supplements that the woman was taking led to the condition.

Still, the new case "highlights the importance of discussing DS [dietary supplement] use," particularly among older patients, who may be taking multiple drugs and are also at greater risk of liver problems, the report said.

The NIH recommends that patients tell their health care providers, including their doctors, pharmacists and dietitians, about which dietary supplements they are taking so that they can discuss what's best for the patients' overall health.

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We are predisposed to forgive, new research suggests

When assessing the moral character of others, people cling to good impressions but readily adjust their opinions about those who have behaved badly, according to new research.

This flexibility in judging transgressors might help explain both how humans forgive -- and why they sometimes stay in bad relationships, said the study's authors.

The research -- conducted by psychologists at Yale, University of Oxford, University College London, and the International School for Advanced Studies -- appeared Sept. 17 in the journal *Nature Human Behaviour*.

"The brain forms social impressions in a way that can enable forgiveness," said Yale psychologist Molly Crockett, senior author of the paper. "Because people sometimes behave badly by accident, we need to be able to update bad impressions that turn out to be mistaken. Otherwise, we might end relationships prematurely and miss out on the many benefits of social connection."

Across a series of experiments, more than 1500 subjects observed the choices of two strangers who faced a moral dilemma: whether to inflict painful electric shocks on another person in exchange for money. While the "good" stranger mostly refused to shock another person for money, the "bad" stranger tended to maximize their profits despite the painful consequences. The subjects were asked their impressions of the strangers' moral character and how confident they were about those impressions.

Subjects rapidly formed stable, positive impressions of the good stranger and were highly confident of their impressions. However, the subjects were far less confident that the bad stranger was truly bad and could change their minds quickly. For instance, when the bad stranger occasionally made a generous choice, subjects' impressions immediately improved -- until they witnessed the stranger's next transgression."

This pattern of impression updating may provide some insight into why people sometimes hold on to bad relationships, Crockett said. "We think our findings reveal a basic predisposition towards giving others, even strangers, the benefit of the doubt. The human mind is built for maintaining social relationships, even when partners sometimes behave badly."

The research also may eventually help shed light on psychiatric disorders involving social difficulties, such as Borderline Personality Disorder.

"The ability to accurately form impressions of others' character is crucial for the development and maintenance of healthy relationships" said Jenifer Siegel, an Oxford doctoral student and lead author of the paper. "We have developed new tools for measuring impression formation, which could help improve our understanding of relational dysfunction."

The research was funded by the Wellcome Trust and the Academy of Medical Sciences.

http://bit.ly/2OyprXz

Large-scale shift causing lower-oxygen water to invade Canada's Gulf of St. Lawrence

The Gulf of St. Lawrence has warmed and lost oxygen faster than almost anywhere else in the global oceans.

The broad, biologically rich waterway in Eastern Canada drains North America's Great Lakes and is popular with fishing boats, whales and tourists.

A new study led by the University of Washington looks at the causes of this rapid deoxygenation and links it to two of the ocean's most powerful currents: the Gulf Stream and the Labrador Current. The study, published Sept. 17 in Nature Climate Change, explains how large-scale climate change already is causing oxygen levels to drop in the deeper parts of this waterway.

"The area south of Newfoundland is one of the best-sampled regions in the ocean," said first author Mariona Claret, a research associate at the UW's Joint Institute for the Study of the Atmosphere and Ocean. "It's also a very interesting area because it's at the crossroads where two big, larger-scale currents interact."

Canada's fisheries agency has tracked rising salinity and temperature in the St. Lawrence region since 1920. Oxygen has only been monitored since 1960, and the declining trend is causing concern.

"Observations in the very inner Gulf of St. Lawrence show a dramatic oxygen decline, which is reaching hypoxic conditions, meaning it can't fully support marine life," Claret said.

Oxygen declines have been seen to affect Atlantic wolffish, Claret said, and threaten Atlantic cod, snow crabs and Greenland halibut that all live in the depths.

"The oxygen decline in this region was already reported, but what was not explored before was the underlying cause," said Claret, who did the work while at Canada's McGill University.

The research confirms a recent study showing that, as carbon dioxide levels rose over the past century due to human emissions, the Gulf Stream has shifted northward and the Labrador Current has weakened. The new paper finds that this causes more of the Gulf Stream's warm, salty and oxygen-poor water to enter the St. Lawrence Seaway.

The new study uses output from NOAA's Geophysical Fluid Dynamics Laboratory model, a high-resolution computer model that simulates the world's oceans with a data point every 8 kilometers (5 miles). This simulation took nine months to run using 10,000 computational nodes -- huge, even by the standards of global climate models.

With this precision, eddies and details of the coastline that can influence ocean circulation begin to appear. Model output combined with the historical observations show that as the carbon dioxide levels go up, Gulf Stream water replaces Labrador Sea water in the deeper parts of the St. Lawrence gulf.

The waters carried by the Labrador Current have been churned up by storms in the Labrador Sea, and so air absorbed at the surface is mixed far below the surface. The Gulf Stream, however, is more stratified in stable horizontal layers; the top layer contains oxygen from the air above, but lower layers' oxygen has been consumed by marine life. What's more, the warmer Gulf Stream is equally dense

at a greater depth, so deeper, more oxygen-deprived layers from the Gulf Stream follow the same density pathway taken by oxygen-rich near-surface water from the Labrador Current.

"We relate a change in oxygen on the coast to a change in large-scale currents in the open ocean," Claret said.

In the model, the shift in the large-scale ocean circulation causing warming and deoxygenation in the Gulf of Saint Lawrence also corresponds with a decline in the Atlantic Meridional Overturning Circulation, an ocean circulation pattern known to strongly influence Northern Hemisphere climate.

"Being able to potentially link the coastal changes with the Atlantic Meridional Overturning Current is pretty exciting," Claret added.

Analysis shows that half the drop in oxygen observed deep in the St. Lawrence River is just due to the warmer water, which can't hold as much oxygen. The other half is likely due to other factors, such as biological activity in the two currents and inside the channel. What will happen next is unknown, Claret said. The oxygen levels in the St. Lawrence will depend on much larger questions, she said, like how much carbon dioxide humans will emit into the atmosphere in the coming decades, and how large-scale ocean currents will respond.

The research was funded by the European Research Council, the Spanish Ministry of Economy and Competitiveness, the Canada Foundation for Innovation and NOAA. Co-authors are Eric Galbraith at the Autonomous University of Barcelona; Jaime Palter at the University of Rhode Island; Daniele Bianchi at the University of California, Los Angeles; Katja Fennel at Dalhousie University in Nova Scotia; Denis Gilbert at Fisheries and Oceans Canada; and John Dunne at NOAA's Geophysical Fluid Dynamics Laboratory.

http://bit.ly/2PIz0Dw

Ceres' lonely ice volcano is only one of many

New research is delving into the little know cryovolcanism of the outer solar system.

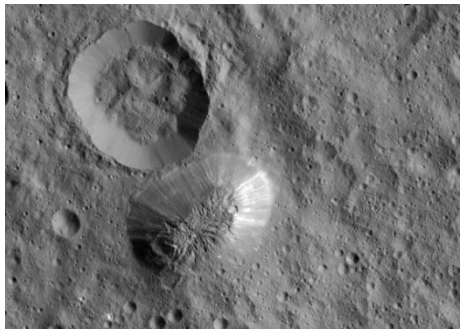
The dwarf planet Ceres has had as many as 22 ice volcanoes, new research suggests.

Images from NASA's Dawn mission has revealed there is currently a single volcano, an icy peak known as Ahuna Mons.

But research based on data from the mission suggests that new volcanoes have appeared around every 50 million years over the past billion. They erupt, build up and then sink back into the surface.

The research, published in *Nature Astronomy*, suggests that Ahuna Mons is relatively young.

"Ahuna Mons has an upper age limit of 240 million years derived from crater size," the researchers, led by University of Arizona planetary scientists Michael Sori, write. "But it may be much younger because the mountain itself is too small and has too few craters to be reliably dated."



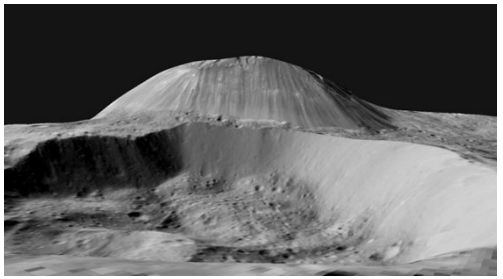
The mysterious mountain Ahuna Mons is seen in this mosaic of images from NASA's Dawn spacecraft. Dawn took these images from its low-altitude mapping orbit, from an altitude of 385 kilometres in December 2015.

NASA/JPL-Caltech/UCLA/MPS/DLR/IDA

Ice volcanoes, or cryovolcanoes, leave less impact on the surface than volcanoes on planets such as Earth. Instead of molten rock, they erupt liquid or gaseous ammonia, water or methane.

Traces of cryovolcanism have been found on several bodies in the outer Solar System.

"Cryovolcanism may be an important planetary phenomenon in shaping the surfaces of many worlds in the outer Solar System and revealing their thermal histories," the researchers say.



A simulated perspective view of Ceres' lonely mountain, Ahuna Mons.

NASA/JPL-Caltech/UCLA/MPS/DLR/IDA

"However, the physics, chemistry and ubiquity of this geologic process remain poorly understood, especially in comparison to the better-studied silicate volcanism on the terrestrial planets."

NASA's Dawn spacecraft discovered Ahuna Mons while orbiting Ceres in 2015.

Sori and colleagues used models of relaxing dome shapes to identify 22 former cryovolcanoes on Ceres in images taken by the Dawn mission. The authors also estimate that the total amount of icy material that has been erupted onto the surface of Ceres is one hundred to one hundred-thousand times less than the volumes of molten rock erupted on the Earth, Moon, Venus or Mars.

Ceres was the first object discovered in the main asteroid belt when Italian astronomer Father Giuseppe Piazzi spotted the object in 1801. It was initially classified as a planet but later classified as an asteroid as more objects were found in the same region.

In recognition of its planet-like qualities, Ceres was designated a dwarf planet in 2006 along with Pluto and Eris.

http://bit.ly/2DbZoEf

Why pandemic influenza is so deadly – revealed

How can a virus be so deadly?

Aartjan te Velthuis Wellcome Trust Fellow, University of Cambridge*

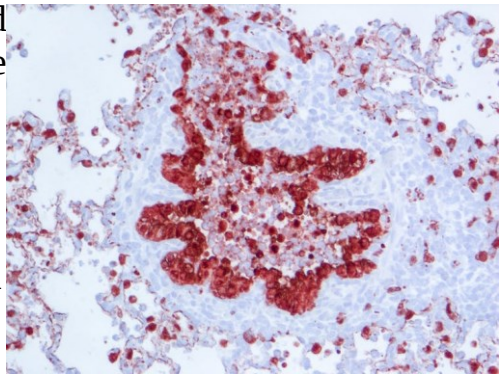
The Spanish flu virus infected a third of the world's population 100 years ago and claimed the lives of up to 100m people. The virus continued to evolve and its descendants went on to cause all subsequent flu pandemics, leading to the 1918 pandemic flu to be called the "mother of all flu pandemics". The US army predicts that if a similar flu virus emerged today, it would kill 2.8m people in the US alone or six times more than the 1918 flu. How can a virus be so deadly?

Flu viruses are tiny particles that can enter the cells of a bird or mammal, such as a human. Viruses do this because they have no resources of their own and need to steal components and energy from our cells to copy themselves. They also constantly mutate and mix their genetic information to adapt to our cells.

To protect us from infection and disease, our immune system can detect flu and fight back in several ways. For instance, specialised proteins look for genetic material of the virus inside our cells and trigger signals to warn neighbouring cells that a virus is present.

If necessary, the immune system will even force infected cells to self-destruct to prevent the virus from spreading. Antibodies can also neutralise viral proteins in our airways or "flag" viruses for destruction by specialised immune cells. This is why we use vaccines: to show our immune system the viral proteins of potential future infections so that our bodies are prepared for them.

Our immune system also plays an important role in the severity of infections with pandemic flu and bird flu. Most of the seasonal flu viruses that we encounter have become well adapted to us as hosts over time and copy themselves relatively undetected by our immune system. But flu viruses can also "jump" between animals, such as from birds to humans. This means that we can suddenly be faced with a type of flu, such as an H5N1 bird flu, that we have never seen before and that is not adapted to our cells. Our immune system detects these viruses and launches a violent counterattack, or "cytokine storm", which is so strong that our lungs fill up with white blood cells, fluid and blood, and we effectively drown.



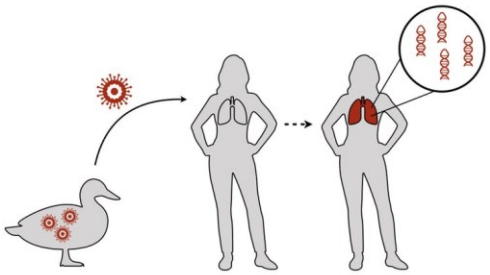
Bronchiole of a lung infected with the 1918 flu virus. Infected cells are stained red. Note the lack of airspace inside the bronchiole due to white blood cell infiltration. **Jurre Siegers and Debby van Riel, Erasmus Medical Centre.**

Spotting viral garbage

We roughly know which viral and cellular proteins contribute to the destructive response. But why it is initiated by pandemic and avian flu viruses is far from clear. In our recent study, we looked at what the immune system "senses" when the genetic information of flu viruses is copied. We found that it focuses strongly on tiny "faulty" molecules of genetic viral information. So our immune system sees viral "garbage", while the normal genome of the virus remains undetected.

The Spanish flu virus and the H5N1 bird flu make more faulty genomes in human lung cells than a virus that is adapted to these cells. Also, when you take the enzyme that copies the genome of a harmless flu virus and change it to make it similar to the enzyme of the Spanish flu virus, this engineered enzyme immediately starts making more faulty molecules and overstimulating the immune response. The original enzyme does not.

Dangerous flu viruses make a molecule that causes disease when these viruses get inside our cells. We think this is because they have not had enough time to adapt and are copying themselves incorrectly. This idea is supported by other recent observations and may be important for diseases caused by other emerging viruses, such as Ebola.



Flu viruses that 'jump' from another animal, such as a bird, cause severe disease in the lungs. During these infections, the virus produces molecules called mini viral RNAs that trigger strong immune responses.

A century after the Spanish flu pandemic, we are finally in a position to better understand what makes pandemic and bird flu viruses deadly. This will help us look for ways to neutralise the harmful molecule and be ready if a new pandemic strikes.

**Aartjan te Velthuis receives funding from the Royal Society, Wellcome Trust, Marmaduke Sheild Fund, and Isaac Newton Trust.*

http://bit.ly/2OzKKba

Single mutation protects TB bacteria from antibiotics, immune assault

People who fall sick with drug-resistant tuberculosis (TB) face daunting odds.

Only about two in three survive the illness, unlike people with drug-sensitive TB, of whom more than 90 percent survive.

Part of the reason drug-resistant TB is so lethal is because some antibiotics of first choice don't kill the TB bacteria, forcing doctors to treat the infection with second-line medications that are often more toxic and less effective.

But the TB bacteria also may be undermining the body's ability to defend itself. Researchers at Washington University School of Medicine in St. Louis have found that the same mutation that makes TB bacteria withstand a first-line drug also elicits a different—and probably weaker—immune response in mice.

"As the bacteria become drug resistant, they change physiologically and trick the immune system to behave differently," said Shabaana A. Khader, Ph.D., an associate professor of molecular microbiology and the study's senior author. "If we're going to fight TB bacteria effectively, we're going to have to understand what the drug-resistant bacteria are doing to the immune system to elicit protection."

The findings are published Sept. 17 in *Nature Microbiology*.

There have been hints for years that drug-resistant bacteria might interact with the body differently than drug-sensitive strains. Anecdotal reports suggest that resistant TB bacteria cause more damage to the lungs and spread more widely through the body.

Khader, working with graduate student and first author Nicole Howard and colleagues, analyzed the immune response in mice infected with Mycobacterium tuberculosis, the bacteria that cause TB. They compared a strain that is resistant to all first- and many second-line antibiotics with a drug-sensitive strain of TB.

The mice's immune systems battled the sensitive bacteria by releasing a powerful immune molecule known as IL-1 beta and ramping up the ability of their immune cells to burn sugar. Both actions are crucial for an effective immune assault on the TB bacteria. But when infected with the drug-resistant strain, the mice failed to pull out the big guns. Their immune cells did not burn more sugar, and they failed to produce much IL-1 beta. Instead, they released a different immune molecule, IFN beta, which is associated with a feeble and sometimes detrimental immune response to TB.

"People always thought that development of drug resistance just meant that there's a change in how bacteria respond to antibiotics," Khader said. "But this shows that the whole immune environment is changing in ways that we haven't been fully aware of."

To find out why drug-resistant bacteria elicit a different immune response, the researchers scanned the whole genomes of several drug-resistant strains. They found that a change of one letter in the genetic code gave bacteria the ability to withstand rifampicin, an important first-line antibiotic, and also altered the immune response.

Treating TB is a long, drawn-out process. The bacteria grow slowly and are wrapped in a protective shell, so it takes a combination of four antibiotics given repeatedly over six months to eradicate them. Boosting the immune response would be like sending in fresh troops to a protracted battle—it could put an end to the fight, quickly and decisively. Clinical trials are already underway to find out whether immune-enhancing drugs combined with antibiotics improves outcomes for people with TB. But because of the inherent dangers of working with drug-resistant bacteria, nearly all research into strengthening the immune response has been conducted using drug-sensitive strains.

"If you're going to do host-directed therapeutics, we need to know what immune pathways to target," Khader said. "And these pathways may turn out to be different for drug-sensitive and drug-resistant TB."

Howard and Khader's findings suggest that the people most in need of better therapeutics—those infected with drug-resistant strains—may not benefit from immune enhancers that are designed based on drug-sensitive bacteria.

"We don't know enough about the differences between resistant and sensitive TB to be confident that the therapeutics and vaccines we're designing are going to work," Khader said. "We're going to have to do those studies."

More information: *Nicole C. Howard et al, Mycobacterium tuberculosis carrying a rifampicin drug resistance mutation reprograms macrophage metabolism through cell wall lipid changes, Nature Microbiology (2018).* *DOI: 10.1038/s41564-018-0245-0*

http://bit.ly/2DleO9A

Zika vaccine shows promise for treating deadly brain cancer

Live, attenuated version of the Zika virus could form the basis of a new treatment

Washington, DC - An international team of researchers has successfully deployed a Zika virus vaccine to target and kill human glioblastoma brain cancer stem cells, which had been transplanted into mice. In a study published this week in mBio®, an open-access journal of the American Society for Microbiology, the team shows that a live, attenuated version of the Zika virus could form the basis of a new treatment option for this fatal brain cancer.

Glioblastoma kills about 15,000 adults in the US each year and is currently incurable because patients experience a high recurrence rate of their cancer even after the standard treatments of surgery, radiation and chemotherapy. Scientists suspect this recurrence is due to cancer stem cells, called glioblastoma stem cells (GSCs), which hide out in nearby brain tissue even after the combination of therapies.

"During the Zika epidemic, we learned that the virus preferentially infects neural progenitor cells in the fetus, and causes the devastating microcephaly seen in babies born to infected mothers," says Pei-Yong Shi, a virologist at University of Texas Medical Branch in Galveston. He co-led the current study with tumor biologist Jianghong Man of the National Center of Biomedical Analysis in Beijing and virologist Cheng-Feng Qin of the Chinese Academy of Military Medical Sciences in Beijing.

"We made the connection that perhaps Zika virus could also specifically infect the GSCs," because these cells have similar properties to neural stem cells, says Man. In previous work, Shi and his collaborators at Washington University in St. Louis showed that Zika virus did indeed attack and kill GSCs grown in the lab dish and in a mouse model of glioblastoma. In addition, the Zika virus was much less efficient at attacking the differentiated, healthy brain cells. (image: transmission electron micrograph of Zika virus, NIAID)

"If we could find a way to specifically target those GSCs that are the source of recurrence, then that might provide an option to prevent recurrence or even a cure," says Qin.

The team's first objective was to determine if there was a safe way to use Zika virus in patients to attack the cancer cells. Shi's lab has developed a promising live-attenuated Zika vaccine candidate called ZIKV-LAV that had been shown to be safe, non-virulent, and effective in protecting against infection in mice and non-human primates. The ZIKV-LAV has a small deletion from the viral genome that prevents it from replicating itself efficiently.

When the team injected this ZIKV-LAV into the brains of mice, they saw no health effects on the mice, no weight loss, and no behavioral abnormalities such as loss of appetite, depression, lethargy, or self-injury. The mice also functioned normally in tests for anxiety and motor function.

Next, the team wanted to show whether the ZIKA-LAV could work to infect and kill human patient-derived GSCs in a mouse model. So they mixed GSCs from two different human patient donors with the ZIKA-LAV and injected the mixture into the brains of mice. Mice that got the injection of the GSCs only rapidly developed tumors. Mice that got the ZIKV-LAV injected as well saw a significant delay in tumor development. Co-implanting the virus along with the GSCs also prolonged the median survival time of the treated mice to around 50 days, compared to around 30 days for the untreated mice who received GSCs alone.

Qin says that perhaps in the future patients would be given the Zika vaccine at the same time as surgery to "let the viruses hunt down the GSCs and eliminate them."

Finally, the team investigated the cellular mechanisms that the modified Zika virus used to kill the GSCs. They took GSCs treated with the ZIKV-LAV and those GSCs not treated and sequenced all the RNA messages being expressed in these two cell populations. Comparing those profiles, the team found that in the treated cells, the virus triggered a strong antiviral response in the cells, which induced inflammation and eventually cell death.

Next, the team will work with clinicians to develop safety tests of the ZIKV-LAV in glioblastoma patients. They may also modify the Zika virus further to make it an even more potent cancer cell killing machine. For example, Man explains, the researchers could add an immune modulator as a 'cargo' in the viral genome. Then, once such a virus infects a cancer cell and kills it, the immune modulator would be released to alert and activate the patient's systemic immune system against the remaining cancer cells.

"As a virologist, I see that we should take advantage of the 'bad' side of viruses," says Shi. "They should have a role to play in cancer treatment."

http://bit.ly/2pjnQtw

Study shows synchronous human energy consumption over the past 10,000 years

University of Wyoming researchers contributed to a study that begins to fill in the knowledge gap of whether human societies grow and decline at the same rate and at the same time.

Erick Robinson, a postdoctoral researcher in UW's Department of Anthropology, and Robert Kelly, a UW professor of anthropology, were part of a study in which a group of anthropologists and sustainability scientists analyzed radiocarbon data going back over 10,000 years—throughout the entire Holocene period—and over four continents.

"We analyzed historical and radiocarbon records to identify synchrony in energy consumption," Robinson says. "Historical records provided information on energy consumption in eight countries since 1880, while radiocarbon records provided estimates of energy consumption in societies from four continents over the past 10,000 years. Energy consumption oscillated at a similar rhythm across both the radiocarbon and historical records."

Radiocarbon dating is the most common method of dating archaeological sites of the past 10,000 years. Synchrony is defined as when changes in the attributes of populations coincide over space and time. When populations synchronize, adverse changes in ecoystems and social systems may cascade from society to society.

Robinson and Kelly are co-authors of a paper, titled "The Synchronization of Energy Consumption by Human Societies throughout the Holocene," that was published Sept. 17 (Monday) in the *Proceedings of the National Academy of Sciences* (PNAS). The journal is one of the world's most prestigious multidisciplinary scientific serials, with coverage spanning the biological, physical and social sciences.

Jacob Freeman, a human ecologist and an assistant professor of anthropology at Utah State University, was the paper's lead author. Other contributors to the paper were from the University of Central Florida and Arizona State University; the Center for Climate and Resilience Research and the Center of Applied Ecology and Sustainability, both in Santiago, Chile; and the Far Western Anthropological Research Group Inc.

"This is the first quantitative comparison of archaeological radiocarbon time-series at a global scale. Until this study, archaeology has approached cultural differences, over time, to be the result of different social and environmental contexts in different regions of the world," says Robinson, of Miami, Okla. "This study shows that, when we zoom out to long millennial time-scales and then compare records at large global scales, the growth of populations on Earth was actually synchronized due to processes similar to what we now call 'globalization.'"

The degree of this rhythmic synchrony decreased with distance, with records from the same continent exhibiting greater synchrony than those from different continents, according to the paper. The decline in synchrony with distance suggests that synchrony in both ancient and modern societies is driven by interactions such as trade, migration and conflict. The results further suggest that the process of globalization may not be a new phenomenon but is, instead, a natural consequence of human societies evolving toward increased carrying capacity, according to the authors.

Robinson says he collected, with Kelly and the help of numerous colleagues and UW students, much of the radiocarbon data in the U.S. for this paper through a six-year, National Science Foundation (NSF)-funded grant for a project called "Populating a Radiocarbon Database for North America." He adds that the two previously published a paper in PNAS that laid the foundation for this current paper.

"For this paper, we used individual radiocarbon dates derived from samples such as charcoal, bone, shell, etc.," Robinson says. "These

are scraps from tens of thousands of individual energy consumption events of humans over the past 10,000 years. We basically took the scraps from the past to build a better picture of it."

The paper's results demonstrate the potential for archaeological radiocarbon records to serve as a basis for millennial-scale comparisons of human energy dynamics and provide a baseline for further cross-cultural research on the long-term growth and decline trajectories of human societies.

"The research helps societies today because, in order to develop policies that favor the sustained use of resources, we must understand the processes that cause the synchrony of human populations," Robinson says. "The financial crisis of 2007-08 is a good recent example. The more tightly connected and interdependent we become, the more vulnerable we are to a major social or ecological crisis in another country spreading to our country. The more we are 'synced,' the more we put all our eggs in one basket, and the less adaptive to unforeseen changes we become."

Robinson has worked on the NSF radiocarbon project since its inception in 2014. He is co-leader, with Freeman, of the Past Global Changes (PAGES) working group, from which this research emerged. The working group is called Paleoclimate and the Peopling of the Earth (PEOPLE 3000).

"As an anthropological archaeologist trained to search for the uniqueness of each region and culture, this is very exciting because it shows that, when we take a broader perspective, we are still interdependent on others, no matter our cultural differences," Robinson says. "This paper shows that, in order to answer some of the central questions about the development of humanity, and to take on some of the central challenges facing contemporary societies, we must move back and forth between different spatial and temporal scales in order to understand the whole picture."

More information: *Jacob Freeman et al. Synchronization of energy consumption by human societies throughout the Holocene, Proceedings of the National Academy of Sciences (2018). DOI: 10.1073/pnas.1802859115*

http://bit.ly/2NsHzpd

Is apple cider vinegar good for you? A doctor weighs in

Historically, vinegar has been used for many ailments.

Gabriel Neal*

When my brother and I were kids back in the ‘80s, we loved going to Long John Silver’s.

But it wasn’t just for the fish.

It was for the vinegar – malt vinegar. We would uncap a bottle at the table and swig that tangy, delicious nectar of the gods straight.

Are most of you repulsed? Probably. Were we way ahead of our time? Apparently.

Some social media and online searches would have us believe that drinking vinegar is a cure-all. Our friends and colleagues will regale us with stories of the healing power of apple cider vinegar for whatever problem we may have just mentioned. “Oh, that backache from mowing? Vinegar.” “That last 10 pounds? Vinegar will melt that right off.” “Syphilis, again? You know it – vinegar.”

As a practicing physician and professor of medicine, people ask me about the benefits of drinking apple cider vinegar all the time. I enjoy those moments, because we can talk about the (extensive) history of vinegar, and then distill the conversations to how it could, maybe, benefit them.

A cure for colds, the plague and obesity?

Historically, vinegar has been used for many ailments. A few examples are that of the famous Greek physician Hippocrates, who recommended vinegar for the treatment of cough and colds, and that of the Italian physician Tommaso Del Garbo, who, during an outbreak of plague in 1348, washed his hands, face and mouth with vinegar in the hopes of preventing infection.

Vinegar and water has been a refreshing drink from the time of Roman soldiers to modern athletes who drink it to slake their thirst. Ancient and modern cultures the world over have found good uses for "sour wine."

While there is plenty of historical and anecdotal testimony to the virtues of vinegar, what does medical research have to say on the subject of vinegar and health?

The most reliable evidence for the health benefits of vinegar come from a few humans studies involving apple cider vinegar. One study demonstrated that apple cider vinegar can improve after-meal blood glucose levels in insulin-resistant subjects. In 11 people who were "pre-diabetic," drinking 20 milliliters, a little more than one tablespoon, of apple cider vinegar lowered their blood sugar levels 30-60 minutes after eating more than a placebo did. That's good – but it was only demonstrated in 11 pre-diabetic people.

Another study on obese adults demonstrated a significant reduction in weight, fat mass and triglycerides. Researchers selected 155 obese Japanese adults to ingest either 15 ml, about one tablespoon, or 30 ml, a little more than two tablespoons, of vinegar daily, or a placebo drink, and followed their weight, fat mass and triglycerides. In both the 15 ml and 30 ml group, researchers saw a reduction in all three markers. While these studies need confirmation by larger studies, they are encouraging.

Studies in animals, mostly rats, show that vinegar can potentially reduce blood pressure and abdominal fat cells. These help build the case for followup studies in humans, but any benefit claims based only on animal studies is premature.

In all, the health benefits we suspect vinegar has need to be confirmed by larger human studies, and this will certainly happen as researchers build on what has been studied in humans and animals to date.

Is there any harm in it?

Is there any evidence that vinegar is bad for you? Not really. Unless you are drinking excessive amounts of it (duh), or drinking a high acetic acid concentration vinegar such as distilled white vinegar used for cleaning (consumable vinegar's acetic acid content is only 4 to 8 percent), or rubbing it in your eyes (ouch!), or heating it in a lead vat as the Romans did to make it sweet. Then, yeah, that's unhealthy. Also, don't heat any kind of food in lead vats. That's always bad.

So have your fish and chips and vinegar. It's not hurting you. It may not be doing you all the good that you're hoping that it will; and it certainly is not a cure-all. But it is something that people all over the world will be enjoying with you. Now raise high that bottle of malt vinegar with me, and let's drink to our health.

*Clinical Assistant Professor of Family Medicine, Texas A&M University

https://wb.md/2xqiKjQ

Low-Carb Diets Linked to Higher All-Cause Mortality

More likely to die from any cause during the subsequent decade than peers who had the highest carbohydrate intake

Marlene Busko

MUNICH — In an observational study that used a one-time snapshot of carbohydrate intake, middle-aged Americans who consumed the least amount of carbohydrates were more likely to die from any cause, heart disease, or cancer during the subsequent decade than their peers who had the highest carbohydrate intake.

In a second part of the study, these findings were replicated in a meta-analysis of seven studies with cohorts from Greece, Japan, Sweden, and the United States that included people followed for almost 2 decades.

"Given the fact that low-carbohydrate diets may be unsafe, it would be preferable not to currently recommend these diets," senior study author Maciej Banach, MD, PhD, Medical University of Lodz, Poland, said during a press conference here at the European Society of Cardiology Congress 2018.

But, he conceded, "probably for a short time" — 6 or 12 months — low-carb diets might be useful for weight loss and good for parameters such as glucose and lipids.

It is impossible to draw conclusions about causation from an observational study, cautioned Michelle L. O'Donoghue, MD, Harvard Medical School, Boston, when asked for comment by *theheart.org | Medscape Cardiology*.

"One strength of the study is that it represents a large, well-characterized US population, and then it was validated in a meta-analysis of seven cohorts," she noted.

However, it also "highlights some of the perils of conducting this type of dietary research," she added. In "the past year, we have seen reports that differ markedly in their conclusions as to whether carbohydrate intake is helpful or hurtful."

Moreover, not all carbs are equal. "One can consume a diet rich in healthy whole-grain carbohydrates," she noted, or a diet full of "highly processed or junk foods." But the current study did not distinguish between types of carb or provide information on whether people in the low-carb group were replacing carbs with unhealthy foods.

Data such as those from the Blue Zone studies suggest that "the healthiest diets appear to have a carbohydrate base with a rich intake of vegetables and limited animal protein consumption," O'Donoghue explained.

"A predominantly plant-based diet," she said, "is what I personally recommend to friends and patients."

Low-Carb Controversy

"There is some controversy surrounding the long-term safety of consuming a low-carb diet, and studies have suggested that low-carb diets may increase the risk of cardiovascular disease and cancer-specific morbidity and mortality," Banach said.

"However," he added, "there are also opposite results suggesting no association in different populations."

To investigate this question, the researchers analyzed data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000 cohort of 24,825 participants who were followed for a mean of 6.5 years. Mean age was 47.6 years, and 48.6% of the participants were men.

The cohort was divided into four quartiles on the basis of carbohydrate intake. The mean percentage of calories from carbohydrates was 66%, 57%, 49%, and 39%, for patients in quartiles 1, 2, 3, and 4, respectively.

To put this in context, the Dietary Guidelines for Americans recommends that carbohydrates make up 45% to 65% of total daily calories (page 97).

Table. Mortality Risk for Highest (Quartile 4) vs Lowest (Quartile 1) Carbohydrate Intake

Cause of Death	Hazard Ratio (95% Confidence Interval)	*P* Value
Any	1.32 (1.14–2.01)	<.001
Cancer	1.35 (1.06–1.69)	<.001
Coronary heart disease	1.51 (1.19–1.91)	<.001
Cerebrovascular disease	1.50 (1.12–2.31)	<.001

The researchers compared outcomes in participants with a lower carb intake (quartiles 2, 3, and 4) with those with the highest carb intake (quartile 1).

In the fully adjusted model, they corrected for between-group differences in age, sex, education, marital status, poverty-to-income

ratio, total energy intake, physical activity, smoking, alcohol consumption, body mass index (BMI), hypertension, serum total cholesterol, and diabetes.

In this model, compared with the participants with the highest intake of carbs (quartile 1), participants with the lowest intake (quartile 4) had a "significant 32% increase in total mortality, 35% increase in cancer mortality, and 51% and 50% increases of coronary artery disease and stroke mortality, respectively," Banach reported.

This increased risk was much more evident in people who were not obese (BMI <30 kg/m²) than those who were obese, and in people 55 years and older than in younger people.

Results were similar, although slightly weaker, in the meta-analysis of almost 500,000 participants who were followed for a mean of 16 years.

During the follow-up period, the risk for all-cause mortality was 15% higher for participants with the lowest intake of carbs (quartile 4) than for those with the highest intake (quartile 1), the risk for cardiovascular disease mortality was 13% higher, and the risk for cancer mortality was 8% higher.

There was a step-wise increase in all-cause and cause-specific mortality as the intake of carbs decreased. Patients in quartiles 1, 2, 3, and 4 consumed 367, 245, 205, and 214 g/day of carbs, respectively.

"We might say we should be careful with the average level of carbohydrates less than 200 g/day...or 39% of energy," Banach told theheart.org | Medscape Cardiology.

Banach has disclosed no relevant financial relationships. O'Donoghue has received research grants from GlaxoSmithKline, Eisai, and AstraZeneca, and honoraria from diaDEXUS

European Society of Cardiology (ESC) Congress 2018: Poster P5409. Presented August 28, 2018. Abstract, Poster

http://bit.ly/2DdarqD

Synthetic Sandalwood Maintains Hair Growth in Human Tissue

The compound engages with a receptor in hair follicle cells and prevents skin cells from dying.

Kerry Grens

A synthetic compound that mimics the smell of sandalwood encourages human scalp tissue in the lab to maintain hair growth, researchers report today (September 18) in *Nature Communications*. The chemical works by triggering an odor receptor in hair follicles, which decreases rates of cell death and boosts the production of a growth factor.

“This is actually a rather amazing finding,” coauthor Ralf Paus of the University of Manchester tells *The Independent*. “This is the first time ever that it has been shown that the remodelling of a normal human mini-organ [a hair] can be regulated by a simple, cosmetically widely-used odorant.”

Paus and his colleagues had zeroed in on the receptor OR2AT4, as previous research by some of the same scientists had found that it was present in human skin and could stimulate the growth of cells known as keratinocytes when exposed to the sandalwood compound during wound healing in vitro.

“Given the intimate connections between hair growth and wound healing,” the researchers explain in their latest report, they decided to apply the chemical to pieces of human scalp, taken from people getting facelifts, for six days in the lab. Compared with untreated tissue, not only did the hair follicles die off more slowly, which prevents hair loss, but they produced more growth factor. Paus’s group determined that OR2AT4 was required for the changes because blocking it inhibited hair growth.

Nicola Clayton of the British Association of Dermatologists who was not involved in the study tells *The Independent*, “It is a fascinating

concept that the human hair follicle, as the authors put it, can 'smell' by utilising an olfactory receptor."

Paus, who consults for a company that has filed a patent on the use of OR2AT4-targeting compounds for hair loss, says there are now clinical trials underway to test the concept in humans.

https://go.nature.com/2xsC1B2

Elimination of senescent cells prevents neurodegeneration in mice

Aggregation of the protein tau is implicated in neurodegenerative diseases in humans. It emerges that eliminating a type of damaged cell that no longer divides can prevent tau-mediated neurodegeneration in mice.

Jay Penney & Li-Huei Tsai

There is strong interest in understanding how neurodegeneration is affected by a cellular state called senescence, in which cells stop dividing, suppress intrinsic cell-death pathways and release pro-inflammatory molecules that can harm healthy neighbours[1,2]. In a paper in *Nature*, Bussian *et al*.[3] examine the role of senescent cells in a mouse model of a type of neurodegeneration that involves aggregation of the protein tau. They find that neuronal expression of mutant tau triggers senescence in glia, the support cells of the brain. Preventing the build-up of senescent glia can block the cognitive decline and neurodegeneration normally experienced by these mice.

Senescent cells are characterized by various molecular and gene-expression changes, including elevated levels of the cell-cycle inhibitor protein $p16^{INK4A}$. Senescence can be identified by a test that stains cells blue if they harbour senescence-associated β-galactosidase (SA-β-Gal) — a form of the β-Gal enzyme that is active at pH 6 (in healthy cells, β-Gal is inactive at this pH)[1,4]. The cells also secrete inflammatory signalling molecules, growth factors and protease enzymes that can impair the function, and ultimately the survival, of non-senescent cells in their vicinity[1,4]. This trait is known as the senescence-associated secretory phenotype (SASP).

The gradual build-up of senescent cells contributes to ageing in multicellular organisms[1,2]. Furthermore, senescence can be induced by various cellular insults. Senescent neurons or glia have been described in people with brain injury or neurodegenerative disorders such as Parkinson's and Alzheimer's diseases[1,2,5,6]. Strategies have been developed that selectively target and eliminate senescent cells, counteracting many of the effects of ageing and age-related disorders in animal models[1,7,8]. But despite intense study, the exact effect of senescent cells in different contexts — including in neurodegeneration — remains unclear.

Bussian *et al*. set out to examine the role of senescence in neurodegeneration. They focused on the aggregation-prone neuronal protein tau, which is associated with multiple forms of neurodegeneration. For instance, a mutation in tau that changes amino-acid residue 301 from proline to serine (dubbed tauP301S) causes frontotemporal dementia[9]. And, when phosphorylated at abnormally high levels, tau forms structures called neurofibrillary tangles (NFTs) that are a hallmark of Alzheimer's disease[9].

The authors made use of mice that have been engineered to express human tauP301S in neurons, and so model human tau-mediated neurodegenerative diseases. They found elevated levels of various senescence-associated genes, including $p16^{INK4A}$, in the brains of tauP301S-expressing mice compared with control animals. Using electron microscopy, the researchers examined which types of brain cell stained for SA-β-Gal in tauP301S mice. They observed no staining in neurons, but SA-β-Gal was detected in the two main types of glia — astrocytes and microglia. The group complemented their electron microscopy with an examination of senescence-associated gene expression in isolated brain-cell types. This, too, provided

evidence of senescence in astrocytes and microglia, but not in neurons.

Importantly, Bussian and colleagues found that senescence-associated gene expression in tauP301S mice increased with age, but preceded NFT deposition and neurodegeneration. This suggests that the emergence of senescent cells could affect the latter two traits. To examine this possibility, the researchers eliminated senescent cells in the animals as they arose, by using a genetic tool that causes expression of a cell-death-promoting enzyme specifically in cells that produce $p16^{INK4A}$. Removal of senescent cells prevented brain shrinkage and thinning of a cognition-related brain region called the dentate gyrus — two characteristics of tau-mediated neurodegeneration typically seen in tauP301S animals. Furthermore, cognitive function was maintained in tauP301S mice lacking senescent cells, whereas tauP301S animals in which senescent cells were retained exhibited short-term memory defects.

Perhaps more surprisingly, given that it indicates complex crosstalk between neurons and senescent glia, genetically eliminating senescent astrocytes and microglia reduced neuronal tau phosphorylation and NFT deposition. Moreover, the authors found similar effects when they treated tauP301S mice with a 'senolytic' compound, which triggers pharmacological removal of senescent cells. Together, Bussian and colleagues' data clearly demonstrate that tauP301S expression in neurons can induce senescence in brain astrocytes and microglia. In turn, these senescent glia affect the ability of neurons to regulate tau phosphorylation and aggregation (Fig. 1). Whether by releasing signalling molecules that directly affect tau or through the effects of SASP factors (or both), glial senescence ultimately promotes neuronal degeneration.

Bussian and co-workers' findings point to several avenues for future study. First, the signals from tauP301S-expressing neurons that induce senescence in glia should be defined. Similarly, the mechanisms by which senescent astrocytes and microglia signal back to neurons remain to be determined. It will also be interesting to understand whether the same glia-derived signals affect both tau pathology and neuronal survival, and whether astrocytes and microglia send the same or distinct signals. The answers to these questions are likely to have broader implications for understanding neurodegenerative diseases more generally.

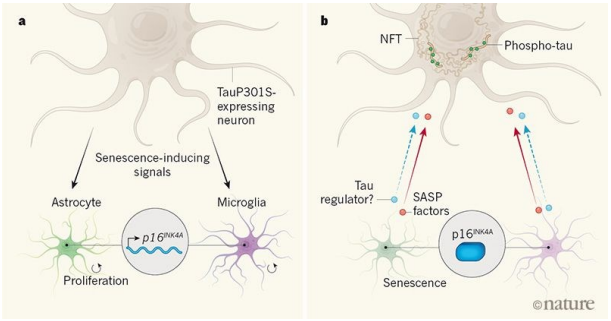


Figure 1 | ***Cell crosstalk in neurodegeneration. Mice that have been genetically engineered so that their neurons produce a mutant form of the protein tau (tauP301S) model some neurodegenerative diseases of humans. a, Bussian et al.[3] provide evidence that tauP301S expression leads neurons in these mice to release unknown signals that induce a cellular state called senescence in neighbouring cells. As a result, genes such as $p16^{INK4A}$ that are associated with senescence are activated in cells called astrocytes and microglia, which can proliferate. b, When senescent, astrocytes and microglia have elevated levels of $p16^{INK4A}$ protein and stop proliferating. They release a group of molecules known as senescence-associated secretory phenotype (SASP) factors that, possibly in combination with other regulators of tau, signal back to neurons. This leads to the phosphorylation of tau and its aggregation into structures called neurofibrillary tangles (NFTs) — two hallmarks of neurodegeneration.***

Finally, the current study adds to the growing body of evidence indicating that senolytic treatments could benefit people who have a wide range of conditions[1,2]. Of immediate interest is whether removal of senescent cells can decrease disease severity in other animal models of neurodegeneration. The authors removed senescent cells throughout the lives of their animals, but it will also be valuable to determine whether senolytics can have beneficial effects if treatment is started once a disease has progressed to symptomatic stages — a

more likely scenario in humans. Finally, it will be crucial to determine whether the processes uncovered in this paper are evolutionarily conserved in humans. If so, perhaps senolytic treatments can benefit people, as promised by this and other mouse studies[1,2]. *doi: 10.1038/d41586-018-06677-7*

http://bit.ly/2PRpcqR

New method enables accurate diagnosis of Alzheimer's disease

New brain imaging method can show the spread of specific tau protein depositions

Diagnosing Alzheimer's disease can be difficult, as several other conditions can cause similar symptoms. Now a new brain imaging method can show the spread of specific tau protein depositions, which are unique to cases with Alzheimer's.

"The method works very well. I believe it will be applied clinically all over the world in only a few years", says Oskar Hansson. Hansson is a professor of clinical memory research at Lund University in Sweden who has led a major international study on the new method.

There are two proteins that are known to be linked to Alzheimer's disease - beta-amyloid, which forms what is known as plaque in the brain, and tau, which forms tangles within the brain cells. Beta-amyloid spreads throughout the brain at an early stage, decades before the patient notices signs of the disease. Tau, on the other hand, starts to spread at a later stage, from the temporal lobes to other parts of the brain.

"It is when tau begins to spread that the neurons start dying and the patient experiences the first problems with the disease. If we scan a patient with memory difficulties and he or she proves to have a lot of tau in the brain, we know with a high degree of certainty that it is a case of Alzheimer's", says senior researcher Rik Ossenkoppele, Lund University and Amsterdam University Medical Center.

He is the first author, and Oskar Hansson the last author, of an article recently published in the reputable medical journal JAMA (Journal of the American Medical Association). The article presents a study of over 700 patients. Besides Lund-Malmö in southern Sweden, researchers from San Francisco and Seoul took part in the study, and the patients were diagnosed in memory clinics from these regions.

The presence of tau in the brain was revealed by a PET scanner, a medical imaging technology which uses radioactive markers that make their way to different areas in the body.

"We administer the special tau marker intravenously to the patient. If the patient has tau in certain parts of the brain, the marker will detect it. The result - whether Alzheimer tau is present or not - is very clearly visible on the PET images," says Oskar Hansson.

The international study showed that the new tau-PET method had both great sensitivity and specificity: it detected 90-95 per cent of all cases of Alzheimer's and gave only few false positive results in patients with other diseases. The tau-PET method had clearly superior diagnostic accuracy compared to MRI, and fewer false positive results than beta-amyloid PET, two methods that are routinely used today. Tau-PET should therefore be of great use in the investigation of patients with memory problems, as soon as the method is approved for clinical use.

"If you are found to have tau in the brain according to tau-PET, it is, with few exceptions, due to Alzheimer's disease. If you have normal tau-PET and mild to moderate dementia, your memory problems are most likely due to other neurological diseases", summarises Oskar Hansson.

Although there is currently no cure for Alzheimer's, it is still important for patients to receive the correct diagnosis. On the one hand, the patient can be given symptom-relieving medication, and on the other, physical activity, a good diet and a correct dosage of the patient's other medication can optimize cognitive ability. The tau-

PET method could also be valuable in trials of new medication against Alzheimer's, as it can show whether new drugs have succeeded in preventing the spread of tau in the brain.

http://bit.ly/2DqZASW

Chinese-led team shows mass extinction happened in geological 'instant'

How long did it take to wipe out the vast majority of life on Earth?

It took less than 30,000 years and maybe only thousands, to kill more than 90% of sea creatures and most land species, according to the most precise study ever published about the mass extinction marking the end of the Permian Period.

Earth's greatest mass extinction, also known as the "Great Dying," occurred about 252 million years ago. By some estimates, over 90% of sea creatures and most land-dwelling reptiles disappeared. Even usually resilient plants and insects suffered near annihilation. But how long did it take to wipe out the vast majority of life on Earth? What could have caused such a massive die-off?

Outcrop photos of the Permian-Triassic boundary interval at Penglaitan. **NIGPAS**

A recent study published in the Geological Society of America Bulletin on September 19 suggests an answer.

Scientists from China, the USA and Canada combined new high-resolution radiometric dating of seven closely spaced layers of volcanic material from South China's Penglaitan section with detailed biostratigraphy and geochemical analyses. Results show the duration of the end-Permian mass extinction to be about 31 thousand years, essentially instantaneous by geological standards.

"The mass extinction may have occurred in only thousands of years, but the analytical uncertainty of current CA-ID-TIMS dating technique prevents us from getting a more meaningful constraint for less than 30,000 years," said Prof. SHEN Shuzhong from the Nanjing Institute of Geology and Palaeontology (NIGPAS) of the Chinese Academy of Sciences, the lead author of this paper.

The study also suggests that the sudden extinction may have been caused by Siberian flood-basalt eruptions, along with local intensive explosive volcanism that may have started some 420 thousand years before the mass extinction. These events may have significantly reduced the stability of Late Permian ecosystems to the point where a single extreme incident finally resulted in a sudden ecosystem collapse.

For decades, scientists have studied the Permian-Triassic boundary at Meishan in Zhejiang Province, South China, which serves as the international reference for the boundary. But this "condensed section" - a lot of time represented by a small thickness of sediments - makes it difficult to discern if the extinctions were abrupt or gradual.

To deal with this problem, SHEN and colleagues from CAS, MIT, the National Museum of Natural History (Washington, D.C.) and the University of Calgary focused their attention on the Penglaitan section in South China's Guangxi Autonomous Region.

The Penglaitan sediments were deposited in shallow, tropical waters where sediments accumulated more than 100 times faster than in the Meishan beds, making the Penglaitan sediment much thicker than Meishan for a comparable period of time. In other words, only a few centimeters of rock at Meishan are equivalent to meters of sediment in Penglaitan. The expanded section at Penglaitan allowed the scientists to study the events at the Permian-Triassic boundary at a much higher temporal resolution.

In addition to the higher sedimentation rates, the Penglaitan section has better geochronologic and stratigraphic controls, and rich

palaeontological data, enabling examination of the fine structure of the extinction and coeval environmental perturbations.

SHEN and his colleagues documented a rich Late Permian biota at Penglaitan, with at least 10 major marine fossil groups, including brachiopods, ammonoids, sponges, corals, conodonts, foraminifera, bryozoans, bivalves, and trilobites. Twenty-nine of the 66 Permian species identified in the section disappeared within or at the top of a single bed of volcanic ash-rich sandstone (Bed 141). Moreover, there is no "survival interval" of Permian taxa extending into the Early Triassic. This highly diverse marine ecosystem suddenly disappeared during the time of deposition of Bed 141.

The radiometric ages of the Siberian Traps volcanism match the radiometric dates recovered from the volcanic ash beds preserved at Penglaitan and Meishan. The overlap in dates suggests that the environmental effects of volcanic gases like carbon dioxide, methane and sulfur dioxide could have been deadly. A lethal greenhouse warming, oceans depleted of dissolved oxygen, acid rain, and atmospheric pollution by heavy metals would have made life difficult.

Previously, scientists working on the problem were not even sure whether there was one pulse or two pulses of extinction at the Permian-Triassic boundary, or whether some Permian species actually survived into the earliest Triassic beds. These problems could not be resolved in condensed sections like Meishan. In contrast, the Permian deposits at Penglaitan contain more than 50 volcanic ash layers and volcanic ash-rich sandstone beds, possibly produced by pyroclastic flows from the nearby volcanic arc eruption centers in South China, thus presenting a clearer picture of the extinction period.

The abrupt change in deposition from the uppermost Permian limestones and ash-rich sandstones to black shale with centimeter-scale limestone interbeds in the lowermost Triassic clearly represents a major shift in the oceanic environment.

The Permian extinction has in the past been linked to a time of rapid climate warming, potentially produced by carbon dioxide and methane emissions from the massive Siberian flood basalt eruptions. High-resolution paleotemperature measurements across the mass extinction interval suggest a substantial warming of up to 10 degrees Celsius immediately after the mass extinction event. "This might explain the shift in sediment type from limestones in the Permian to early Triassic black shales, indicating ocean anoxia," said SHEN.

A warming climate may cause ocean currents to become sluggish while at the same time bringing increased nutrients into the sea from increased weathering and river runoff. The reduction in mixing of oxygen-rich waters from the ocean surface with deeper waters, and the increase in ocean productivity triggered by the increased nutrient supply, could have led to increased organic carbon deposition and resulting ocean anoxia.

http://bit.ly/2pmOstR

Discovery could explain failed clinical trials for Alzheimer's, and provide a solution

Vicious feedback loop in Alzheimer's disease may explain why so many drug trials have failed

Researchers at King's College London have discovered a vicious feedback loop underlying brain degeneration in Alzheimer's disease which may explain why so many drug trials have failed. The study also identifies a clinically approved drug which breaks the vicious cycle and protects against memory-loss in animal models of Alzheimer's.

Overproduction of the protein beta-amyloid is strongly linked to development of Alzheimer's disease but many drugs targeting beta-amyloid have failed in clinical trials. Beta-amyloid attacks and destroys synapses - the connections between nerve cells in the brain - resulting in memory problems, dementia and ultimately death.

In the new study, published in Translational Psychiatry, researchers found that when beta-amyloid destroys a synapse, the nerve cells make more beta-amyloid driving yet more synapses to be destroyed. "We show that a vicious positive feedback loop exists in which beta-amyloid drives its own production," says senior author Dr Richard Killick from the Institute of Psychiatry, Psychology & Neuroscience (IoPPN). "We think that once this feedback loop gets out of control it is too late for drugs which target beta-amyloid to be effective, and this could explain why so many Alzheimer's drug trials have failed."

"Our work uncovers the intimate link between synapse loss and beta-amyloid in the earliest stages of Alzheimer's disease," says lead author Dr Christina Elliott from the IoPPN. "This is a major step forward in our understanding of the disease and highlights the importance of early therapeutic intervention."

The researchers also found that a protein called Dkk1, which potently stimulates production of beta-amyloid, is central to the positive feedback loop. Previous research by Dr Killick and colleagues identified Dkk1 as a central player in Alzheimer's, and while Dkk1 is barely detectable in the brains of young adults its production increases as we age.

Instead of targeting beta-amyloid itself, the researchers believe targeting Dkk1 could be a better way to halt the progress of Alzheimer's disease by disrupting the vicious cycle of beta-amyloid production and synapse loss.

"Importantly, our work has shown that we may already be in a position to block the feedback loop with a drug called fasudil which is already used in Japan and China for stroke." says Dr Killick. "We have convincingly shown that fasudil can protect synapses and memory in animal models of Alzheimer's, and at the same time reduces the amount of beta-amyloid in the brain."

The researchers found that in mice engineered to develop large deposits of beta-amyloid in their brains as they age, just two weeks of treatment with fasudil dramatically reduced the beta-amyloid deposits.

Researchers at King's College London are now seeking funding to run a trial in early stage sufferers of Alzheimer's to determine if fasudil improves brain health and prevents cognitive decline.

Professor Dag Aarsland from the IoPPN said "As well as being a safe drug, fasudil appears to enter the brain in sufficient quantity to potentially be an effective treatment against beta-amyloid. We now need to move this forward to a clinical trial in people with early stage Alzheimer's disease as soon as possible."

The research was funded by the Medical Research Council.

http://bit.ly/2QIZki9

'Plant blindness' is a real thing: why it's a real problem too

Many urbanites unable to notice or recognise plants in their own environment

Angelique Kritzinger*

If you lived in London at the height of William Shakespeare's fame, in the 15th century, you probably knew a fair amount about plants. The famous playwright often alluded to potions and poisons derived from plants, and most of his audience would have recognised them. By comparison, research has shown that most modern Londoners can't name more than a few wild flowers.

This is true of most people in most cities in the world.

There's a name for this inability to notice or recognise plants in one's own environment: "plant blindness". Part of the reason for this is that urban dwellers have been separated from nature; there's a disconnect between us and the environment, and we're blind to the natural world around us.

Two botanists, James Wandersee and Elisabeth Schussler, have proposed that our inability to see and notice plants is because they lack visual attention cues. They don't have a face; they don't move

in the way that animals do; and they aren't threatening. Our eye-brain system and the visual cortex filter out so much "data" from what we see daily that most of the visual information about the plants we see is discarded.

Humans have also placed themselves above animals and plants for centuries.

So why is plant blindness a problem? Many of our biggest challenges of the 21st century are plant based: global warming, food security and the need for new pharmaceuticals that might help in the fight against diseases. Without a basic knowledge of plant structure, function and diversity, there's little hope of addressing these problems.

Another issue is that children who are not taught about plants have an incomplete knowledge of the world around them. They grow into adults who don't care about the environment and the natural resources we rely on every day. The lack of in-depth plant sciences education in schools perpetuates the problem, as students do not know that there are various careers in the plant sciences.

Without well trained scientists, many potential threats such as the effects of global warming and devastating plant diseases could be missed.

How plant blindness happens

Plant blindness begins in childhood, exacerbated by how little attention is paid to botanical content in school. For example, in South Africa only about 11 hours are devoted to plant related content in the foundation phase at school (grade R-3). In the senior phases (grade 7-9) only 11 hours are devoted to content that's specifically focused on plants.

This lack of botanical content is echoed in school curricula worldwide. In the US, school science textbooks devote only between 14 and 20% of their content to plants. This hampers a positive attitude towards plants and the development of a relationship with the environment. It does not inspire pupils to want to know more about plants or to care for their environment.

The problem extends into higher education. The number of students studying botany and plant sciences at universities has declined so much that universities across the US are shutting their herbaria. In the United Kingdom, you can no longer enrol for a Botany degree.

Statistics about the standing of botany or plant sciences education in South Africa and elsewhere in Africa aren't readily available. However, the advancing age of practising botanists together with an inadequate of training of young botanists is a source of concern. This leaves a worrying gap – for example when it comes to things like crop diseases.

Scientists are a first line of defence against these and can play a key role in managing any threat. For example, in 1971 a fungal infection decimated most of the US's corn crops. Plant scientists were able to identify the problem and take steps to mitigate it, avoiding a major disaster.

Plant scientists also contribute to food security on many different levels. Medical or ethnobotanists are involved in the discovery of new drugs.

Possible solutions

So can plant blindness be solved? The general consensus among researchers is "yes" – but it will not be easy.

For starters, countries must prioritise scientific and social education about plants among children. But, since psychological studies have shown that education alone is typically not enough to alter behaviour, it's important for kids also so get hands on with plants. Direct experiences allow people to connect with plants on a cognitive and emotional level. For example, parents can encourage their children to plant some vegetables and then cook dinner from the harvest.

There are also many botanical gardens around the world with sections especially designed to foster interests in plants. If there's

one in your city, go and visit – it's a great way to open your eyes to the existence and value of plants.

Governments have a role to play, too. South Africa's Department of Science and Technology has placed a large emphasis on plants in growing its bio-economy strategy.

In broad terms, this involves using activities such as agriculture and biotechnology to generate economic output. But for this to work, the government needs well trained scientists who can work in the relevant different sectors.

The government must work to develop existing plant scientists, and put in place incentives to draw new people to the field. Funding, access to next-generation technologies and good communication strategies that show the importance of plant sciences would all be useful approaches.

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Disclosure statement

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http://bit.ly/2QNU3pk

NASA's Beloved Mars Rovers Are Having a Rough Year

One was felled by a dust storm. And now the other has been sidelined by a technical glitch.

Marina Koren

At the start of 2018, NASA had two active rovers on Mars. Now, it has one—and it's having some issues.

Earlier this summer, the Opportunity rover stopped communicating with Earth after a massive dust storm swept the planet and prevented sunlight from reaching its solar panels. The storm has mostly cleared, but NASA hasn't heard from the rover since June, and engineers are listening daily for any faint pings.

Then on Saturday, the other rover, Curiosity, experienced a technical problem that has prompted engineers to temporarily turn off all its science instruments while they troubleshoot.

"Over the past few days, engineers here at [NASA's Jet Propulsion Library] have been working to address an issue on Curiosity that is preventing it from sending much of the science and engineering data stored in its memory," wrote Ashwin Vasavada, the project scientist for Curiosity, in a blog post on Wednesday. "The rover remains in its normal mode and is otherwise healthy and responsive."

According to Vasavada, the problem appeared Saturday night in the rover's main computer. The issue means that Curiosity can't properly store or send data it collects from its science instruments.

The rover is still able to transmit some data, including about its well-being. It can uplink information to a Mars orbiter as it passes overhead, or beam it directly to the Deep Space Network, a series of antenna back on Earth. Vasavada said engineers have instructed Curiosity to send more data about its status, which doesn't require the rover to dip into previously stored information.

If needed, engineers will switch operations over from the main computer to a backup computer. That backup computer actually used to be the rover's primary system, but it experienced a couple of technical glitches of its own in 2013. Those were eventually fixed, so engineers could make a switch again.

Curiosity arrived on Mars six years ago to explore the composition of the rocky terrain and perhaps find organic compounds. The rover travels at the very unhurried pace of less than mile per hour and stops every now and then to burrow its drilling equipment into the ground. This week, Curiosity tried to drill in a new location, but couldn't penetrate the rock more than a few millimeters. "Who'd have thought that ridge rocks could be so hard?" a blog post from the rover's

science team reported. Curiosity drove off, bound for a new drilling target. Then the mysterious glitch emerged.

As engineers work to determine the cause of the problem, Vasavada and his fellow scientists are planning for the rover's next moves. "Curiosity's science team is using the time to pore over data gathered on Vera Rubin Ridge and come up with the best location for another drilling attempt," he said. "We're looking at any clues that tell us the rocks are weaker and better for drilling."

The situation doesn't sound as dire as the one Opportunity is in. But the news will no doubt be painful for the scientists and engineers involved, for whom the rovers are more than just an amalgamation of metal and wires. They have formed strong emotional attachments to both rovers over the years, and that bond has been on full display recently.

Last month, NASA officials announced plans for rescue attempts for Opportunity. The dust of the storm had settled and sunlight was peeking through the atmosphere, which meant that Opportunity would soon—if it could—wake up. Officials said they would spend 45 days actively listening for signals from the rover, after which it would need to think seriously about letting go.

The response from former and current members of the mission was fierce. They criticized the plan as arbitrary, the timeframe as too short. There was "a lot of anger, some sadness, some shock" among members of the team, one employee said. They weren't ready to give up on Opportunity.

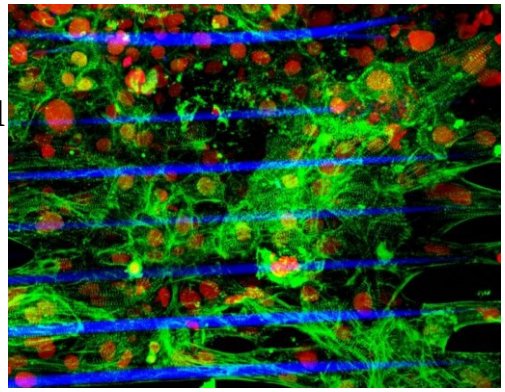
If Curiosity's situation worsens, the rover will be met with the same protectiveness. Humans have a tendency to anthropomorphize robots, even if they're millions of miles away. Research has shown that the more "alive" a robot appears, the more likely people are to react to it the way they would with living beings. For fans of Opportunity and Curiosity, the rovers are quite alive: They move around, they take selfies, they have names. And, as we've learned this year, they can get sick and, perhaps, die.

http://bit.ly/2QINOmS

Can a common heart condition cause sudden death?

A new model system offers clues

SAN FRANCISCO, CA - About one person out of 500 has a heart condition known as hypertrophic cardiomyopathy (HCM). This condition causes thickening of the heart muscle and results in defects in the heart's electrical system. Under conditions of environmental stress such as exercise, HCM can result in sudden death. In other cases, patients may go undiagnosed, with their heart function declining gradually over decades.



The image shows the human stem cell-derived cardiac microtissue grown on a fiber-based scaffold fabricated using a laser-guided bioprinting technology (Red: cell nuclei, Green: cardiomyocytes, Blue: fibers). **Zhen Ma, PhD**

3-D Construction Builds a Better Model of the Heart

Although the genetic defects that lead to HCM are known, it has been difficult to understand how those mutations result in disease, in part because cells in a two-dimensional culture dish do not interact the same way cells in a three-dimensional organ do. Now, using the most advanced techniques in gene editing, stem cell generation, and three-dimensional cell culture, researchers from UC Berkeley and the Gladstone Institutes in San Francisco have for the first time developed a "microtissue" model of the heart in which they can study how common environmental stress affects normal and abnormal heart tissue.

The study, published in Nature Biomedical Engineering, was a collaboration between the labs of Kevin Healy, PhD, the Jan Fandrianto and Selfia Halim Distinguished Professor of Engineering in the Departments of Bioengineering and Materials Science & Engineering at UC Berkeley, and Bruce Conklin, MD, a senior investigator at the Gladstone Institutes and professor of medicine at UC San Francisco.

With these new microtissue models, the researchers compared heart tissue grown from normal heart muscle cells to heart tissue in which all the cells had a mutation in the gene encoding myosin binding protein C (MYBPC3), the gene that is most often altered in HCM patients.

For the study, the scientists used laser-guided three-dimensional printing to make a microscopic scaffold on which to grow heart cells. By varying the thickness of the scaffold, the scientists could mimic the stresses that heart cells experience under different conditions. The myocytes were able to contract together to move the scaffolding, similar to the movement of an accordion's bellows under pressure.

When the scientists used normal cells to build microtissues, they found that they were able to adapt well to stress, comparable to the way a normal heart would pump harder to meet an increased oxygen demand during exercise. However, when the microtissues were built from mutant cells, they contracted abnormally and arrhythmically under conditions of elevated mechanical stress, similar to the way HCM patients may experience arrhythmias when heart pressure is elevated due to the demands of exercise.

"With these microtissues we were able to observe how the human heart can develop this syndrome," explained Zhen Ma, one of the lead authors of the study who was a postdoctoral fellow with Healy's laboratory group, and who now is an assistant professor of biomedical and chemical engineering at Syracuse University. "Even though this is a microscopically tiny part of the heart, we could measure its contraction, the mechanical forces generated, and the calcium flow associated with the electrical signaling that triggers contraction of heart muscle."

A Discovery with Broad Applications to Improve Human Health

"This advance gives us an opportunity to study cardiac disease in a much more precise manner," said Healy. "We think it paves the way for new therapies because these precise tissue models will give us a way to better target new therapies to optimize responses in sub-populations of patients."

Conklin, a world leader in using stem cell technologies and gene editing to create cells and living tissues that mimic human heart disease, is also excited about how microtissues might be used to address other scientific problems. "Some of the worst drug safety issues are due to problems with side effects on the heart, so we need better ways to test drugs for potential cardiac effects," Conklin said. "It's possible that in the future microtissues might become the preferred choice for their capability to capture a fuller range of cardiac physiology."

About the Research Project

The paper, "Contractile deficits in engineered cardiac microtissues as a result of MYBPC3 deficiency and mechanical overload," was published online in Nature Biomedical Engineering *on September 10, 2018. The study was funded in part by the National Institutes of Health (grants R01HL096525, R01HL108677, U01HL100406, U01HL098179, R21EB021003 HL007544 and UH3TR000487), by the National Science Foundation (grant 1804875), by an American Heart Association postdoctoral fellowship (16POST27750031) by the Nappi Family Foundation Research Scholar Project, by a Canadian Institute of Health Research Postdoctoral Fellowship (grant 129844), and by the California Institute for Regenerative Medicine (grant TBI-01197).*

The other lead authors of the study are Nathaniel Huebsch, a former postdoctoral fellow with both Healy's and Conklin's laboratory groups, and who now is an assistant professor of biomedical engineering at Washington University in St. Louis, and Sangmo Koo, PhD, who was a PhD student with Costas Grigoropoulos' laboratory group in the Department of Mechanical Engineering at UC Berkeley, and is now an assistant professor of mechanical engineering at Incheon National University, Republic of Korea. Other contributors were Grigoropoulos, Brian Siemons and Steven Boggess of UC Berkeley and Mohammad Mandegar, of the Gladstone Institutes and UC San Francisco.

http://bit.ly/2xwNlv6

Bye bye bugs? Scientists fear non-pest insects are declining

A staple of summer—swarms of bugs—seems to be a thing of the past. And that's got scientists worried.

Seth Borenstein

In this May 26, 2010 file photo, a Coccinellidae, more commonly known as a ladybug or ladybird beetle, rests on the petals of a rose in Portland, Ore. A study estimates a 14 percent decline in ladybugs in the United States and Canada from 1987 to 2006. **(AP Photo/Don Ryan)**

Pesky mosquitoes, disease-carrying ticks, crop-munching aphids and cockroaches are doing just fine. But the more beneficial flying insects of summer—native bees, moths, butterflies, ladybugs, lovebugs, mayflies and fireflies—appear to be less abundant.

Scientists think something is amiss, but they can't be certain: In the past, they didn't systematically count the population of flying insects, so they can't make a proper comparison to today. Nevertheless, they're pretty sure across the globe there are fewer insects that are crucial to as much as 80 percent of what we eat.

Yes, some insects are pests. But they also pollinate plants, are a key link in the food chain and help decompose life.

"You have total ecosystem collapse if you lose your insects. How much worse can it get than that?" said University of Delaware entomologist Doug Tallamy. If they disappeared, "the world would start to rot."

He noted Harvard biologist E.O. Wilson once called bugs: "The little things that run the world."

The 89-year-old Wilson recalled that he once frolicked in a "Washington alive with insects, especially butterflies." Now, "the flying insects are virtually gone."

It hit home last year when he drove from suburban Boston to Vermont and decided to count how many bugs hit his windshield. The result: A single moth.

Windshield Test

The un-scientific experiment is called the windshield test. Wilson recommends everyday people do it themselves to see. Baby Boomers will probably notice the difference, Tallamy said.

Several scientists have conducted their own tests with windshields, car grilles and headlights, and most notice few squashed bugs. Researchers are quick to point out that such exercises aren't good scientific experiments, since they don't include control groups or make comparisons with past results. (Today's cars also are more aerodynamic, so bugs are more likely to slip past them and live to buzz about it.)

Still, there are signs of decline. Research has shown dwindling individual species in specific places, including lightning bugs, moths and bumblebees. One study estimated a 14 percent decline in ladybugs in the United States and Canada from 1987 to 2006. University of Florida urban entomologist Philip Koehler said he's seen a recent decrease in lovebugs—insects that fly connected and coated Florida's windshields in the 1970s and 1980s. This year, he said, "was kind of disappointing, I thought."

University of Nevada, Reno, researcher Lee Dyer and his colleagues have been looking at insects at the La Selva Biological Station in Costa Rica since 1991. There's a big insect trap sheet under black light that decades ago would be covered with bugs. Now, "there's no insects on that sheet," he said.

But there's not much research looking at all flying insects in big areas.

The Evidence

Last year, a study that found an 82 percent mid-summer decline in the number and weight of bugs captured in traps in 63 nature preserves in Germany compared with 27 years earlier. It was one of the few, if only, broad studies. Scientists say similar comparisons can't be done elsewhere because similar bug counts weren't done decades ago.

"We don't know how much we're losing if we don't know how much we have," said University of Hawaii entomologist Helen Spafford.

The lack of older data makes it "unclear to what degree we're experiencing an arthropocalypse," said University of Illinois entomologist May Berenbaum. Individual studies aren't convincing in themselves, "but the sheer accumulated weight of evidence seems to be shifting" to show a problem, she said.

After the German study, countries started asking if they have similar problems, said ecologist Toke Thomas Hoye of Aarhus University in Denmark. He studied flies in a few spots in remote Greenland and noticed an 80 percent drop in numbers since 1996.

"It's clearly not a German thing," said University of Connecticut entomologist David Wagner, who has chronicled declines in moth populations in the northeastern United States. "We just need to find out how widespread the phenomenon is."

The Suspects

Most scientists say lots of factors, not just one, caused the apparent decline in flying insects.

Suspects include habitat loss, insecticide use, the killing of native weeds, single-crop agriculture, invasive species, light pollution, highway traffic and climate change.

"It's death by a thousand cuts, and that's really bad news," Wagner said.

To Tallamy, two causes stand out: Humans' war on weeds and vast farmland planted with the same few crops.

Weeds and native plants are what bugs eat and where they live, Tallamy said. Milkweeds, crucial to the beautiful monarch butterfly, are dwindling fast. Manicured lawns in the United States are so prevalent that, added together, they are as big as New England, he said.

Those landscapes are "essentially dead zones," he said.

In this June 27, 2017 file photo, mayflies swarm around the bright lights of a ballpark during a baseball game in Cincinnati. Experts say light pollution is a big problem for some species of insects. Certain bugs are attracted to brightness, where they become easy prey and expend energy they should be using to get food, said University of Delaware entomologist Doug Tallamy.
(AP Photo/John Minchillo)

Light pollution is another big problem for species such as moths and fireflies, bug experts said. Insects are attracted to brightness, where they become easy prey and expend energy they should be using to get food, Tallamy said.

Jesse Barber of Boise State is in the middle of a study of fireflies and other insects at Grand Teton National Park. He said he notices a distinct connection between light pollution and dwindling populations.

"We're hitting insects during the day, we're hitting them at night," Tallamy said. "We're hitting them just about everywhere."

Lawns, light pollution and bug-massacring highway traffic are associated where people congregate. But Danish scientist Hoye found a noticeable drop in muscid flies in Greenland 300 miles (500 kilometers) from civilization. His studies linked declines to warmer temperatures.

Other scientists say human-caused climate change may play a role, albeit small.

Restoring Habitat

Governments are trying to improve the situation. Maryland is in a three-year experiment to see if planting bee-friendly native wildflowers helps.

University of Maryland entomology researcher Lisa Kuder says the usual close-crop "turf is basically like a desert" that doesn't attract flying insects. She found an improvement—70 different species and records for bees—in the areas where flowers are allowed to grow wild and natural alongside roads.

The trouble is that it is so close to roadways that Tallamy fears that the plants become "ecological traps where you're drawing insects in and they're all squashed by cars."

Still, Tallamy remains hopeful. In 2000, he moved into this rural area between Philadelphia and Baltimore and made his 10-acre patch all native plants, creating a playground for bugs. Now he has 861 species of moths and 54 species of breeding birds that feed on insects.

Wagner, of the University of Connecticut, spends his summers teaching middle schoolers in a camp to look for insects, like he did decades ago. They have a hard time finding the cocoons he used to see regularly.

"The kids I'm teaching right now are going to think that scarce insects are the rule," Wagner said. "They're not realizing that there could be an ecological disaster on the horizon."

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Choosing to Do--or Not Do--a Genital Exam

Choosing Wisely Recommendations From AAFP

Kenneth W. Lin, MD, MPH

Hello, everyone. I'm Dr Kenny Lin, a family physician at Georgetown University Medical Center in Washington, DC, and I blog at Common Sense Family Doctor.

After a 5-year hiatus, the American Academy of Family Physicians (AAFP) recently added five new recommendations to its Choosing Wisely list of medical tests and interventions that patients and physicians should question, and withdrew a previous recommendation, bringing its total of active recommendations to 19. Today I will discuss three of the five additions that emphasized the lack of benefits of genital examinations or testing for genital herpes simplex in asymptomatic patients.

Because genital exams have long been considered part of a complete physical exam, there may be some resistance to skipping them. When, in 2014, the American College of Physicians first recommended not performing screening pelvic examinations in asymptomatic, nonpregnant adult women,[1] the American College of Obstetricians and Gynecologists responded by reaffirming their existing guidance on well-woman exams,[2] which states that "a pelvic examination [should] be performed on an annual basis in all patients aged 21 years and older." For what purpose is not clear.

Screening for chlamydia and gonorrhea in women can be performed on urine samples with nucleic acid amplification tests.[3] A systematic review of the bimanual pelvic examination found that it is highly inaccurate as a screening test for ovarian cancer, with a positive predictive value of only 1% in a typical screening population.[4]

Although the US Preventive Services Task Force (USPSTF) found insufficient evidence to assess the balance of benefits and harms of screening pelvic examinations,[5] the AAFP has concluded that these exams are not warranted in nonpregnant women unless necessary for guideline-appropriate screening for cervical cancer.

Turning to men, the AAFP recommended not screening for testicular cancer in asymptomatic adolescents and adults. As a colleague and I concluded in a review performed for the USPSTF's 2011 recommendation against routine testicular exams,[6] the low incidence and the high cure rates of testicular cancer make any

theoretical benefits of screening unlikely to outweigh harms of false-positive tests and unnecessary procedures.

Incidentally, though not included in their most recent set of Choosing Wisely recommendations, the AAFP continues to recommend against routinely screening for prostate cancer using a digital rectal exam. A recent systematic review of studies of digital rectal exam screening in primary care[7] found that the test has low sensitivity and specificity, and could lead to considerable overdiagnosis and overtreatment.

Finally, the AAFP recommended against serologic screening for genital herpes in asymptomatic adults, including pregnant women. Many adults with detectable antibodies to HSV-1 or HSV-2 will never develop genital symptoms, and "a positive test can cause considerable anxiety and disruption of personal relationships." When a patient without genital lesions asks to be tested for sexually transmitted infections, this is a test to leave off the laboratory order.

Although genital examinations can seem harmless, and these Choosing Wisely recommendations may contradict what we learned in training, family physicians do patients no favors by performing tests that are more likely to make their health worse rather than better. This has been Dr Kenny Lin for Medscape Family Medicine. Thank you for listening.

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https://go.nature.com/2O7Eaf0

World's first animal was a pancake-shaped prehistoric ocean dweller

Fossils of ancient sea creatures answer a long-standing question about how animals became bigger and more complex.

Jeremy Rehm

Fossil imprints that resemble the rippled underside of a mushroom's cap are remnants of the oldest-known animals in Earth's history. The finding, published in *Science* on 20 September[1], is based on a chemical analysis of fatty molecules preserved in the fossils. It could alter the current story of how animals and other complex life arose.

The strange sea creatures known as Dickinsonia, shown here in fossil form, lived 558 million years ago.

Researchers first discovered the pancake-shaped creatures — a group known as *Dickinsonia* — in the late 1940s. The species were among the most common residents of the world's oceans 558 million years ago, during the Ediacaran period. Whereas most living things during that time ranged in size from microscopic to a few millimetres long, some *Dickinsonia* grew up to 1.4 metres in length.

The creatures' large size has puzzled scientists because *Dickinsonia* lived tens of millions of years before the Cambrian explosion, the period 541 million years ago when living things became bigger and most major animal groups emerged. Scientists have since debated whether *Dickinsonia* were primitive animals, giant single-celled organisms called protists, bacterial colonies or something else entirely.

The latest study attempts to end that debate by analysing chemical biomarkers preserved in a unique set of *Dickinsonia* fossils from Russia, rather than by examining the ancient species' body characteristics.

Fossil fats

A team led by Jochen Brocks, a palaeobiogeochemist at the Australian National University in Canberra, examined ring-like fat molecules called sterols that infiltrate the membrane surrounding a cell to keep it flexible and fluid. Plants, animals, fungi and bacteria all contain sterols, but the type of sterol that predominates in each group differs. Animals mainly make cholesterol, and the fungi that form colourful, crusty lichens found on boulders have only ergosterol. Under the right conditions, these chemicals can persist for millions of years, and so help to determine a fossilized organism's evolutionary relationships.

Fossils that contain these preserved biomarkers are rare, but strewn around the shores of the White Sea in northwestern Russia lie Ediacaran fossils — including *Dickinsonia* — embedded in a fossilized mat of algae, with their organic matter and fats perfectly preserved. "They are, in principle, mummified dickinsonians," Brocks says. "It's just incredibly lucky."

But the team's analysis revealed dramatic differences in the composition of the biomarker samples. Whereas the surrounding rocks and algal mats contained only about 10% cholesterol and 75% of another sterol that is common in green algae, the *Dickinsonia* fossils contained 93% cholesterol — suggesting that they were ancient animals living 17 million years before the Cambrian explosion.

The technique provides an entirely different way of determining *Dickinsonia*'s place on the evolutionary tree, says Guy Narbonne, a palaeobiologist at Queen's University in Kingston, Canada. "I think it's quite imaginative." The findings from the chemical analysis reinforce other evidence that *Dickinsonia* were primitive animals, he says. This includes fossil 'footprints' that show the organisms moved from place to place for food, and growth patterns that match those of most animals today.

The latest findings also suggest that the transition between the Cambrian and the Precambrian, which includes the Ediacaran, was just another extinction event in which one animal community replaced another, Brocks says. "But now the jury's out on all the other weirdos."

Analyses that have compared the DNA of living creatures today to trace back their evolutionary trees suggest that animals originated more than 100 million years before the Cambrian — well before even *Dickinsonia*[2]. But finding the fossils of these creatures, and then proving they are animals, remains challenging.

Rangeomorphs, strange Ediacaran frond-like creatures with tubes branching in a fractal pattern, for example, remain a mysterious group whose relation to any living organisms is uncertain. "This would be for us the next big challenge," Brocks says. "Trying to get hold of those strange creatures and find out what they were."

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http://bit.ly/2QSj3Me

Nerve cells in the human brain can 'count'

Study by the Universities of Bonn and Tübingen shows how human neurons process quantity information

How do we know if we're looking at three apples or four? Researchers at the Universities of Bonn and Tübingen are now one step closer to answering this question. They were able to demonstrate that some brain cells fire mainly for quantities of three, others for quantities of four and others for other quantities. A similar effect can be observed for digits: In humans, the neurons activated in response to a "2" are for instance not the same as the neurons activated for a "5". The results also demonstrate how we learn to handle number symbols in comparison to quantities. The study is published online in the journal *Neuron*.

We are born with the ability to count: Shortly after birth, babies can estimate the number of events and even perform simple calculations. But what exactly happens in the brain? And do we process abstract numbers differently from concrete quantities? Researchers from the Department of Epileptology at the University of Bonn and neurobiologists from the University of Tübingen have investigated these two questions. They benefited from a special feature of Bonn University Hospital: The epileptology clinic located there specializes in brain surgery. With this, doctors try to cure epilepsy patients by means of an operation in which they remove the diseased nerve tissue. In some cases, they first have to insert electrodes into the affected person's brain in order to ascertain the location of the epileptogenic focus. As a side effect, researchers can use this to watch patients think.

Algorithm recognizes how many points test subjects see

This is also the case in the current study: The nine participants were epilepsy patients who had microelectrodes as fine as a single hair inserted into their temporal lobes. "This enabled us to measure the reaction of individual nerve cells to visual stimuli," explains Prof. Dr. Dr. Florian Mormann, head of the Cognitive and Clinical Neurophysiology group. The scientists now showed their subjects a different number of points on a computer screen - sometimes only one, sometimes four or even five. "We were able to demonstrate that certain nerve cells fired primarily in response to very specific quantities," explains Esther Kutter, lead author of the study. "For example, some were activated mainly by three dots, others by one."

Each quantity therefore creates a specific activity pattern in the human brain. "We have written a classification algorithm that evaluates this pattern," Mormann explains. "This allowed us to use the arousal state of the nerve cells to read how many points our respective subject could see."

The scientists also observed an interesting effect: Although the neurons were "set" to a certain quantity, they also responded to slightly different quantities. A brain cell set to quantities of three also fired in response to two or four points, but then weaker. With one or five points, however, it could hardly be activated. Experts call this the "Numerical Distance Effect". Prof. Dr. Andreas Nieder from the University of Tübingen, co-supervisor of the study, already demonstrated the same phenomenon in experiments on monkeys. "Numbers are processed in our brains in exactly the same way as in the brains of monkeys," he emphasizes. "This confirms monkeys as an indispensable model for research into the processing of quantitative information."

We learn digits differently from characters

How we process digits, i.e. symbols that represent quantities, can hardly be answered with the help of animals. The scientists have now been able to show for the first time that this works in principle in a similar way as with quantities: When we see a certain digit, certain brain cells fire. However, the digit neurons and the quantity neurons are not identical: The digit "3" excites completely different nerve cells than a quantity of three points.

Another observation is even more exciting: "The digit neurons also have a numerical distance effect," says Mormann. "They are also stimulated not only by the exact digit, but also by its neighbors - but

only very weakly." Nevertheless, this phenomenon shows that we learn digits differently from simple characters: In a sense, the neurons have learned that the value of a 3 is only slightly different from a 2 or a 4, otherwise they would not also respond to these two digits. Digits therefore seem to be firmly interwoven with a certain idea of quantity.

The researchers hope that their results will also contribute to a better understanding of dyscalculia, a developmental disorder accompanied, among other things, by a poorer understanding of quantity.

Publication: Esther F. Kutter, Jan Bostroem, Christian E. Elger, Florian Mormann and Andreas Nieder: Single neurons in the human brain encode numbers; DOI: 10.1016/j.neuron.2018.08.036

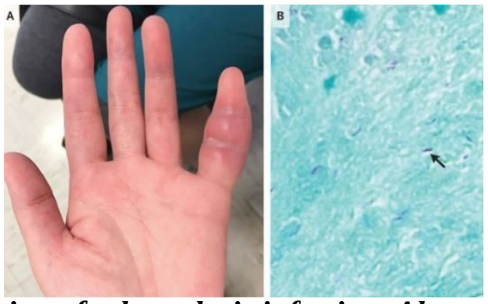
http://bit.ly/2NCOufN

Woman's Swollen Pinkie Finger Was Rare Sign of Tuberculosis

Tuberculosis can potentially infect any part of the body

By Rachael Rettner, Senior Writer

A swollen finger is often the symptom of a simple sprain, but for one woman in California, a puffy pinkie was a rare sign of tuberculosis, according to a new report of the case.



A woman's swollen finger was a rare sign of tuberculosis infection. Above, an image of the woman's finger (panel A), and a microscopic view of the infection (panel B). An arrow points to the tuberculosis bacteria. **The New England Journal of Medicine ©2018.**

The 42-year-old woman went to the doctor after a week of swelling and pain in her pinkie finger. However, she hadn't injured her finger at all, according to the report from doctors at the University of California, San Francisco.

An X-ray and CT scan showed swelling of the soft tissue in her finger, but no problems with her bones. (Soft tissues include muscles, tendons and skin.)

When doctors performed a biopsy of the woman's skin tissue, they found *Mycobacterium tuberculosis* bacteria, the bacteria that cause tuberculosis.

According to the report, the woman had lupus and was taking medications to suppress her immune system, which made her more susceptible to infectious diseases — including tuberculosis.

Tuberculosis bacteria are spread through the air and usually affect the lungs. But the bacteria can potentially infect any part of the body, including the kidneys, spine and brain, according to Mayo Clinic.

Infection of the finger "is a rare extrapulmonary [outside the lungs] manifestation of tuberculosis," the authors wrote in the report, which was published online Sept. 19 in The New England Journal of Medicine. Still, this diagnosis is important to consider in people with weakened immune systems, they said.

But how exactly did the patient contract the disease? An investigation pointed to the woman's husband, who had recently traveled to China and developed a cough. He was later diagnosed with active tuberculosis.

The woman was treated with several anti-tuberculosis drugs for nine months, and her symptoms went away completely, the report said.

http://bit.ly/2Q1pM5o

Preventing a dengue outbreak at the 2020 Summer Olympics

A PLOS Neglected Tropical Diseases press release

In 2014, a dengue outbreak unexpectedly occurred in Tokyo. What does that mean for the 2020 summer Olympics and Paralympics being held in the city? Researchers report this week in *PLOS Neglected Tropical Diseases* that new controls and frameworks are

recommended to detect dengue and other infectious diseases and help prevent their spread during the summer games.

Dengue is a mosquito-borne disease that, in rare severe cases, can cause mortality if left untreated. Although the disease is mostly endemic in tropical and subtropical areas, it has recently been observed expanding to more temperate areas, including Japan. International sporting events such as the Olympics put spectators at particular risk of acquiring locally endemic diseases.

In the new work, Naoki Yanagisawa, of the Harvard T.H. Chan School of Public Health, USA, and colleagues used a failure mode and effects analysis (FMEA) to test the vulnerability and resiliency of Japan's current preparedness plans and design ways to strengthen those plans. Publicly available national resources were used to input data on protocols and trends related to Japan's tourism, public health, and infectious diseases.

The team identified 20 critical points for detection of disease, assessment of disease, and patient communication. Overall, they described the current controls for dengue detection-- which include guidelines and services to update both physicians and travelers on infections-- as robust. However, there were gaps related to missed cases at accommodations, failure to diagnose dengue cases in some situations, and communication failures. Suggested action plans to close these gaps, such as formal training seminars about dengue, were outlined in the new paper.

"We specifically applied the FMEA framework to health preparedness for dengue infection for Tokyo 2020. However, this framework could be expanded and tailored to other diseases or mass gatherings as well," the researchers say. "Given that dengue was introduced, chikungunya and Zika could be problematic as well. Although an outbreak has not been recognized in Japan to date, there is always the possibility that these infections would cause an outbreak."

Peer-reviewed | Simulation/modelling
Citation: Yanagisawa N, Wada K, Spengler JD, Sanchez-Pina R (2018) Health preparedness plan for dengue detection during the 2020 summer Olympic and Paralympic games in Tokyo. PLOS Neglected Tropical Diseases *12(9): e0006755.* https://doi.org/10.1371/journal.pntd.0006755
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http://bit.ly/2xKjfEE

Breaking down backbones

Study examines how mammal backbones changed during evolution

Cambridge, MA - Just about any elementary school student can rattle off the characteristics that make mammals special - they're warm-blooded, have fur or hair and nearly all are born alive.

A new study suggests mammals are unique in one more way - the makeup of their spine.

Led by Associate Professor of Organismic and Evolutionary Biology and Curator of Vertebrate Paleontology Stephanie Pierce and postdoctoral researcher Katrina Jones, the study challenges the notion that specialization in mammal backbones date back to the earliest land animals. The research is described in a September 21 paper in *Science*.

"The spine is basically like a series of beads on a string, with each bead representing a single bone - a vertebra." said Pierce. "In most four-legged animals, like lizards, the vertebrae all look and function the same. But mammal backbones are different. The different sections or regions of the spine - like the neck, thorax, and lower back - take on very different shapes. They function separately and so can adapt to different ways of life, like running, flying, digging, and climbing."

To understand how those specialized regions came to be, Pierce and Jones decided to look back at the fossil record.

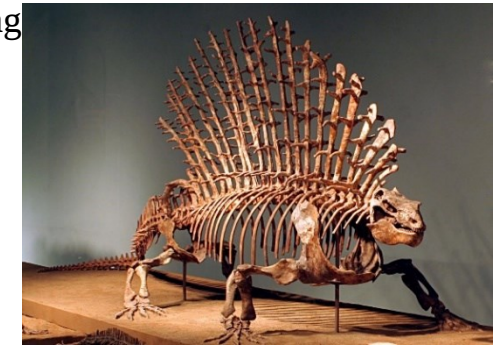
"There are no animals alive today that can record the transition from a 'reptile-like' ancestor to a mammal" said Jones, the lead author of the study. "To do that we must dive into the fossil record and look at the extinct forerunners of mammals, the non-mammalian synapsids." But studying fossils isn't easy.

"Fossils are scarce and finding extinct animals with all 25 plus vertebrae in place is incredibly, incredibly rare," Jones explained. To tackle this problem, the researchers combed museum collections from around the world to study the most perfectly preserved fossils, which lived some 320 million years ago.

Pierce and Jones, along with co-author Ken Angielczyk from the Chicago's Field Museum, examined dozens of fossil spines, as well as over 1,000 vertebrae from living animals, including mice, alligators, lizards, and amphibians.

The goal was to test if mammal regions were as ancient as previously thought, or if mammals were doing something unique.

"If vertebral regions had remained unchanging through evolution, as hypothesized, we would expect to see the same regions in the non-mammalian synapsids that we see in mammals today," said Pierce.



Edaphosaurus, an early mammal relative that lived around 300 million years ago, which had a more primitive backbone with just three different regions. **Field Museum**

The evidence suggests that isn't the case. When the researchers compared the positioning and shape of the vertebrae, they found something surprising - the spine gained regions during mammal evolution.

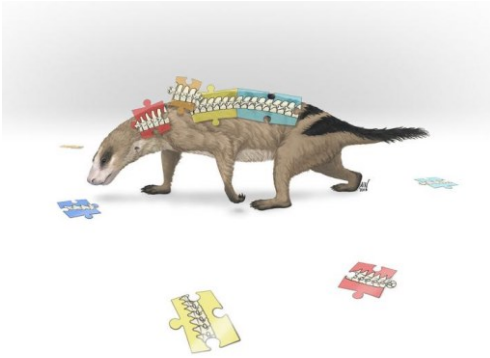
"The earliest non-mammalian synapsids had fewer regions than living mammals." Jones explained.

Around 250 million years ago, a new region evolved in close proximity to the shoulders and front legs, as dramatic changes began to appear in the forelimbs of animals known as non-mammalian therapsids. Those simultaneous changes, Pierce and Jones believe, likely occurred in conjunction with changes in how creatures walked and ran.

"There appears to be some sort of cross-talk during development between the tissues that form the vertebrae and the shoulder blade," Pierce said. "We hypothesize that this interaction resulted in the addition of a region near the shoulder as the forelimbs of our ancestors evolved to take on new shapes and functions."

Later, a region emerged in the ancestor of modern mammals near the pelvis.

"It is this last region, the ribless lumbar region, that appears to adapt most to different environments," adds Pierce. That final step in building the mammal backbone may be linked to changes in Hox genes, the genetic blueprint for laying out spine regions early in development.



This is an illustration showing an early mammal relative, Thrinaxodon, which was part of the first group to have an extra fourth section of their backbones. **April Neander**

"What I think is exciting here is that we've been able make connections between changes to the skeletons of extinct animals and ideas from modern development and genetics." Jones said. "This combined approach is helping us to understand what makes a mammal a mammal."

"Mammals can be found on continents and in oceans around the world," says Dena Smith, a program director in the National Science

Foundation's Division of Earth Sciences, which funded the research. "Looking into the ancient past, an early change in mammals' spinal columns was an important first step in their evolution. Changes in the spine over time allowed mammals to develop into the myriad species we know today."

This research was supported with funding from the National Science Foundation and a AAA Postdoctoral Fellowship.

http://bit.ly/2O4wmup

Japan's largest complete dinosaur skeleton comes to life

The unearthed bones of Mukawaryu, Japan's largest complete dinosaur skeleton, have now been prepared and pieced together, giving us a fuller and clearer image of the 72 million-year-old dinosaur.

Excavations of Mukawaryu, the largest complete dinosaur skeleton in Japan, began in 2013 in the Hobetsu district of Mukawa Town on Japan's northernmost island of Hokkaido by the Hokkaido University Museum and Hobetsu Museum research teams.

Although many bones have not yet been identified, the majority have been, and those which can be pieced together now present a more accurate depiction of the dinosaur's anatomy.

Hokkaido University

Mukawaryu was recovered from marine deposits dating back to the Late Cretaceous Period around 72 million years ago. The skeleton has been identified as a duck-billed dinosaur (Hadrosauridae). These herbivores thrived in Eurasia, North and South America, and Antarctica.

The Mukawaryu skeleton revealed in 2017 was defined as a complete skeleton, as it contained more than 50 percent of the bones, but now an estimated 60 percent of the bones have been confirmed as well as 80 percent of the entire expected skeletal volume. With a significant amount of cranial bones pieced together in addition to more shoulder, forelimb, hip, hindlimb, and backbones, the skeleton is now more discernible.

"There are still many unidentified bones and fossils that need to be restored," said Associate Professor Yoshitsugu Kobayashi of the research team. "We will continue researching Mukawaryu, analyzing its bones, and unraveling more details of this creature. We also hope to further clarify its systematic position, determine any related species and the ecology of the environment it lived in."

http://bit.ly/2DrEFwq

Scientists grow human esophagus in lab

Tiny organoids enable personalized disease diagnosis, regenerative therapies

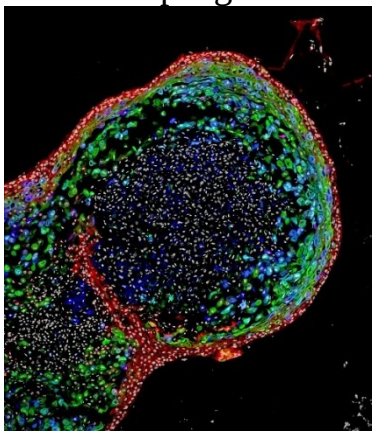
CINCINNATI - Scientists working to bioengineer the entire human gastrointestinal system in a laboratory now report using pluripotent stem cells to grow human esophageal organoids.

Published in the journal Cell Stem Cell the study is the latest advancement from researchers at the Cincinnati Children's Center for Stem Cell and Organoid Medicine (CuSTOM). The center is developing new ways to study birth defects and diseases that affect millions of people with gastrointestinal disorders, such as gastric reflux, cancer, etc. The work is leading to new personalized diagnostic methods and focused in part on developing regenerative tissue therapies to treat or cure GI disorders.

The newly published research is the first time scientists have been able to grow human esophageal tissue entirely from pluripotent stem cells (PSCs), which can form any tissue type in the body, according to the authors. Cincinnati Children's scientists and their multi-institutional collaborators already have used PSCs to bioengineer human intestine, stomach, colon and liver.

"Disorders of the esophagus and trachea are prevalent enough in people that organoid models of human esophagus could be greatly beneficial," said Jim Wells, PhD, chief scientific officer at CuSTOM and study lead investigator. "In addition to being a new model to study birth defects like esophageal atresia, the organoids can be used to study diseases like eosinophilic esophagitis and Barrett's metaplasia, or to bioengineer genetically matched esophageal tissue for individual patients."

The study involves collaboration from researchers in the divisions of Developmental Biology, Oncology, Allergy and Immunology, and Endocrinology at Cincinnati Children's and the Gladstone Institutes in San Francisco. This includes study first author Stephen Trisno, a graduate student and member of the Wells laboratory.



This confocal microscopic image shows a two-month-old human esophageal organoid bioengineered by scientists from pluripotent stem cells. About 700 micrometers (0.027 inches) in size, the organoid is stained to visualize key structural proteins expressed in mature esophagus, such as involucrin (green) and cornulin (blue). Researchers report in the journal Cell Stem Cell the organoids enhance the study of esophageal disorders, personalized medical and the development of regenerative tissue therapies for people.
Cincinnati Children's

The Food Channel

The esophagus is a muscular tube that actively passes food from the mouth to the stomach. The organ can be affected by congenital diseases, such as esophageal atresia--a narrowing or malformation of the esophagus caused by genetic mutations.

Additionally, there are several diseases that can afflict people later in life. Some include esophageal cancer, gastroesophageal reflux disease (GERD), or a rare ailment called achalasia--a disease affecting the muscles of the lower esophagus that prevents contraction of the organ and the passage of food.

All of the conditions need better treatments, researchers note. This requires a more precise understanding of the genetic and biochemical mechanisms behind their cause--a need filled by the ability to generate and study robust, functional, genetically matched models of human esophageal tissue that can be grown from a person's own cells.

Tracing Nature's Path

The scientists based their new method for using human PSCs to general esophageal organoids on precisely timed, step-by-step manipulations of genetic and biochemical signals that pattern and form embryonic endoderm and foregut tissues. They focused in part on the gene Sox2 and its associated protein--which are already known to trigger esophageal conditions when their function is disrupted. --The scientists used mice, frogs and human tissue cultures to identify other genes and molecular pathways regulated by Sox2 during esophagus formation.

The scientists report that during critical stages of embryonic development, the Sox2 gene blocks the programming and action of genetic pathways that direct cells to become respiratory instead of esophageal. In particular, the Sox2 protein inhibits the signaling of a molecule called Wnt and promotes the formation and survival of esophageal tissues.

In another test to help confirm the importance of Sox2 expression on esophageal formation, researchers studied the complete loss of Sox2 during the development process in mice. The absence of Sox2 resulted in esophageal agenesis--a condition in which the esophagus terminates in a pouch and does not connect to the stomach.

After successfully generating fully formed human esophageal organoids--which grew to a length of about 300-800 micrometers in about two months--the bioengineered tissues were compared biochemically to esophageal tissues from patient biopsies. Those

tests showed the bioengineered and biopsies tissues were strikingly similar in composition, according to the authors.

The research team is continuing its studies into the bioengineering process for esophageal organoids and identifying future projects to advance the technology's eventual therapeutic potential, according to Wells. This includes using the organoids to examine the progression of specific diseases and congenital defects affecting the esophagus.

Funding support for the research came in part from the National Institutes of Health (P01 HD093363-01, R37 A1045898, and T32 GM-063483).

http://bit.ly/2I8brkO

Gut branches of vagus nerve essential components of brain's reward and motivation system

Novel gut-to-brain neural circuit establishes vagus nerve as an essential component of brain system regulating reward and motivation

A novel gut-to-brain neural circuit establishes the vagus nerve as an essential component of the brain system that regulates reward and motivation, according to research conducted at the Icahn School of Medicine at Mount Sinai and published September 20 in the journal Cell. The study provides a concrete link between visceral organs and brain function, especially in regards to reward, and may help to inform novel targets for vagal stimulation therapy, particularly for eating and emotional disorders.

Previous research established the gut as a major regulator of motivational and emotional states but until now, the relevant gut-brain neuronal circuitry remained elusive. The vagus nerve, the longest of the cranial nerves, contains motor and sensory fibers and passes through the neck and thorax to the abdomen. Traditionally, scientists believed that the nerve exclusively mediated suppressive functions such as fullness and nausea; in contrast, circulating hormones, rather than vagal transmission, were thought to convey reward signals from the gut to the brain.

"Our study reveals, for the first time, the existence of a neuronal population of 'reward neurons' amid the sensory cells of the right branch of the vagus nerve," says Ivan de Araujo, DPhil, Senior Faculty in the Department of Neuroscience at the Icahn School of Medicine at Mount Sinai and senior author of the paper. "We focused on challenging the traditional view that the vagus nerve is unrelated to motivation and pleasure and we found that stimulation of the nerve, specifically its upper gut branch, is sufficient to strongly excite reward neurons lying deep inside the brain."

The branches of the vagus nerve are intricately intermingled, making it extremely difficult to manipulate each organ separately. To address this challenge, the research team employed a combination of virally delivered molecular tools that allowed them to exclusively target the vagal sensory neurons connected to the stomach and upper intestine. Specifically, researchers combined different viruses carrying molecular tools in a way that allowed them to optically activate vagal neurons connected to the gut while vagal neurons leading to other organs remained mute. The approach, a state-of-the-art technique known as "optogenetics," allows investigators to use light to manipulate the activity of a prespecified set of neurons.

The study revealed that the newly identified reward neurons of the right vagus nerve operate under the same constraints attributed to reward neurons of the central nervous system, meaning they link peripheral sensory cells to the previously mapped populations of reward neurons in the brain. Strikingly, neurons of the left vagus were associated with satiety, but not with reward. The research team's anatomical studies also revealed, for the first time, that the right and left vagal branches ascend asymmetrically into the central nervous system.

"We were surprised to learn that only the right vagal branch eventually contacts the dopamine-containing reward neurons in the brainstem," explained Wenfei Han, MD, PhD, Assistant Professor of

Neuroscience at the Icahn School of Medicine at Mount Sinai and lead author of the study. Dopamine is a neural transmitter known to be essential for reward and motivation.

The uncovering of right gastrointestinal vagal neurons as conveyors of reward signals to the brain opens opportunities for novel, more specific stimulation targets that may increase the efficacy of vagal nerve stimulation therapy, a treatment that involves delivering electrical impulses to the vagus nerve, for patients suffering from emotional and eating disorders.

Researchers from The John B. Pierce Laboratory, Yale University School of Medicine, Duke University, and University of São Paulo contributed to this study.

https://wb.md/2IfuxG1

For Stubborn COPD, Airway Ablation Bolsters Drug Effects

COPD significantly reduced by an outpatient ablation procedure

PARIS — Symptoms and exacerbations of persistent chronic obstructive pulmonary disease (COPD) can be significantly reduced when an outpatient ablation procedure that opens obstructed airways is added to drug therapy, results from the AIRFLOW-2 trial (NCT02058459) show.

"It's a new mechanism of treatment that will not replace drugs but really strengthens them," said Dirk-Jan Slebos, MD, PhD, from University Medical Center in Groningen, the Netherlands. "From my point of view, it's really a step-up approach at the moment."

"We should use pharmaceutical treatments, smoking cessation, vaccinations, and exercise training as first-line, but if patients are uncontrolled and there is disease progress, this is something that can be considered," he told *Medscape Medical News*.

The targeted lung denervation procedure improved lung function in COPD patients and cut respiratory problems, such as shortness of breath, by more than half, he reported here at the European Respiratory Society International Congress 2018.

There was also a significant reduction in infections and hospitalizations, he added.

Targeted Lung Denervation

The approach appears to maximize the benefits of the anticholinergic drugs that are often prescribed for patients with COPD, Slebos explained.

During the procedure, performed under general anesthesia, a bronchoscope is used to insert a balloon catheter, which contains a radiofrequency probe, into the airway. Nerves are selectively ablated to target the cholinergic pathway that regulates the inflammatory response and smooth muscle constriction. The esophagus is protected from electrodes with a tissue-mimicking gel during the 75-minute procedure.

Slebos and his colleagues assessed 82 patients in their 16-site multinational trial. Half the participants were men and half were women, and average age was 64 years. The 6-month follow-up was completed by 81 patients.

Half the participants underwent targeted lung denervation and the other half underwent a sham procedure. In addition, all received tiotropium, an anticholinergic bronchodilator.

Fewer patients in the denervation group than in the sham group experienced an adverse COPD-related event in the 3 to 6 months after the procedure (32% vs 70%; $P = .0008$).

And during the year after the procedure, patients in the denervation group experienced about half as many hospitalizations for respiratory complications as those in the sham group. "The magnitude of the additional effect for the treatment group was highly significant," Slebos said.

Transient coughing was common after the procedure because of airway penetration. About 12% of patients in the denervation group experienced gastrointestinal problems, such as nausea, bloating, and discomfort, but all had resolved by 6 months. The brief

gastroesophageal symptoms, also seen after cardiac ablation, could be the result of high-dose energy being used near the parasympathetic nervous system, Slebos pointed out.

None of the procedure-related adverse events required treatment and there were no deaths during the study period.

A larger phase 3 trial is now in the planning stages, Slebos reported.

It's easier to pick up a medication from the pharmacy than to undergo a procedure.

Many COPD patients might benefit from this "very promising" treatment, Marlies van Dijk, MD, also from University Medical Center but not involved in the study, said after the presentation.

"It seems to also have an effect on mucus secretion, and it would be really nice to have something to treat patients who have a lot of mucus," she told *Medscape Medical News*.

However, the benefits of targeted lung denervation need to be balanced with the inconvenience of undergoing a procedure that requires general anesthesia, she said.

"It's easier to pick up a medication from the pharmacy than to undergo a procedure," van Dijk pointed out. "You need a whole medical team to do these procedures."

Slebos reports financial relationships with Aeris Therapeutics, Asthmatx, Boston Scientific, Broncus Technologies, CSA Mecial, Free Flow Medical, PneumRx/BTG, Olympus, Portaero, PulmonX, and Nuvaira. Van Dijk has disclosed no relevant financial relationships.

https://nyti.ms/2Q15Uzn

'Latent' Tuberculosis? It's Not That Common, Experts Find

Active infections kill 4,000 people a day worldwide, more than AIDS does. But the notion that a quarter of the global population harbors silent tuberculosis is "a fundamental misunderstanding."

By Donald G. McNeil Jr.

Although experts frequently assert that nearly 1.7 billion people carry dormant tuberculosis worldwide, that figure may be a "gross exaggeration" of the real threat, a recent study concludes.

The study, published last month in the journal BMJ, found that nearly everyone who falls seriously ill with TB does so within two years of getting infected. So-called latent infections only rarely become active, even in old age.

Researchers "have spent hundreds of millions of dollars chasing after latency, but the whole idea that a quarter of the world is infected with TB is based on a fundamental misunderstanding," said Dr. Lalita Ramakrishnan, a tuberculosis expert at the University of Cambridge and one of the study's authors.

The challenge to conventional wisdom comes at an opportune time. On Sept. 18, the World Health Organization issued its annual TB report, and on Sept. 26, the United Nations General Assembly will hold its first high-level meeting on the disease.

No one questions how great a threat active tuberculosis is. Around the world, the disease kills more than 4,000 people a day; in 2015, tuberculosis surpassed AIDS as a cause of death.

(TB has not become more lethal, nor AIDS less so. The difference is that 20 million people, mostly in Africa, are now on H.I.V.-suppressing drugs.)

Although the incidence of TB is falling slowly around the world, some regions fare much worse than others. For example, South Africa, Mozambique and the Philippines have especially high infection rates.

Drug-resistant TB remains a crisis, the W.H.O. reported, and just three countries — India, China and Russia — account for almost half the cases. And the "global treatment success rate" is dropping. The figure was 82 percent in 2016, down from 86 percent three years earlier.

Success in treating drug-resistant forms is even lower, at 55 percent, although some relatively poor countries, like Bangladesh, Ethiopia, Kazakhstan, Myanmar and Vietnam, do better than average.

The BMJ study was accompanied by an editorial endorsing its conclusions, written by Dr. Soumya Swaminathan, a tuberculosis expert and deputy director-general of the W.H.O. She argued that experts should focus on the 55 million people at highest risk of active infection: young children with infected relatives, the severely malnourished, and people with H.I.V. or other immunosuppressive conditions.

Experts at nonprofits like the TB Alliance and the International Union Against Tuberculosis and Lung Disease agreed with the major conclusions of the new study and the need to focus on active rather than latent disease.

But finding tests to tell which carriers of latent infections are most likely to fall ill is still crucial, said Dr. Daniel E. Everitt, the alliance's senior medical officer.

Dr. Ramakrishnan's study analyzed reports of local TB outbreaks going back to the 1930s, before antibiotics were invented, in places like the Faroe Islands that were so sparsely populated that it was possible to pinpoint exactly who infected whom and when.

Reports on outbreaks as recent as three years ago in the Netherlands and Canada similarly showed that the vast majority of active cases came from recent infections, not latent infections that became active.

The misconception that 1.7 billion people are walking time bombs, potentially capable of developing and communicating full-blown TB, comes from the fact that skin and blood tests for the bacterium confirm only that the body once mounted an immune reaction to exposure.

The tests do not tell if the bacteria are still alive in the body, said Dr. Paul H. Edelstein, an infectious disease specialist at the University of Pennsylvania and a co-author of the new study.

Who succumbs is probably determined in part by genetic makeup, said Dr. Ramakrishnan, who studies the genetics of TB in zebrafish. She cited the "Lübeck disaster," a famous incident in the history of vaccines.

In 1929, 250 German infants were given a TB vaccine that was accidentally contaminated with live bacteria. About a third died, and another third fell seriously ill — but a third survived unscathed, possibly because they had innate resistance.

At next week's U.N. meeting, member states are expected to pledge to increase efforts to treat the infected and to do more research. The organization has estimated that an additional $3.5 billion a year is needed for tuberculosis treatment, along with over $1.3 billion more for research.

In August, the W.H.O. issued new treatment guidelines for drug-resistant TB that rely on newer oral drugs like bedaquiline and delamanid, rather than older injectables with harsh side effects.

But newer drugs are expensive, and months of tense behind-the-scenes negotiations preceded the high-level meeting, according to the Intellectual Property Watch website. The debate pitted South Africa and the medical charity Doctors Without Borders against the United States delegation, which was defending the interests of pharmaceutical companies.

The South Africans and the charity wanted the meeting's declaration to acknowledge that, under international treaties going back to 1994, poor countries may override patents and import generic drugs when they cannot afford prices that pharmaceutical companies charge.

The final language did not spell that out, but cited the treaties and said intellectual property rights should be interpreted to "promote access to medicines for all."

Donald G. McNeil Jr. is a science reporter covering epidemics and diseases of the world's poor. He joined The Times in 1976, and has reported from 60 countries.

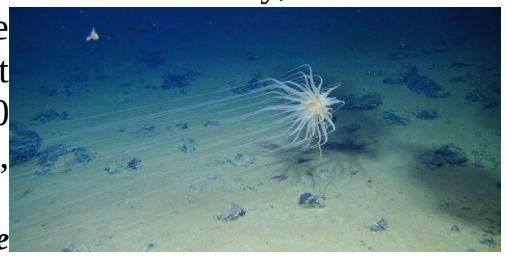
https://go.nature.com/2MYnzWg

Discovery of vibrant deep-sea life prompts new worries over seabed mining

"Gummy squirrels," single-celled organisms the size of softballs and strange worms thrive in a Pacific Ocean zone some considered an underwater desert.

Amy Maxmen

Deep in the eastern central Pacific Ocean, on a stretch of sea floor nearly as big as the continental United States, researchers are discovering species faster than they can name them. And they are exploring newfound fossil beds of whales that lived up to 16 million years ago. The findings — many reported for the first time last week at the Deep-Sea Biology Symposium in Monterey, California — have come as a shock. Some scientists had thought these vast underwater plains, 4,000–5,500 metres below the ocean surface, were relatively lifeless.



A new species of the sea-anemone-like Relicanthus clings to a sponge stalk on the floor of the Pacific Ocean. **D. J. Amon & C. R. Smith**

But that is changing just as nations and corporations prepare to mine this patch of the Pacific sea bed for cobalt, manganese and other elements for use in technologies such as smartphones and electric cars.

Researchers are now pushing the International Seabed Authority (ISA), the body that oversees mining in international waters, to limit environmental damage from future activity. The ISA, which is developing rules for mining in the ocean, is accepting comments on a draft plan until 30 September. Its goal is to release final rules by 2020, clearing the way for mining to start.

"What we do right now is going to have huge implications for decades to come," says Diva Amon, a deep-sea biologist at the Natural History Museum in London. "We have a chance to do things as rigorously and responsibly as we can."

The surprising diversity in the Clarion–Clipperton zone includes red shrimp (Cerataspis monstrosus), a rattail fish (Coryphaenoides yaquinae) and crustaceans called amphipods. **Astrid B. Leitner, Craig R. Smith, Jeff C. Drazen, DeepCCZ project**

Hidden world

The ISA began issuing contracts to explore the Clarion–Clipperton Zone (CCZ), a 6-million-square-kilometre swathe of the Pacific Ocean floor that stretches from Hawaii to Mexico, in 2011. The agency has given 29 companies permission to explore mining in international sea beds, including at 17 sites in the CCZ. Those companies, and the nations sponsoring them, must produce environmental assessments of their plots to satisfy the ISA's mandate to enable mining while preserving the ocean environment.

These assessments ultimately help the ISA determine how best to protect deep-sea life. "Scientists have to show that the overall structure of the ecosystem will not be affected — and that is a huge task," says Malcolm Clark, a marine scientist who sits on the legal and technical commission that advises the ISA.

Seafloor surveys are just beginning to map the vibrant life in areas marked for mining. Craig Smith, an oceanographer at the University of Hawaii at Manoa in Honolulu, helped lead expeditions in 2013 and 2015 to a territory in the eastern CCZ claimed by the United Kingdom. He was surprised to find hills and mountains rising across deep undersea plains. The landscape was teeming with life more diverse than that seen at similar depths elsewhere.

Seventy percent of the 154 marine worm species found by Smith's team seem to be unknown to science. The researchers discovered sea cucumbers they nicknamed "gummy squirrels", and a new species in the order *Relicanthus* that is related to sea anemones. The organism attaches itself to the stalk of a sponge and extends spindly tendrils into the current. The team also spotted rare worms that resemble squid.

Adrian Glover, a deep-sea biologist at the Natural History Museum in London, has found that potato-sized nodules of manganese and other metals in the eastern CCZ harbour geometric sponges and other tiny, rarely seen invertebrates. And swathes of the sea floor are covered with enigmatic xenophyophores — ornate single-celled creatures that can be larger than a softball, and that exude slime as they feed. Most of the xenophyophores that scientists have found in the area were previously unknown, expanding the number of recognized species by about 30%.

These eels have never before been seen at such depths. **Astrid B. Leitner, Jeff C. Drazen, DeepCCZ project**

Murky waters

But the wave of discoveries in the eastern CCZ is not limited to living species. Amon stunned the audience at the deep-sea symposium with photos of fossilized whale skulls encrusted in metallic residues. Her preliminary analyses suggest the bones belong to perhaps 6 extinct species of whale that died between 1 million and 16 million years ago. A study published[1] in August suggests that modern beaked whales feed on the seafloor in the eastern CCZ. The authors speculate that the whales ingest metallic nodules to regulate their buoyancy underwater.

Amon is among the scientists who argue that their findings should prompt the ISA to conserve a section of the eastern CCZ. In 2012, the agency set aside nine preserves in the CCZ, relying largely on satellite images showing the density of plankton in the sea. But none of these areas is in the east, where researchers have begun to document surprisingly complex sea-floor ecosystems.

Christopher Williams, managing director of Seabed Resources, the company that is working with the UK government to develop deep-sea mining in the eastern CCZ, is surprised to hear about such diversity. Williams says that he would not object if the ISA decided to establish a new sea-floor preserve in the east — outside the UK's mining territory.

Amon also wants companies to report when they discover fossils on their mining plots, so that those finds can be analysed by scientists. "It's important to consider information that tells us about the history of our planet," she says. On land, the United Nations Educational, Scientific and Cultural Organization (UNESCO) works to protect archaeological, cultural and palaeontological relics from mining and other development. Amon argues that UNESCO's oversight should extend to the deep sea.

And Smith is pushing the ISA to support research in the open waters above sea-floor mining zones. He and his colleagues say that silt and toxins discharged by the mining of metallic nodules could prevent some marine organisms from breathing and eating, block bioluminescent light that some use to attract prey and find mates, and pollute the food web.

Others are more philosophical. Clark says that researchers will never know everything that lives on the deep-sea plains, and must plan around this uncertainty as they advise the ISA. "Scientists have to recommend a course of action that includes a learning process, so that if things start to go off the rails we can get back on course," he says.

In the meantime, the ISA is under pressure to finalize its mining regulations by 2020 so that large-scale operations can begin. Japan began extracting deep sea minerals late last year at a test site near the island of Okinawa. And a Belgian company, Global Sea Mineral Resources in Ostend, plans to test its equipment in the CCZ next year.

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To Live Longer, Forget the Treadmill and Play Tennis

Socially interactive leisure sports may translate to a considerably higher life expectancy

Diana Swift

Socially interactive leisure sports such as tennis, badminton, and soccer may translate to a considerably higher life expectancy than running alone on a treadmill, although a causal relationship could not be proven, an observational study has found.

Peter Schnohr, MD, DMSc, a cardiologist at Frederiksberg Hospital in Copenhagen, Denmark, and colleagues published their findings online September 4 in *Mayo Clinic Proceedings*.

The researchers studied the link between longevity and eight leisure-time sports activities among 8577 participants from the population-based Copenhagen City Heart Study. In this cohort, 1042 (12%) reported being sedentary and 5674 (66%) reported playing at least one of the selected sports. All the sports studied were associated with a longer life span; however, tennis was linked to the top gain of 9.7 years.

"Although several authors have found that observational studies and randomized controlled studies usually produce similar results, our study was observational and not a randomized trial, and therefore, we cannot be sure that the associations observed in our study represent a causal relationship," the authors write.

Participants were followed for as long as 25 years from time of enrollment in 1991 to 1994 until 2017, during which period 4448 died. Compared with inactivity, variable-adjusted longevity gains varied from a low of 1.5 years for solitary health club activities such as lifting weights to 3.7 years for cycling, 4.7 years for soccer, and 6.2 years for badminton. The benefit from swimming came in at 3.4 years, and from jogging at 3.2 years, whereas calisthenics translated to a benefit of 3.1 years.

"This is in line with previous studies consistently showing that social isolation is among the strongest predictors of reduced life expectancy," the authors explain.

Social isolation has been reported to pose as much of a risk for premature death as traditional medical factors such as hypertension, and to increase the likelihood of cardiovascular events.

The study's sedentary group tended to be older, with a mean age of 61 years, whereas the youngest participants were soccer players, with a mean age of 39 years, followed by joggers with a mean age of 40 years. Overall, cycling was the most prevalent activity in the cohort, with 56% participation. Men predominated in soccer, tennis, and badminton, whereas women were more likely to swim or do calisthenics.

The average weekly volume for all sports activities was 411 minutes (approximately 7 hours), but varied widely from 58 minutes among swimmers to 386 minutes among cyclists, who devoted more than twice the time to pedaling as those participating in other sports. Tennis players spent an average of 103 minutes per week in their sport of choice.

The group that had the longest total duration of all activities combined was the group whose activity of choice was health club activities, with 599 minutes per week spent on all leisure type physical activities. This group experienced the smallest gain in terms of life expectancy, however. "Possibly, the observed differences in mortality benefits were due to the differing social aspects of the various sports studied," the authors write.

Notably, tennis players more frequently had high household incomes and university degrees, parameters previously associated with healthier lifestyles. Tennis players and joggers had the cohort's lowest body mass index, both 23 kg/m^2.

The authors note that other studies show that golf is associated with robust health benefits, with one large observational study reporting that playing golf regularly could raise life expectancy by approximately 5 years.

Although having a limited social network was a risk factor for all-cause mortality, it did not diminish the association between the different sports and mortality, the authors note. They call for further study of the effect of social interaction during sports activity.

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CHMP Backs Galcanezumab for Migraine Prevention

CHMP has recommended marketing authorization for the humanized monoclonal antibody galcanezumab for migraine prevention in adults

Deborah Brauser

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended marketing authorization for the humanized monoclonal antibody galcanezumab (*Emgality*, Eli Lilly) for migraine prevention in adults.

The indication for the drug is as treatment only for patients who have at least 4 monthly migraine days (MMDs).

The once-monthly, self-injectable drug is the second calcitonin gene-related peptide (CGRP) antagonist to receive the committee's recommendation for migraine prevention. As reported by *Medscape Medical News*, the EU panel endorsed erenumab (*Aimovig*, Amgen/Novartis) in May 2018.

The US Food and Drug Administration is expected to give an answer on galcanezumab by the end of this month, following its approval earlier this year of erenumab and another anti-CGRP agent, fremanezumab-vfrm (*Ajovy*, Teva), for prevention of migraine.

The CHMP's recommendation today is based on three phase 3 trials: EVOLVE-1, EVOLVE-2, and REGAIN, with total participants including 1117 patients with chronic migraine and 1780 patients with episodic migraine.

Among those treated with the active drug, patients with chronic migraine had an average reduction of 2 MMDs compared with placebo, while those with episodic migraine had an average reduction of 1.9 MMDs. The most commonly reported adverse events were injection site pain and reactions, vertigo, and constipation.

"It is estimated that approximately 15% of the population of the European Union suffers from migraine," the CHMP reports in a statement.

"There is no cure for migraine and these two medicines [galcanezumab and erenumab] widen the therapeutic options for this disease," they add. "There are other available treatments to tackle the symptoms and reduce the frequency of migraine days. However, existing preventative treatments do not always work well and may have unpleasant side effects."

"If approved, we're very excited about the potential to offer Emgality as a new option for migraine prevention that could provide more migraine-free days to people living with this debilitating disease," Gudarz Davar, MD, vice president, Neurology Department at Lilly Bio-Medicines, said in a press release.

The opinion from the CHMP will now be sent to the European Commission for a decision on EU-wide marketing authorization.