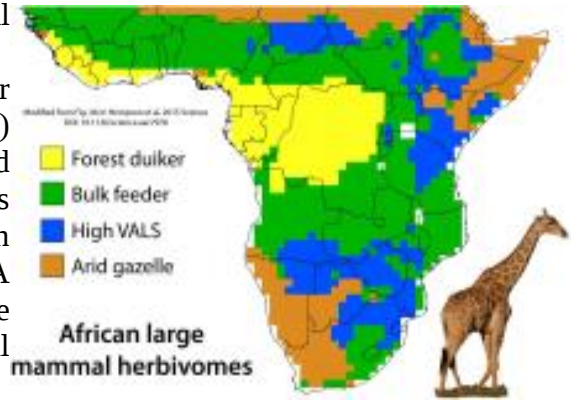
http://www.eurekalert.org/pub_releases/2015-11/uotw-aww112615.php

# African wildlife: What it looked like 1000 years ago and why this is important

***A team of local scientists have wound back the clock by 1000 years to reconstruct wildlife populations across Africa to help us better understand how they have shaped the world we live in.***

This is important, because to understand the ecology of Africa, and much of the rest of the globe, you have to include animals - and now we have the means to do so, says lead researcher Dr Gareth Hempson, postdoctoral researcher at School of Animal, Plant and Environmental Sciences at Wits University.

Hempson, together with Professor Sally Archibald (Wits University) and Professor William Bond (University of Cape Town), has published a paper in Science, an international journal, titled: A continent-wide assessment of the form and intensity of large mammal herbivory in Africa.




***Sub-Saharan Africa was classified into four herbivory regimes, or 'herbivomes' based on analyses of the abundance and community composition of different herbivore functional types. These ecoregions support previously held views on the distinctiveness of forest, desert, nutrient-rich savanna and nutrient poor savanna systems.*** **Dr Gareth Hempson"**

Animals matter and ecologists across the world are starting to realise that many ecosystems cannot be understood without including animals and their impact into their thinking," says Hempson.

"The problem is that in most places, natural wildlife populations are extinct. The challenge that we took up was to try and bring them back."

Hempson says Africa is the only place left where they could conduct this study because there are fewer cases of extinction here. There are many protected areas where animal populations are still intact in Africa. The team focused on large mammal herbivores - plant-eating animals like antelope, zebra, elephants, rhino and pigs. These mammals form an integral level in the food pyramid, both consuming vegetation and themselves being consumed by carnivores.

"We used wildlife census data from as many of these protected areas as possible, and then analysed how factors like rainfall, soil fertility and vegetation types influenced the abundance of different species.

"With that information and the knowledge about what rainfall, soils and vegetation used to be like - we were able predict how many animals of each species there were in all the places that are now so radically transformed," Hempson explains.

The researchers recognised 'herbivory regimes' across Africa. Dry areas - where there is not much food and very wet areas - where the food is almost all out of reach in the forest canopy and had relatively few animals. The in-between areas, says Hempson, are really interesting. "They are your classic African savannas." The drier savannas are packed with a kaleidoscope of African wildlife, and the wetter savannas are dominated by elephants and fire.

"All those patterns are of themselves really interesting, and lend strong support to previous ideas about the large-scale ecology of Africa. But there is much more that we can do with this new information," says Hempson.

**How does this help us?**

This research provides a platform for fitting animals into the global ecosystem models that are used to predict where planet Earth is headed.

It allows us to look outside of Africa - for example towards South America - and compare the ecology of our continent with one that lost its big animals thousands of years ago. It raises questions such as: Did they help shape their own ecology, so that the world changed when they were lost, or were they merely passive users of ecosystems shaped by climate and soils?

It also lets us explore the evolution of animal-associated groups like thorny plants, or dung beetles, because we can now make sense of their current distributions that were shaped by animals in the past.

Back in Africa, livestock have replaced wildlife over vast areas. This research will bring us closer to answering where has this occurred? What are the implications of this shift? Are they simply interchangeable, or are there consequences for how ecosystems work?

http://www.eurekalert.org/pub_releases/2015-11/uov-mde112615.php

# Microbiologists discover enigmatic comammox microbes

***New chapter in environmental microbiology***

Nitrogen is a key chemical element for life and an essential nutrient for all living organisms. In particular, modern intensive agriculture totally depends on nitrogen fertilizers. However, fertilization with nitrogen compounds has its drawbacks. Following chemical conversion by nitrification, the nitrogen from fertilizers ends up in groundwater, rivers and lakes and disturbs the ecological balance in these waters. This problem is aggravated by additional nitrogen from domestic and industrial waste especially in countries that lack proper wastewater treatment.

**Enigmatic Nitrification**

Anthropogenic nitrogen deposition affects the natural nitrogen cycle where specific microorganisms convert nitrogen compounds. Among these microbes are the nitrifiers, which carry out the nitrification process where ammonium (a common nitrogen fertilizer) is oxidized to nitrite and, subsequently, nitrite is oxidized to nitrate. For 125 years, the two nitrification steps were known to be always catalyzed by different microorganisms: the ammonia oxidizers and the nitrite oxidizers, whose cooperation is required for complete nitrification. This textbook knowledge was the basis for hundreds of studies on nitrification in the environment and in wastewater treatment plants (where nitrification also is important). However, no microbiologist ever understood why labor is divided in nitrification. A single microbe capable of catalyzing both nitrification steps would actually benefit from conserving more energy. Microbiologists have coined a term to describe such a "complete" nitrifier: "comammox" ("complete ammonia oxidizer"). However, the existence of comammox remained an unresolved question for more than a century.

**Surprise in a Russian Oil Exploration Well**

A group of scientists led by Holger Daims and Michael Wagner, microbiologists at the Department for Microbiology and Ecosystem Science at the University of Vienna, has now solved the comammox conundrum together with cooperation partners from Russia, Denmark and Germany. The team analyzed a bacterial culture from a 1,200 m deep oil exploration well in Russia. Although this culture oxidized ammonia completely to nitrate, the only nitrifiers present were Nitrospira, so far known to be strict nitrite oxidizers. They could carry out the second step of nitrification, but any known ammonia oxidizers needed for the first step were absent. "This was an incredibly exciting moment. We assumed that this culture contained something new, but we did not expect the big surprise awaiting us" Holger Daims says. A complete genomic analysis of all bacterial species in the culture revealed the answer. "The Nitrospira bacteria possessed all genes for oxidizing both ammonia and nitrite, meaning complete nitrification. This seemed to be the long-sought comammox organism", Michael Wagner adds.

**Comammox is everywhere but was overlooked**

Physiological experiments with the culture and a proteome analysis confirmed that the Nitrospira bacteria were comammox. Michael Wagner explains: "Nitrospira are well-known nitrite oxidizers that occur almost everywhere. The function as comammox of some Nitrospira was overlooked for decades". Once the comammox Nitrospira had been discovered, the team was able to detect them in many soils, inland waters and in wastewater treatment plants. "This finding opens a new chapter of environmental microbiology" Daims says. "Our picture of the nitrogen cycle, which is essential for all life on Earth, was incomplete. Our next task will be to investigate more properties of comammox and its importance in nature and wastewater treatment plants."

The research on comammox was funded by the Austrian Science Fund (FWF) and the European Research Council (ERC).

The findings of the microbiologists from the University of Vienna are published in Nature back to back with a study by colleagues from Nijmegen (The Netherlands), who also identified comammox Nitrospira. "The Nijmegen team is among the leading experts on the nitrogen cycle. When we learned by chance that both groups had made similar discoveries, we agreed to synchronize publication of our work to avoid an unnecessary race for the first paper", Wagner states.

*"Complete Nitrification by Nitrospira Bacteria": Holger Daims, Elena V. Lebedeva, Petra Pjevac, Ping Han, Craig Herbold, Mads Albertsen, Nico Jehmlich, Marton Palatinszky, Julia Vierheilig, Alexandr Bulaev, Rasmus H. Kirkegaard, Martin von Bergen, Thomas Rattei, Bernd Bendinger, Per H. Nielsen, Michael Wagner; in Nature, DOI: 10.1038/nature16461*

***http://www.eurekalert.org/pub_releases/2015-11/jcu-gml112615.php***

## Good medicine left on the shelf?

***A controversial new paper by James Cook University scientist claims many useful new treatments are being left on the shelf by medical researchers.***

JCU's Dr David Kault, a medical doctor and mathematician, has examined the way clinical trials of medical treatments are judged.

"Traditional assessment of a clinical trial is based on whether we can blame chance for a favourable outcome," said Dr Kault. "But there is little consideration of background and context, which sometimes leads to ignoring common sense."

Dr Kault said a well-known parody on the subject published in the British Medical Journal pointed out that, under current conditions and rules, it was not clear that parachutes were strictly necessary for people to safely jump out of aircraft - as some people using parachutes were injured and some people survived falls from aircraft without parachutes.

He said followers of the currently-used Evidence Based Medicine approach argue that allowing consideration of common sense in assessing treatments introduces subjectivity and there were some instances of apparent common sense being seriously misleading.

But Dr Kault believes effective drugs and treatments are being discarded unnecessarily by this approach. "There are rigid decisions made, with little consideration of the background - whether in the given context, chance was a reasonable explanation," he said.

Dr Kault said his new method produced a probability that a treatment worked, rather than a straight yes or no answer. "It shows a compromise approach is

possible which should lead to better decisions. It shows that sometimes it's possible to calculate an objective probability that a treatment works."

He said his method suggests researchers have been dismissing treatments which have a small degree of effectiveness.

"It appears up to 20% of all older treatments reassessed may have been mistakenly labelled as ineffective. These mistakes usually occurred in the case of treatments with only very modest degrees of effectiveness, which should have remained available to patients if they were low cost."

***http://www.eurekalert.org/pub_releases/2015-11/uoh-ete112715.php***

## Even the elderly can recover from a severe traumatic brain injury

***Even patients over the age of 75 may recover from severe traumatic brain injury***

According to a study completed at the Helsinki University Hospital Department of Neurosurgery, even patients over the age of 75 may recover from severe traumatic brain injury. This is the first study to describe the results of surgically treated elderly patients with acute subdural hematomas.

It is generally accepted that elderly patients who suffer from an acute subdural hematoma should not be treated surgically, as few survive and even fewer recover to an independent life. However, the world's population is rapidly ageing leading to an increased rate of fall accidents. In the worst case, falling may result in brain hemorrhage.

Age is one of the most significant outcome predictors in patients with traumatic brain injury. If the patient is young, an acute subdural hematoma is normally treated through a neurosurgical operation. However, even among young patients, mortality and significant morbidity are highly common, despite surgical treatment. In older patients, the success rate of the surgery are made worse by the fact that many patients are typically using oral anticoagulant medications to treat other cardiovascular diseases.

The Neurosurgical Department in Helsinki University Hospital has been an exception in its policy to also treat elderly patients with acute subdural hematomas surgically. Researchers from the University of Helsinki and Helsinki University Hospital have now determined how the patients' functional status before the injury and the use of oral anticoagulant medications influence the prognosis of patients 75 years or older operated on for an acute subdural hematoma.

The study showed that no patients who had been brought to hospital unconscious, who had not been independent before the trauma, or who had used anticoagulants were alive at one year after the surgery.

"What was surprising, however, was that patients who were conscious at presentation, who were not using anticoagulants or were independent before the operation, recovered quite well. The expected lifespan of these patients was comparable to their age-matched peers," says MD, PhD Rahul Raj, one of the main authors.

"One should be careful to make to strong conclusions from such a small number of patients", Raj points out, "but it seems that in approximately half of all cases, even elderly patients may benefit from surgery and recover to an independent life. It is important to note that included patients had an isolated acute subdural hematoma with no injuries to the brain tissue itself. This means that the results cannot be applied to patients with contusions or other intracranial injuries, whose treatment and prognosis are different."

### The decision to operate should not be based on age alone

According to Raj, the study throws new light on the old assumption that surgical treatment of the elderly is not a sensible course of action: "The decision to treat through surgery should not be based on age alone, even though this is common."

Surgery of an acute subdural hematoma followed by intensive care and rehabilitation involve major costs and can cause significant suffering to patients and relatives. Thus, it is important to perform surgery on only the patients who are likely to benefit from it.

"But how do you define a bad prognosis? If only one in ten patients recovers sufficiently to live at home, is the treatment worthwhile? If half of the treated patients die within the year, is the treatment worthwhile? This is not a medical decision," the researchers emphasize. They believe that in the future, surgical treatment will be increasingly restricted to patients with the highest likelihood of recovering.

***http://www.eurekalert.org/pub_releases/2015-11/ncsu-rfn113015.php***

## Researchers find new phase of carbon, make diamond at room temperature

***Researchers from North Carolina State University have discovered a new phase of solid carbon, called Q-carbon, which is distinct from the known phases of graphite and diamond.***

They have also developed a technique for using Q-carbon to make diamond-related structures at room temperature and at ambient atmospheric pressure in air.

Phases are distinct forms of the same material. Graphite is one of the solid phases of carbon; diamond is another.

"We've now created a third solid phase of carbon," says Jay Narayan, the John C. Fan Distinguished Chair Professor of Materials Science and Engineering at NC State and lead author of three papers describing the work. "The only place it may be found in the natural world would be possibly in the core of some planets."

Q-carbon has some unusual characteristics. For one thing, it is ferromagnetic -- which other solid forms of carbon are not. "We didn't even think that was possible," Narayan says.

In addition, Q-carbon is harder than diamond, and glows when exposed to even low levels of energy. "Q-carbon's strength and low work-function -- its willingness to release electrons -- make it very promising for developing new electronic display technologies," Narayan says. But Q-carbon can also be used to create a variety of single-crystal diamond objects. To understand that, you have to understand the process for creating Q-carbon.

Researchers start with a substrate, such as such as sapphire, glass or a plastic polymer. The substrate is then coated with amorphous carbon -- elemental carbon that, unlike graphite or diamond, does not have a regular, well-defined crystalline structure. The carbon is then hit with a single laser pulse lasting approximately 200 nanoseconds. During this pulse, the temperature of the carbon is raised to 4,000 Kelvin (or around 3,727 degrees Celsius) and then rapidly cooled. This operation takes place at one atmosphere -- the same pressure as the surrounding air. The end result is a film of Q-carbon, and researchers can control the process to make films between 20 nanometers and 500 nanometers thick.

By using different substrates and changing the duration of the laser pulse, the researchers can also control how quickly the carbon cools. By changing the rate of cooling, they are able to create diamond structures within the Q-carbon.

"We can create diamond nanoneedles or microneedles, nanodots, or large-area diamond films, with applications for drug delivery, industrial processes and for creating high-temperature switches and power electronics," Narayan says. "These diamond objects have a single-crystalline structure, making them stronger than polycrystalline materials. And it is all done at room temperature and at ambient atmosphere - we're basically using a laser like the ones used for laser eye surgery. So, not only does this allow us to develop new applications, but the process itself is relatively inexpensive." And, if researchers want to convert more of the Q-carbon to diamond, they can simply repeat the laser-pulse/cooling process.

If Q-carbon is harder than diamond, why would someone want to make diamond nanodots instead of Q-carbon ones? Because we still have a lot to learn about this new material.

"We can make Q-carbon films, and we're learning its properties, but we are still in the early stages of understanding how to manipulate it," Narayan says. "We know a lot about diamond, so we can make diamond nanodots. We don't yet know how to make Q-carbon nanodots or microneedles. That's something we're working on."

NC State has filed two provisional patents on the Q-carbon and diamond creation techniques.

*The work is described in two papers, both of which were co-authored by NC State Ph.D. student Anagh Bhaumik. "Novel Phase of Carbon, Ferromagnetism and Conversion into Diamond" will be published online Nov. 30 in the Journal of Applied Physics. "Direct conversion of amorphous carbon into diamond at ambient pressures and temperatures in air" was published Oct. 7 in the journal APL Materials. The work was supported in part by the National Science Foundation, under grant number DMR-1304607.*

***http://www.eurekalert.org/pub_releases/2015-11/nion-drf112815.php***

## DNA repair factor linked to breast cancer may also play a role in Alzheimer's disease

***NIH-funded research suggests deficient DNA repair may lead to dementia***

Mutant forms of breast cancer factor 1 (BRCA1) are associated with breast and ovarian cancers but according to new findings, in the brain the normal BRCA1 gene product may also be linked to Alzheimer's disease. The results, published in Nature Communications, suggest that low levels of BRCA1 protein in the brain may contribute to dementia. The study was funded by the National Institutes of Health.

"It's extremely interesting that one molecule can be critically involved in two apparently opposing conditions: cancer, in which too many cells are born and neurodegenerative disease, in which too many brain cells die off," said senior author Lennart Mucke, M.D., director of the Gladstone Institute of Neurological Disease, San Francisco, and the Joseph B. Martin Distinguished Professor of Neuroscience, and professor of neurology at the University of California, San Francisco.

Dr. Mucke and his colleagues suspected that defects in DNA repair mechanisms could contribute to cognitive decline in AD and focused their studies on BRCA1. BRCA1 plays a key role in repairing deoxyribonucleic acid (DNA), our genetic code. DNA is a double helix structure that is made of two strands and resembles a twisted ladder. Occasionally, one or both of the strands will develop breaks, which are fixed by DNA repair proteins including BRCA1. This process is critical for cell survival because if DNA is not repaired properly, the cell may die.

When Dr. Mucke's group examined brains of patients who died with Alzheimer's, they discovered low levels of BRCA1. In addition, the researchers found reductions of BRCA1 in the brains of mouse models of Alzheimer's. In fact, experimental reduction of BRCA1 levels in brains of healthy mice made their brain cells shrink and become dysfunctional.

Dr. Mucke's team also investigated the effects of BRCA1 on cognition. After researchers reduced BRCA1 levels in the brains of healthy mice, the animals developed problems with learning and memory. Mouse models of Alzheimer's showed even greater declines in learning and memory following reductions of

BRCA1. In addition, lowering BRCA1 caused increased DNA damage in the brains of Alzheimer's mice.

One of the hallmarks of Alzheimer's disease is accumulation of a protein fragment known as beta-amyloid, which is toxic to brain cells and can lead to neuronal death. Dr. Mucke's team found that adding amyloid beta to neurons in a dish lowered levels of BRCA1.

According to Dr. Mucke and his colleagues, the findings suggest that accumulation of beta-amyloid lowers levels of BRCA1, which increases DNA damage in brain cells and may contribute to dementia.

"An emerging theme in neurodegeneration research is that normal DNA repair protects against damage that causes neurons to die in dementia and related disorders. This study supports and strengthens that theme by showing that beta-amyloid decreases the levels of the DNA repair gene BRCA1, and at the same time inhibits the ability to form new memories," said Roderick Corriveau, Ph.D., program director at NIH's National Institute of Neurological Disorders and Stroke, which provided funding for the study.

"The functions of BRCA1 in the brain remain to be fully elucidated," said Dr. Mucke, "but our findings suggest that it may play an important role in supporting critical brain functions in both health and disease."

Further research is necessary to determine whether BRCA1 may be a potential therapeutic target for treating dementia, and whether BRCA1 mutations that lead to cancer also affect brain function.

*This work was supported by grants from the NIH (NS065780, AG011385).*

*Suberbielle E et al. "DNA Repair Factor BRCA1 Depletion Occurs in Alzheimer Brains and Impairs Cognitive Function in Mice." Nature Communications, November 30, 2015.*

***http://www.eurekalert.org/pub_releases/2015-11/uob-sos113015.php***

## Scientists offer sweet solution to marathon fatigue

***It turns out a spoonful of sugar might not just help the medicine go down, but could also help stave off tiredness faced by weary marathon runners - or other long-distance athletes - when they hit the wall.***

According to health researchers at the University of Bath, stirring in table sugar from the baking cupboard into a water bottle before a big physical event could be the difference between success and failure.

In their new study, published in the leading international journal the American Journal of Physiology - Endocrinology & Metabolism, the scientists assessed the impact of endurance exercise on liver glycogen levels (stored carbohydrates in the body) and tested what could be done to prevent fatigue.

They tested various sucrose- and glucose-based drinks to see how different carbohydrates could help. Their experiment, conducted on long-distance cyclists, showed that ingesting carbohydrates in the form of either glucose or sucrose prevents the decline in liver glycogen 'carbohydrate stores' and can avert tiredness.

Both sucrose - in the form of table sugar - and glucose are important carbohydrates often referred to as 'simple sugars'. The major difference between them is that each sucrose molecule is made up of one glucose and one fructose molecule linked together. It appears combining different sources of sugars improves the rate at which we can absorb these from the gut.

Although an increasing number of sports-performance drinks designed to provide energy during exercise now use sucrose, or mixtures of glucose and fructose, many still rely on glucose alone. The researchers warn that such glucose-only drinks could produce gut discomfort and suggest sucrose-based alternatives, or sugar in water, can help make exercise easier.

Lead researcher Dr Javier Gonzalez explained: "The carbohydrate stores in our liver are vitally important when it comes to endurance exercise as they help us to maintain a stable blood sugar level. However, whilst we have a relatively good understanding of the changes in our muscle carbohydrate stores with exercise and nutrition, we know very little about optimising liver carbohydrate stores during and after exercise.

"Our study showed that ingesting carbohydrates during exercise can prevent the depletion of carbohydrate stores in the liver but not in muscle. This may be one of the ways in which carbohydrate ingestion improves endurance performance.

"We also found that the exercise felt easier, and the gut comfort of the cyclists was better, when they ingested sucrose compared to glucose. This suggests that, when your goal is to maximise carbohydrate availability, sucrose is probably a better source of carbohydrate to ingest than glucose."

The scientists behind the new study recommend that if your goal is optimal performance during exercise lasting over two and half hours then consume up to 90g of sugar per hour - diluted to 8g sugar per 100ml.

*To find out more about this work and read the study 'Ingestion of Glucose or Sucrose Prevents Liver but not Muscle Glycogen Depletion During Prolonged Endurance-type Exercise in Trained Cyclists' see http://dx.doi.org/10.1152/ajpendo.00376.2015.*

***http://www.eurekalert.org/pub_releases/2015-11/uoms-nsa112515.php***

## New study: Air evacuation may do further harm in patients with brain injury

***Findings could have major implications for treatment of military injuries***

Baltimore, MD – Over the past 15 years, more than 330,000 U.S. soldiers have suffered a traumatic brain injury (TBI). It is one of the leading causes of death and disability connected to the country's recent conflicts in Afghanistan and Iraq. Many of these patients were evacuated by air from these countries to Europe and

the U.S. for further treatment. In general, these patients were flown quickly to hospitals outside the battle zone, where more extensive treatment was available.

But now a new study by researchers at the University of Maryland School of Medicine has found evidence that such air evacuations may pose a significant added risk, potentially causing more damage to already injured brains. The study is the first to suggest that air evacuation may be hazardous for TBI patients. The study was published today in the Journal of Neurotrauma.

"This research shows that exposure to reduced barometric pressure, as occurs on military planes used for evacuation, substantially worsens neurological function and increases brain cell loss after experimental TBI - even when oxygen levels are kept in the normal range. It suggests that we need to carefully re-evaluate the cost-benefit of air transport in the first days after injury," said lead researcher Alan Faden, MD, the David S. Brown Professor in Trauma in the Departments of Anesthesiology, Anatomy & Neurobiology, Neurology, and Neurosurgery, and director, Shock, Trauma and Anesthesiology Research Center (STAR) as well as the National Study Center for Trauma and Emergency Medical Services.

About a quarter of all injured soldiers evacuated from Afghanistan and Iraq have suffered head injuries.

Faden and his colleagues tested rats that were subjected to TBI, using a model that simulates key aspects of human brain injury. Animals were exposed to six hours of lowered air pressure, known as hypobaria, at levels that simulated conditions during transport; control animals were exposed to normal pressure. All the animals received extra oxygen to restore normal oxygen concentrations in the blood. In another study, animals received oxygen, either as in the first study or at much higher 100 percent concentration, which is often used during military air evacuations. On its own, low air pressure worsened long-term cognitive function and increased chronic brain inflammation and brain tissue loss. Pure oxygen further worsened outcomes.

Faden and his colleagues believe the findings raise concerns about the increased use of relatively early air evacuation, and suggest that this potential risk should be weighed against the benefits of improved care after evacuation. It may be necessary, he says, to change the current policy for TBI patients and delaying air evacuation in many cases.

In an accompanying editorial, Patrick Kochanek, MD, a leading expert on TBI and trauma care at the University of Pittsburgh, called the findings "highly novel and eye-opening," and said that they could have "impactful clinical relevance for the field of traumatic brain injury in both military and civilian applications."

Faden and colleagues believe that one of the mechanisms by which hypobaria worsens TBI is by increasing persistent brain inflammation after injury. They are currently examining how this process occurs and have tested treatments that can reduce the risks of air evacuation. Early results are promising. Scientists suspect that breathing pure oxygen could worsen TBI by increasing production of dangerous free radicals in the brain. After brain injury, these free radicals flood the site of injury, and pure oxygen may further boost these levels. Several recent studies from trauma centers, including from the R Adams Cowley Shock Trauma Center at the University of Maryland Medical Center, have found evidence that using 100 percent oxygen in trauma patients may be counterproductive.

*The research was funded by the U.S. Air Force.*

*"This research has the potential to connect bench to bedside in an important, potentially lifesaving way," said Dean E. Albert Reece, MD, PhD, MBA, who is also Vice President of Medical Affairs, the University of Maryland and the John Z. and Akiko Bowers Distinguished Professor. "Dr. Faden is part of an impressive group of scientists at the School who are helping to unlock the mysteries of the brain."*

***http://www.eurekalert.org/pub_releases/2015-11/uoc--neu112315.php***

## Newly evolved, uniquely human gene variants protect older adults from cognitive decline

### *Humans evolved unique gene variants that protect older adults from neurodegenerative disease, thus preserving their valuable contributions and delaying dependency*

Many human gene variants have evolved specifically to protect older adults against neurodegenerative and cardiovascular diseases, thus preserving their contributions to society, report University of California, San Diego School of Medicine researchers in the November 30 issue of Proceedings of the National Academy of Sciences.

"We unexpectedly discovered that humans have evolved gene variants that can help protect the elderly from dementia," said Ajit Varki, MD, Distinguished Professor of Medicine and Cellular and Molecular Medicine at UC San Diego School of Medicine, adjunct professor at the Salk Institute for Biological Studies and co-director of the UC San Diego/Salk Center for Academic Research and Training in Anthropogeny (CARTA). "Such genes likely evolved to preserve valuable and wise grandmothers and other elders, as well as to delay or prevent the emergence of dependent individuals who could divert resources and effort away from the care of the young." Varki led the study, along with Pascal Gagneux, PhD, associate professor of pathology and associate director of CARTA.

The standard model of natural selection predicts that once the age of reproduction ends, individuals die. That's because selection early in life strongly favors variants that benefit reproductive success, even at the cost of negative consequences late in

life -- one major reason we age. This is indeed the case in almost all vertebrates. Humans (and certain whales) are an exception to this rule, living decades beyond reproductive age. Such elders contribute to the fitness of younger individuals by caring for grandchildren and also by passing down important cultural knowledge. Age-related cognitive decline compromises these benefits, and eventually burdens the group with the need to care for dependent older members.

In this first-of-its kind discovery, Varki, Gagneux and their teams initially focused on the gene that encodes the CD33 protein. CD33 is a receptor that projects from the surface of immune cells, where it keeps immune reactions in check, preventing "self" attack and curtailing unwanted inflammation. Previous studies suggested that a certain form of CD33 suppresses amyloid beta peptide accumulation in the brain. Amyloid beta accumulation is thought to contribute to late-onset Alzheimer's disease, a post-reproductive condition that uniquely affects humans and is aggravated by inflammation and cerebral vascular disease.

The researchers compared CD33 regulation in humans and our closest living relatives, chimpanzees. They found that levels of the CD33 variant that protects against Alzheimer's are four-fold higher in humans than chimpanzees.

They also found human-specific variations in many other genes involved in the prevention of cognitive decline, such as APOE. The ancestral form of the gene, APOE4, is a notorious risk factor for Alzheimer's and cerebral vascular disease. But this study finds that variants APOE2 and APOE3 seem to have evolved to protect from dementia. All of these protective gene variants are present in Africa, and thus predate the origin of our species. This finding is in keeping with the valuable role of the elderly across human societies.

"When elderly people succumb to dementia, the community not only loses important sources of wisdom, accumulated knowledge and culture, but elders with even mild cognitive decline who have influential positions can harm their social groups by making flawed decisions," Gagneux said. "Our study does not directly prove that these factors were involved in the selection of protective variants of CD33, APOE and other genes, but it is reasonable to speculate about the possibility. After all, inter-generational care of the young and information transfer is an important factor for the survival of younger kin in the group and across wider social networks or tribes."

*Additional study co-authors include Flavio Schwarz, Stevan A. Springer, Tasha Altheide, Nissi M. Varki, all of UC San Diego.*

*This research was funded, in part, by the National Institutes of Health (grants P01HL107150 and R01GM095882) and the Harold and Leila Mathers Foundation.*

*Full study: http://doi.org/10.1073/pnas.1517951112*

***http://www.eurekalert.org/pub_releases/2015-11/giot-lb3112515.php***

## Looking back 3.8 billion years into the root of the 'Tree of Life'

***NASA-funded researchers at the Georgia Institute of Technology are tapping information found in the cells of all life on Earth, and using it to trace life's evolution.***

They have learned that life is a master stenographer - writing, rewriting and recording its history in elaborate biological structures.

Some of the keys to unlocking the origin of life lie encrypted in the ribosome, life's oldest and most universal assembly of molecules. Today's ribosome converts genetic information (RNA) into proteins that carry out various functions in an organism. But the ribosome itself has changed over time. Its history shows how simple molecules joined forces to invent biology, and its current structure records ancient biological processes that occurred at the root of the Tree of Life, some 3.8 billion years ago.

By examining variations in the ribosomal RNA contained in modern cells, scientists can visualize the timeline of life far back in history, elucidating molecular structures, reactions and events near the biochemical origins of life.

"Biology is a great keeper of records," said Loren Williams, a professor in the Georgia Tech School of Chemistry and Biochemistry, and principal investigator for the NASA Astrobiology Institute's Georgia Tech Center for Ribosome Adaptation and Evolution from 2009-2014. "We are figuring out how to read some of the oldest records in biology to understand pre-biological processes, the origin of life, and the evolution of life on Earth."

The study is scheduled to be reported November 30 in the Early Edition of the journal Proceedings of the National Academy of Sciences.

Like rings in the trunk of a tree, the ribosome contains components that functioned early on in its history. The center of the trunk records the tree's youth, and successive rings represent each year of the tree's life, with the outermost layer recording the present. Just as the core of a tree's trunk remains unchanged over time, all modern ribosomes contain a common core dating back 3.8 billion years. This common core is the same in all living organisms, including humans.

"The ribosome recorded its history," said Williams. "It accreted and got bigger and bigger over time. But the older parts were continually frozen after they accreted, just like the rings of a tree. As long as that tree lives, the inner rings will not change. The very core of the ribosome is older than biology, produced by evolutionary processes that we still don't understand very well."

While exploiting this record-keeping ability of the ribosome reveals how biology has changed over time, it can also point to the environmental conditions on Earth

in which that biology evolved, and help inform our search for life elsewhere in the Universe.

"This work enables us to look back in time past the root of the tree of life - the ancestor of all modern cells - to a time when proteins and nucleic acids had not yet become the basis for all biochemistry," said Carl Pilcher, interim director of the NASA Astrobiology Institute. "It helps us understand some of the earliest stages in the development of life on Earth, and can guide our search for extraterrestrial environments where life may have developed."

By rewinding, reverse engineering, and replaying this ancient ribosomal tape, researchers are uncovering the secrets of creation and are answering foundational, existential questions about our place in the Universe.

By studying more additions to the ribosome, the research team - with key contributions by Georgia Tech Research Scientist Anton Petrov - found "molecular fingerprints" that show where insertions were made, allowing them to discern the rules by which it grew. Using a technique they call the Structural Comparative Method, the researchers were able to model the ribosome's development in great detail.

"By taking ribosomes from a number of species - humans, yeast, various bacteria and archaea - and looking at the outer portions that are variable, we saw that there were very specific rules governing how they change," said Williams. "We took those rules and applied them to the common core, which allowed us to see all the way back to the first pieces of RNA."

Some clues along the way helped. For instance, though RNA is now responsible for creating proteins, the very earliest life had no proteins. By looking for regions of the ribosome that contain no proteins, the researchers could determine that those elements existed before the advent of proteins. "Once the ribosome gained a certain capability, that changed its nature," Williams said.

While the ribosomal core is the same across species, what's added on top differs. Humans have the largest ribosome, encompassing some 7,000 nucleotides representing dramatic growth from the hundred or so base pairs at the beginning.

"What we're talking about is going from short oligomers, short pieces of RNA, to the biology we see today," said Williams. "The increase in size and complexity is mind-boggling."

The researchers obtained their ribosomes from structure and sequence databases that have been produced to help scientists identify new species. Ribosomes can be crystallized, which reveals their three dimensional structures.

Beyond understanding how evolution played out over time, this knowledge of the ribosome's development could have more practical modern-day health applications.

"The ribosome is one of the primary target for antibiotics, so understanding its architecture and consistently throughout biology could be of great benefit," said Williams. "By studying the ribosome, we can start thinking about biology in a different way. We can see the symbiotic relationship between RNA and proteins."

As a next step, Williams and colleagues are now using experiments to verify what their model shows.

"We have a coherent and consistent model that accounts for all the data we have going all the way back to a form of biology that is very primitive compared to what we have now," Williams explained. "We plan to continue testing the predictions of the model."

*In addition to those already named, the research included Burak Gulen, Ashlyn Norris, Chad Bernier, Nicholas Kovacs, Kathryn Lanier, Stephen Harvey, Roger Wartell and Nicholas Hud from Georgia Tech, and George Fox from the University of Houston.*

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***http://www.eurekalert.org/pub_releases/2015-11/uoc--sfo113015.php***

## Safe form of estrogen helped multiple sclerosis patients avoid relapses in UCLA led clinical trial

***Estriol, taken along with conventional medications, helped patients with relapsing-remitting multiple sclerosis (RRMS) avoid relapses***

Taking the pregnancy hormone estriol along with their conventional medications helped patients with relapsing-remitting multiple sclerosis (RRMS) avoid relapses, according to results of a Phase II randomized, placebo-controlled study led by UCLA researchers.

The study, published online in Lancet Neurology, was truly translational. The UCLA team took observations from the bedside, tested them in the laboratory and took those findings back again to patients in clinical trials, said the study's lead author Dr. Rhonda Voskuhl, professor in the UCLA Department of Neurology and director of UCLA's Multiple Sclerosis Program.

It's long been observed that during the second half of pregnancy, women with RRMS have reduced relapses, but the reason was unclear. It is also during this period that the fetal placenta produces estriol, increasing the hormone levels in the blood. This protection during pregnancy occurs not only in MS, but also in other autoimmune diseases such as psoriasis and rheumatoid arthritis.

Voskuhl took this information to the lab. She hypothesized that increased estriol in the blood might play a role in suppressing a woman's immune system so that the fetus is not rejected as being foreign, having half of the father's proteins. This temporary suppression of the immune system would be good for pregnant mothers

with autoimmune diseases. Her team found that treatment with estriol was protective in the MS model. That led to a successful pilot clinical trial in 2002 at UCLA and then the Phase II trial, launched in 2007 at UCLA and 15 other sites across the United States.

"The beauty of estriol is that it is not a shot and can be taken in pill form, and also that it's not a new drug. It has decades of safety behind it," said Voskuhl, who holds the Jack H. Skirball Chair for Multiple Sclerosis in the UCLA Department of Neurology. "Also, current MS treatments are very complex to manufacture. These findings hopefully will pave the way for oral, safe treatments that are more widely accessible, since estriol is simple and naturally occurring."

Multiple sclerosis is an autoimmune disease of the central nervous system where immune cells from the blood attack the tissue surrounding the brain's nerve fibers. Called myelin, this tissue is like the insulation wrapped around an electrical wire. When the myelin is damaged, it interferes with the ability of the nerves to send signals to and from the brain, resulting in symptoms including cognitive problems, difficulty with walking, poor vision and other disabilities.

In RRMS, there are clear episodes of inflammatory activity, or relapses. During a relapse, there are new or worsening symptoms, accompanied by inflammatory lesions in the brain. A relapse can continue anywhere from several days to months. Relapses are usually followed by remission, or improvement. However, some residual symptoms may remain, and after many years people with RRMS often transition to a progressive form of the disease. During the progressive phase, there are no longer relapses, but instead gradual worsening of permanent disabilities and loss of brain volume or atrophy.

In the lab, Voskuhl and her team discovered that estriol potentially provides a one-two punch against the disease, both reducing the ability of immune cells to attack the brain, while also making brain cells more resistant to damage if any immune cells do make it through. Specifically, they showed that estriol treatment improved cognition and prevented atrophy of the cognitive region of the brain. It seems that during pregnancy, estriol can both suppress the immune system and protect the brain, for not only is it important to avoid rejection of the fetus as foreign, it is also critical to protect the developing fetal brain. While these two effects may be designed to protect the fetus, they may also be exactly what the doctor ordered for women with MS.

In 2002, Voskuhl completed the pilot study, in which 10 non-pregnant women with MS were given estriol, yielding a greater than 70 percent drop in inflammatory lesions in the brain within only six months of treatment.

In the Phase II study, researchers enrolled 164 patients, with 83 allocated to the estriol group and 81 to the placebo group. Both arms continued their conventional medication, injectable glatiramer acetate. The team found that the patients taking estriol had a third to a half as many relapses compared to those taking the placebo, with this improvement occurring over and above that provided by their conventional treatment. In addition, when estriol levels were the highest, there was improved cognitive function and less atrophy of the brain area related to cognition. The treatment was well tolerated during the two years the volunteers took estriol and the only significant side effect was irregular menstruation. To date, there is no FDA approved treatment for MS that improves disabilities.

These two trials are very unique in that neither were funded by a pharmaceutical company. Rather, they were funded by the National Institutes of Health (NIH) and the National Multiple Sclerosis Society, consistent with the new NIH policy that more research should focus on sex differences in disease. Additional major funding was from the Conrad N. Hilton Foundation, whose mission it is to improve the lives of disadvantaged people throughout the world. Synthetic Biologics, Inc., provided estriol and placebo for the multicenter trial and has licensed certain rights from UCLA.

Going forward, Voskuhl hopes to see a Phase III trial conducted to replicate these findings, since this is necessary for FDA approval of estriol for MS. She continues to seek support to advance this as well as other MS research projects.

It is estimated that more than 2.1 million people are affected by MS worldwide. Approximately 85 percent of patients are diagnosed at onset with RRMS, the most common form of MS.

***http://bit.ly/1NuLdHp***

## Scans prove there's no such thing as a 'male' or 'female' brain

***Scans prove there's no such thing as a 'male' or 'female' brain***

You may have read that having a male brain will earn you more money. Or maybe that female brains are better at multitasking. But there is no such thing as a female or male brain, according to the first search for sex differences across the entire human brain. It reveals that most people have a mix of male and female brain features. And it also supports the idea that gender is non-binary, and that gender classifications in many situations are meaningless.

"This evidence that human brains cannot be categorised into two distinct classes is new, convincing, and somehow radical," says Anelis Kaiser at the University of Bern, Switzerland. The idea that people have either a "female" or "male" brain is an old one, says Daphna Joel at Tel Aviv University in Israel. "The theory goes that once a fetus develops testicles, they secrete testosterone which masculinises the brain," she says. "If that were true, there would be two types of brain."

To test the theory, Joel and her colleagues looked for differences in brain scans taken from 1400 people aged between 13 and 85. The team looked for variations

in the size of brain regions as well as the connections between them. In total, the group identified 29 brain regions that generally seem to be different sizes in self-identified males and females. These include the hippocampus, which is involved in memory, and the inferior frontal gyrus, which is thought to play a role in risk aversion.

When the group looked at each individual brain scan, however, they found that very few people had all of the brain features they might be expected to have, based on their sex. Across the sample, between 0 and 8 per cent of people had "all-male" or "all-female" brains, depending on the definition. "Most people are in the middle," says Joel.

This means that, averaged across many people, sex differences in brain structure do exist, but an individual brain is likely to be just that: individual, with a mix of features. "There are not two types of brain," says Joel.

**Spatial awareness**

Although the team only looked at brain structure, and not function, their findings suggest that we all lie along a continuum of what are traditionally viewed as male and female characteristics. "The study is very helpful in providing biological support for something that we've known for some time – that gender isn't binary," says Meg John Barker, a psychologist at the Open University in Milton Keynes, UK.

The findings will still come as a surprise to many, including scientists, says Bruce McEwen at the Rockefeller University in New York. "We are beginning to realise the complexity of what we have traditionally understood to be 'male' and 'female', and this study is the first step in that direction," he says. "I think it will change peoples' minds."

Markus Hausmann at Durham University, UK, isn't surprised by the findings, however. He has been studying sex differences in cognition, such as whether men, as commonly believed, really do have better spatial awareness than women.

"Across all kinds of spatial skills, we find very, very few that are sensitive to sex," says Hausmann. "We have also identified spatial problems where women outperform men – the black-and-white idea of a male or female brain is clearly too simple."

**Cultural expectations**

Despite persisting stereotypes, girls are no worse than boys at science and maths subjects, either. "People get wedded to the idea that being male or female is highly predictive of having different aptitudes or career choices," says Margaret McCarthy, who studies brain sex differences at the University of Maryland School of Medicine in Baltimore. "This study fights against the idea that these outcomes are based on biological differences, as opposed to cultural expectations." Other body systems are also often wrongly considered to be either male or female, says Joel.

Alexandra Kautzky-Willer, head of the Gender Medicine Unit at the Medical University of Vienna in Austria, agrees that things aren't so simple. "There are differences between men and women when you look in large groups, and these are important for diagnosis and treatment," she says. "But there are always more differences within genders. We always need to look at culture, environment, education and a person's role in society," she says.

If a neuroscientist was given someone's brain without their body or any additional information, they would still probably be able to guess if it had belonged to a man or a woman. Men's brains are larger, for example, and are likely to have a larger number of "male" features overall. But the new findings suggest that it is impossible to predict what mix of brain features a person is likely to have based on their sex alone.

**Genderless future**

Joel envisions a future in which individuals are not so routinely classified based on gender alone. "We separate girls and boys, men and women all the time," she says. "It's wrong, not just politically, but scientifically – everyone is different."

But other scientists contacted by New Scientist don't think that will ever be possible – as a sexually reproductive species, identifying a person's biological sex will always be of paramount importance to us, they say.

Even so, Joel's findings can be used to help many people understand the non-binary nature of gender, says Barker. After all, some people don't identify as either male or female, and others feel their gender identity shift over time. "It's a shame that people's experience alone isn't enough for us to recognise as a society that non-binary gender is legitimate."

"We need to start thinking a lot more carefully about how much weight we give to gender as a defining feature of human beings, and stop asking for it in situations where it simply isn't relevant," says Barker.

*Ref: PNAS, DOI: 10.1073/pnas.1509654112*

***http://www.eurekalert.org/pub_releases/2015-12/nrts-ccc113015.php***

## Chemotherapy can cause tumor evolution

***Russian scientists have found that neoadjuvant chemotherapy in patients with breast cancer can stimulate evolution of the tumor.***

The results of the research conducted by Nicholay Litvyakov, D.Sc. at Cancer Research Institute, Head of the Tumor Virology Laboratory, and TSU researcher Marina Ibragimova, were published in "Siberian Journal of Oncology."

Scientists conducted a study in which they analyzed biopsies of women with breast cancer and preparing for operation. In each biopsy, researchers examined the genetic landscape - chromosomal abnormalities that are present in it.

Before the operation, the women received 2-4 courses of neoadjuvant chemotherapy (NAC). Repeated analyzes were taken after surgery to see the therapy effect on the tumor.

TSU scientists have found that chemotherapy fully or partially destroyed the tumor clones in the majority of patients, but 23% of women surveyed showed new tumor formation under the influence of NHT. Some chromosomes or parts of them doubled in these clones, and the tumor cells became more resistant. This phenomenon is called amplification, and is a negative consequence of chemotherapy - almost all of these patients experienced development of metastases, while the remaining patients had not metastases in the five-year period of observation.

The researchers concluded that under the influence of chemotherapy it is possible to stimulate the evolution of a resistant tumor - one that does not respond to the effects of chemotherapy.

- We have preliminary results indicating that chemotherapy may cause the appearance of mutations which had not been observed before in the form of amplifications of chromosomal regions. In some cases it was a reason for occurrence of hematogenous metastasis - says Marina Ibragimova. We should find out the causes and methods for anticipating tumor development. Thus there is no doubt that chemotherapy shall have strictly personalized character, depending on the properties of tumor and patient.

Most of chemotherapy drugs are inherently mutagens; chemotherapy may cause genetic disorders in tumor cells. These genetic disorders may lead to illumination of tumor cells or to their changes. Thus we can observe occurrence of "clones" of the tumor cells, which are able to cope with the chemotherapy. Nowadays the researchers attempt to discover in which cases and how the tumor may develop under effect of chemotherapy.

That is very interesting observation, - says Marina Ibragimova. - Now we are extending our samples in order to check these observations. If we succeed we would create a technology allowing to predict development of tumor in a specific patient and to define whether this patient needs chemotherapy and which medicines should be prescribed.

Obtained results will help to personalize treatment process for woman with breast cancer. For now chemotherapy is one of the main tumor treatment instruments for the oncologists. Report on this topic was held at the plenary session of the 19th Russian Cancer Congress http://www.rosoncoweb.ru/news/society/2015/11/17-1/.

http://www.eurekalert.org/pub_releases/2015-12/e-tad120115.php

## The accidental discovery of how to stay young for longer

***Scientists extend young adulthood in worms and discover new metric to track aging***

Living longer usually means a longer dotage, but wouldn't it be enticing to extend young adulthood instead? It's such an appealing prospect that scientists who are announcing success with roundworms are keen to be clear they are a long way from achieving it in humans.

"We don't want people to get the impression they can take the drug we used in our study to extend their own teens or early twenties," says lead author Michael Petrascheck from The Scripps Research Institute (TSRI), California.

"We may have done this in worms, but there are millions of years of evolution between worms and humans. "We think it is exciting to see that extending lifespan by extending young adulthood can be done at all," he says.

In the study to be published in the journal eLife, the TSRI-led team administered an antidepressant called mianserin to Caenorhabditis elegans, a type of roundworm used frequently in research. In 2007, they discovered that the drug increases the lifespan of roundworms by 30-40 per cent. Their new goal was to investigate how.

The team treated thousands of worms with either water or mianserin and looked at the activity of genes as the worms aged. First, they measured the activity of genes in young adults as a reference point against which to monitor the aging process. Reproductive maturity begins in day-old roundworms and they live for 2-3 weeks on average. As the worms aged, the team observed dramatic changes in gene expression. However, the changes occurred in a way that came as a complete surprise. Groups of genes that together play a role in the same function were found to change expression in opposing directions.

They have called this newly-discovered phenomenon 'transcriptional drift'. By examining data from mice and from 32 human brains aged 26 to 106 years, they confirmed that it also occurs in mammals.

"The orchestration of gene expression no longer seemed coordinated as the organism aged and the results were confusing because genes related to the same function were going up and down at the same time," says Petrascheck.

"Transcriptional drift can be used as a new metric for measuring age-associated changes that start in young adulthood," says first author Sunitha Rangaraju.

"Until now we have been dependent on measuring death rates, which are too low in young adults to provide much data. Having a new tool to study aging could help us make new discoveries, for example to treat genetic predispositions where aging starts earlier, such as Hutchinson-Gilford progeria syndrome," she says.

Using this new metric revealed that treatment with mianserin can suppress transcriptional drift, but only when administered at the right time of life. By 10 days old, treated worms still had the gene expression characteristics of a three-day-old -- physiologically they were seven days younger. But by 12 days, the physiological changes required to extend lifespan were complete and lifelong exposure to the drug had no additional effect. Mortality rates were shifted parallel by 7-8 days across the treated worms' lifespan, confirming the finding.

Mianserin blocked signals related to the regulation of serotonin and this delayed physiological changes associated with age, including the newly-identified transcriptional drift and degenerative processes that lead to death. The effect only occurred during young adulthood and the duration of this period of life was significantly extended.

"How much of our findings with regards to lifespan extension will spill over to mammals is anyone's guess, for example the extension of lifespan might not be as dramatic," says Petrascheck. "However, we are already excited about the fact that we observed the phenomenon of transcriptional drift in species ranging from worms, mice to humans."

The findings have opened up many new avenues of research for the team and are likely to spawn a wealth of research by others. For example, a significant next step for the team will be to test the effect in mice and to investigate whether there are any side effects. Different environments could produce different results and this will need to be explored. They would also like to test whether the impact is different for different organs in the body.

The discovery of 'transcriptional drift' raises the prospect of the phenomenon providing a new general metric for aging, but again this requires further research.

In terms of extending teenage and young adult life in humans, just the idea invites a wealth of questions about the potential social implications and whether this would be as desirable as it first seems.



**http://www.eurekalert.org/pub_releases/2015-12/nu-t2d113015.php**

## Type 2 diabetes reversed by losing fat from pancreas

***A team from Newcastle University, UK, has shown that Type 2 diabetes is caused by fat accumulating in the pancreas -- and that losing less than one gram of that fat through weight loss reverses the diabetes.***

Affecting two and a half million people in the UK -- and on the increase -- Type 2 diabetes is a long-term condition caused by too much glucose, a type of sugar, in the blood. The research led by Professor Roy Taylor is being published online today in Diabetes Care and simultaneously he is presenting the findings at the World Diabetes Conference in Vancouver.

**Bariatric surgery**

In a trial, 18 people with Type 2 diabetes and 9 people who did not have diabetes were measured for weight, fat levels in the pancreas and insulin response before and after bariatric surgery. The patients with Type 2 diabetes had been diagnosed for an average of 6.9 years, and all for less than 15 years. The people with Type 2 diabetes were found to have increased levels of fat in the pancreas.

The participants in the study had all been selected to have gastric bypass surgery for obesity and were measured before the operation then again eight weeks later. After the operation, those with Type 2 diabetes were immediately taken off their medication.

Both groups lost the same amount of weight, around 13% of their initial body weight. Critically, the pool of fat in the pancreas did not change in the non-diabetics but decreased to a normal level in those with Type 2 diabetes.

This shows that the excess fat in the diabetic pancreas is specific to Type 2 diabetes and important in preventing insulin being made as normal. When that excess fat is removed, insulin secretion increases to normal levels. In other words, they were diabetes free.

**Drain excess fat out of the pancreas**

Professor Taylor of Newcastle University who also works within the Newcastle Hospitals as part of the Newcastle Academic Health Partners said: "For people with Type 2 diabetes, losing weight allows them to drain excess fat out of the pancreas and allows function to return to normal.

"So if you ask how much weight you need to lose to make your diabetes go away, the answer is one gram! But that gram needs to be fat from the pancreas. At present the only way we have to achieve this is by calorie restriction by any means -- whether by diet or an operation."

In patients who had started with Type 2 diabetes, fat levels in the pancreas (pancreatic triglyceride) decreased by 1.2% over the 8 weeks. Very exact methods were needed to be able to measure this and a new method using a special MRI scan was developed. With an average pancreas for a person with Type 2 diabetes having a volume of 50 ml, this is the equivalent of around 0.6 grams of fat.

However, the patients who had never had diabetes saw no change in the level of fat in their pancreas demonstrating that the increase in fat in the pancreas is specific to people who develop Type 2 diabetes. Importantly, individuals vary in how much fat they can tolerate in the pancreas before Type 2 diabetes occurs.

**Transforming the thinking on Type 2 diabetes**

Traditionally, Type 2 diabetes has been thought of as a progressive condition, controlled by diet initially then tablets, but which may eventually require insulin injections.

It affects 9% of the global population and was once known as adult-onset diabetes but is now found in young adults and children. It causes too much glucose in the blood due to the pancreas not producing enough insulin -- a hormone which breaks down glucose into energy in the cells -- together with insulin resistance, a condition in which the body responds poorly to insulin.

Previous work by Professor Taylor and his team highlighted the importance of weight loss through diet in reversing Type 2 diabetes. This work in 2011 transformed the thinking in diabetes as it was the first time that it had been demonstrated that diet could remove fat clogging up the pancreas allowing normal insulin secretion to be restored.

Professor Taylor adds: "This new research demonstrates that the change in level of fat in the pancreas is related to the presence of Type 2 diabetes in a patient. The decrease in pancreas fat is not simply related to the weight loss itself. It is not something that might happen to anyone whether or not they had diabetes. It is specific to Type 2 diabetes.

"What is interesting is that regardless of your present body weight and how you lose weight, the critical factor in reversing your Type 2 diabetes is losing that 1 gram of fat from the pancreas."

Newcastle Academic Health Partners is a collaboration involving Newcastle University, Newcastle Upon Tyne Hospitals NHS Foundation Trust and Northumberland, Tyne and Wear NHS Foundation Trust. This partnership harnesses world-class expertise to ensure patients benefit sooner from new treatments, diagnostics and prevention strategies.

*Information on the diet that can reverse diabetes and an information sheet for medical teams can be found here: http://www.ncl.ac.uk/magres/research/diabetes/reversal.htm*
*http://www.ncl.ac.uk/icm/people/profile/roy.taylor*
*http://www.ncl.ac.uk/press/news/2015/10/type2diabetes/*

***http://www.eurekalert.org/pub_releases/2015-12/uod-ccc113015.php***

## Cancer cells can poison normal cells

***Like bacteria and viruses, cancer cells have the potential to infect normal cells and promote cancer progression.***

Cancer cells are continuously produced in our bodies, where most of them are recognized by our immune systems and destroyed. Some, however, escape this innate surveillance system and find a place to survive and grow.

Several factors expelled by tumor cells are concentrated in the area immediately surrounding the tumor, called the tumor microenvironment. While it is established that these factors support and enhance cancer cell growth and multiplication, it was not known whether these factors influence neighboring normal cells.

Now a team of researchers from the University of Delaware, Nemours/A.I. duPont Hospital for Children, St. Joseph's Hospital and Medical Center in Phoenix and Therapy Architects LLC in Wilmington, Delaware, has reported that cancer cells can actually cause neighboring normal cells to become cancerous. The research is documented in the current online edition of the Journal of Cell Science.

The researchers used a three-dimensional co-culture system where they grew normal cells and cancer cells together, mimicking the situation inside the body.

They found that cancer cells produce an enzyme--a protease--which splits a cell-cell adhesion molecule called E-cadherin from normal cells. The action of the protease liberates the segment of E-cadherin that projects outside the cells. This segment, designated soluble E-cadherin, or sE-cad, then associates with a signaling molecule called epidermal growth factor receptor on normal cells and converts them to cancerous cells.

"The serum of adult cancer patients contains high levels of sE-cad," says Pratima Patil, who received her doctorate in biological sciences from the University of Delaware earlier this year. "Our finding documents that tumor cells modify normal epithelial cells, disrupting their cellular architecture, and use them as accomplices to generate sE-cad, which is known to facilitate tumor progression."

Ayyappan Rajasekaran, University of Delaware adjunct professor in materials science and engineering and president of Therapy Architects, says this is the first time research has demonstrated that a cancer cell can sequentially induce early and late stages of cancer development in neighboring normal cells--a fundamental finding that can inform future studies.

"Like bacteria and viruses, cancer cells have the potential to infect normal cells and promote cancer progression," he adds.

This finding opens up new cancer research areas, including determining how cancer cells interact with neighboring normal cells and promote cancer development.

From a clinical perspective, the discovery raises the question of whether reducing sE-cad levels in cancer patients will slow the progression of cancer and improve treatment options. "These future studies should give a new dimension to our understanding of cancer development and treatment," Rajasekaran says.

*The paper, "Carcinoma Cells Induce Lumen Filling and EMT in Epithelial Cells by soluble E-cadherin-Mediated Activation of EGFR," was co-authored by Pratima Patil, Julia D'Ambrosio, Landon Inge, Robert Mason, and Ayyappan Rajasekaran.*

*This research was supported by funds from the National Institutes of Health (NIH grant DK56216), Nemours Research Programs and COBRE grant P20GM103464.*

http://www.eurekalert.org/pub_releases/2015-12/au-ndt120115.php

# New discovery: This is why we do not constantly get ill despite viruses and bacteria

***New research breaks with existing knowledge about how our immune system works.***

Experiments at Aarhus University have shown how the body mobilises a hitherto unknown defence against viruses and bacteria. This also explains why we do not constantly get ill despite the viruses around us.

Fever, sore muscles and other influenza-like symptoms are typical signs that your immune system is fighting against viruses and bacteria. The unpleasant condition is, among other things, due to the body forming a substance called interferon, which must defeat the virus. For many years researchers and doctors have assumed that this was the body's earliest response when attacked by various infections.

But new research shows that the body's very first defence mechanism is not interferon, but rather a hitherto unknown mechanism, which begins working even earlier.

The newly discovered immune reaction is activated when the body's mucous membranes are disrupted, as they are when viruses and bacteria attempt to establish an infection. The immune system recognises the virus and produces a substance that neutralises the uninvited guest. The process goes on continuously without us being aware of it. If this first immune reaction is not sufficient to suppress the virus, the infection establishes itself in the body. This in turn triggers the next reaction involving interferon, which not only helps to fight the virus, but also means we become ill. The discovery has just been published in the scientific journal Nature Immunology.

**Alters our understanding of the immune system**

The discovery alters the way in which researchers and doctors previously understood the immune system.

"Our study fundamentally alters our understanding of how the body begins its defence against viruses. This can help to explain how we can be constantly exposed to the viruses and bacteria that always surround us, without activating the entire immune system every time, something that would lead to more frequent influenza-like symptoms," says Soren Riis Paludan, professor at the Department of Biomedicine at Aarhus University.

He has headed the research project in Aarhus, while also collaborating with researchers from the University of Copenhagen as well as from universities in the USA and Germany.

**May explain serious diseases**

Experiments on mice have shown that mice, lacking this first defence mechanism, become ill if they are exposed to herpes virus, while normal mice remain healthy.

"We do not yet know the precise significance of this mechanism, but it may explain why some people become more ill from viral infections such as influenza than others. The same may apply to other viral infections that are initiated on mucous membranes such as HIV and herpes. We will now begin to map out the molecules that are involved. Once we have done this, it will be possible to identify people with defects in the mechanism, just as there is a potential to develop new forms of treatment. At the same time, the mechanism may turn out to have significance also for non-viral diseases, so continued research into this area shows great potential," says Soren Riis Paludan.

*The Danish Council for Independent Research's Sapere Aude programme, as well as the Lundbeck Foundation and the Novo Nordisk Foundation, have financed the research.*

*Read the scientific article "An innate antiviral pathway acting before interferons at epithelial surfaces" in Nature Immunology.*

http://www.eurekalert.org/pub_releases/2015-12/ncsu-rco120115.php

# Researchers confirm original blood vessels in 80 million-year-old fossil

***Confirmation that blood vessel-like structures in an 80 million-year-old fossil are original to the animal, and not biofilm or other contaminants***

***Blood vessels from demineralized bone of Brachylophosaurus canadensis are shown.***
**M. Schweitzer, NC State University**

Researchers from North Carolina State University have. Their findings add to the growing body of evidence that structures like blood vessels and cells can persist over millions of years, and the data not only confirm earlier reports of protein sequences in dinosaurs, they represent a significant advance in methodology.

Molecular paleontologist Tim Cleland, currently a postdoctoral researcher at the University of Texas at Austin, began the work while a graduate student at NC State. He demineralized a piece of leg bone from a Brachylophosaurus canadensis, a 30-foot-long hadrosaur that roamed what is now Montana around 80 million years ago. Cleland analyzed the demineralized bone with high resolution mass spectroscopy and found several distinct proteins from the cellular components of

the blood vessels. One of these proteins, myosin, is found in the smooth muscles associated with the walls of blood vessels.

The researchers confirmed their results by performing the same process with bones from modern archosaurs, such as chicken and ostrich, which are living relatives of the dinosaurs. In both the modern and ancient samples, peptide sequences matched those found in blood vessels. Their methodology also allowed the researchers to validate previously reported sequences and recover additional sequences because only the vessels were extracted, which increased the observance of cellular proteins.

"This study is the first direct analysis of blood vessels from an extinct organism, and provides us with an opportunity to understand what kinds of proteins and tissues can persist and how they change during fossilization," Cleland says. "This will provide new avenues for pursuing questions regarding the evolutionary relationships of extinct organisms, and will identify significant protein modifications and when they might have arisen in these lineages."

Elena Schroeter, a postdoctoral researcher at NC State, is a co-author who worked on the analysis of the mass spectrometry data. "Paleoproteomics is a challenging pursuit. It requires us to think about how to support our conclusions from different angles," says Schroeter. "This project is significant because it shows the power of using multiple experimental methods--as well as multiple ways to analyze the results of those methods--to address a scientific question."

"Part of the value of this research is that it gives us insight into how proteins can modify and change over 80 million years," says Mary Schweitzer, a molecular paleontologist at NC State and co-author of the paper describing the research. "It tells us not only about how tissues preserve over time, but gives us the possibility of looking at how these animals adapted to their environment while they were alive."

*The findings appear in the Journal of Proteome Research. The research was funded by the NSF (EAR 0541744, DGE-0750733) and the David and Lucile Packard Foundation. The dinosaur sample was provided by the Museum of the Rockies. Neil Kelleher, Paul Thomas, Dorothy Ahlf, and John Tran from Northwestern University, Leonid Zamdborg and Ji Eun Lee at University of Illinois-Urbana-Champaign, and Marshall Bern at Protein Metrics were critical for the development of mass spectrometry techniques and analysis used. Raghu Kalluri, Michael Duncan, and Valerie Lebleu from Harvard University and Megan Zheng at NC State provided key insights into conducting the immunological staining of the blood vessels.*

*"Mass Spectrometry and Antibody-based Characterization of Blood Vessels from Brachylophosaurus Canadensis" DOI: 10.1021/acs.jproteome.5b00675*

http://www.eurekalert.org/pub_releases/2015-12/uocb-rda120215.php

## Researchers develop antibody to save cancerous bones

***Treatment with a specific antibody reduces up to 80% of bone degradation***

Bone Cancer Primary bone cancer called Osteosarcoma (OS) is a rare cancer most often affecting adolescents and children. While most bone cancers have their origin in other body tissues and spread to the bones through metastases, OS originates in the bone tissue. Common for all, is that they degrade the bones and are associated with high mortality.

At the Finsen Laboratory, Rigshospitalet and BRIC, University of Copenhagen a research group lead by Dr. Niels Behrendt and Dr. Lars Engelholm now shows that OS cells degrade the bone tissue through a completely different process than metastasised bone cancer. Through treatment with a specific antibody, the researchers blocked the process and reduced up to 80% of bone degradation in a cancer mouse model. Future treatment of OS patients with this type of antibody could reduce amputations among young patients and future studies will clarify if such a treatment strategy will also block lethal spreading of the OS cells to other organs.

**Specialised cancer cells do their own dirty work**

When cancer cells from eg breast or lung tumours invade the bones through metastasis, the bone tissue is degraded. Metastasized cancer cells then stimulate other cells in the bones to degrade the bone tissue, a mechanism also believed to take place in OS. However, examining OS tumours the research team behind the new results found that OS cancer cells express special enzymes and receptors, enabling them to degrade bone tissue themselves.

'By treating mice with OS with the new antibody, we could block the micro processes OS cells use to degrade the bones and thereby effectively protect the bone tissue', explains Lars Engelholm.

**Antibody treatment may reduce amputations**

The research team has great hopes for the use of this new type of antibody in development of new treatment for OS patients.

- A large proportion of new targeted cancer therapies are based on antibodies. We developed this antibody for basic studies of the molecule uPARAP, but when we discovered shown that this molecule is upregulated in OS tumours, we became interested in the possible treatment effect, says Niels Behrendt.

Treatment of OS includes removal of the cancerous bone. To prevent complete amputation of arms or legs, pre-treatment with chemotherapy is used to shrink the tumour before operation. Limitation of bone degradation in this pre-treatment period is crucial and where the researchers see a clear potential for their finding.

Surgeon Clement Trovik from Haukeland University hospital in Bergen, collaborator on the research project states:

'For cancer patients, especially children and young adults, amputation of an arm or a leg is a very serious consequence of illness and we have for years been searching for therapeutics to prevent cancer-induced bone degradation. These new results show promising results for such future treatments'. Treatment with the new antibody will - in addition to the traditional treatment enable us to save more bone tissue for reconstruction and thereby prevent amputations.

**uPARAP**

Tumor cells in primary bone cancer degrade bone tissue by means of specialised enzymes and receptor proteins. A receptor is a molecule placed on the cell membrane which, in some cases, can direct material from the surroundings to be taken up by the cell and degraded, In the degradation of bone tissue, the receptor uPARAP plays a central role. It has long been known that uPARAP is active in bone growth and development in the healthy body. Cancer cells acquire their destructive ability through an abuse of the same mechanisms that are involved in the normal development of the same tissues and organs.

***http://www.eurekalert.org/pub_releases/2015-12/uow-tsc120115.php***

## The Sun could release flares 1000x greater than previously recorded

***University of Warwick researchers suggest the similarity between the flare on KIC9655129 and our own Sun's flares demonstrates the potential for the Sun to superflare***

The Sun demonstrates the potential to superflare, new research into stellar flaring suggests.

Led by the University of Warwick, the research has found a stellar superflare on a star observed by NASA's Kepler space telescope with wave patterns similar to those that have been observed in solar flares.

Superflares are thousands of times more powerful than those ever recorded on the Sun, and are frequently observed on some stars.

Found in the Milky Way, the binary star, KIC9655129, is known to superflare. The researchers suggest due to the similarities between the superflare on KIC9655129 and the Sun's solar flares, the underlying physics of the flares might be the same, supporting the idea that our Sun could also produce a superflare.

Typical solar flares can have energies equivalent to a 100 million megaton bombs, but a superflare on the Sun could release energy equivalent to a billion megaton bombs.

If the Sun were to superflare the Earth's communications and energy systems could be at serious risk of failing.

Lead researcher, Chloë Pugh from the University of Warwick's Centre for Fusion, Space and Astrophysics, explains:

"Our solar system is filled with plasma, or ionised gas, originating from the Sun as a result of the solar wind and other more violent solar eruptions, such as solar flares. Stars very similar to the Sun have been observed to produce enormous flares, called superflares. To give us a better indication of whether the Sun could produce a catastrophic superflare, we need to determine whether the same physical processes are responsible for both stellar superflares and solar flares.

"Solar flares are commonly observed to consist of a series of regularly occurring pulses. Often these pulsations resemble waves, with a wavelength that relates to various properties of the region of the Sun that is producing the flare. The study of waves such as these is referred to as coronal seismology. Occasionally solar flares contain multiple waves superimposed on top of one another, which can easily be explained by coronal seismology. We have found evidence for multiple waves, or multiple periodicities, in a stellar superflare, and the properties of these waves are consistent with those that occur in solar flares.

Discussing the potential consequences of the Sun superflaring, Chloë Pugh says:

"If the Sun were to produce a superflare it would be disastrous for life on Earth; our GPS and radio communication systems could be severely disrupted and there could be large scale power blackouts as a result of strong electrical currents being induced in power grids.

"Fortunately the conditions needed for a superflare are extremely unlikely to occur on the Sun, based on previous observations of solar activity."

The researchers used time series analysis to detect wave patterns in the light curve of a flare emanating from KIC9655129, using data collected by the Kepler space telescope. Research co-author Dr Anne-Marie Broomhall from the University of Warwick explains:

"When a flare occurs we typically see a rapid increase in intensity followed by a gradual decline. Usually the decline phase is relatively smooth but occasionally there are noticeable bumps, which are termed 'quasi-periodic pulsations' or QPPs. We used techniques called wavelet analysis and Monte Carlo modelling in order to assess the periodicity and statistical significance of these QPPs."

The researcher's analysis revealed not one but two significant periodicities, with less than a 1% probability that these pulsations would be observed by chance.

"We then fitted a model to the flare light curve that described both the exponential decay phase and the two periodicities. The periods were found to be 78 minutes

and 32 minutes respectively. The properties of the periodicities, such as their decay times, imply that the two periodicities are independent", says Dr Broomhall. "The most plausible explanation for the presence of two independent periodicities is that the QPPs were caused by magnetohydrodynamic (MHD) oscillations, which are frequently observed in solar flares. This result is, therefore, an indication that the same physical processes are involved in both solar flares and stellar superflares. The latter finding supports the hypothesis that the Sun is able to produce a potentially devastating superflare".

*The research, A Multi-Period Oscillation in a Stellar Superflare, is published by The Astrophysical Journal Letters and was funded by a European Research Council project led by Professor Valery M. Nakariakov.*

***http://www.eurekalert.org/pub_releases/2015-12/acs-cct120215.php***

## Coffee compounds that could help prevent type 2 diabetes identified

***Much to coffee lovers' delight, drinking three to four cups of coffee per day has been shown to decrease the risk of developing type 2 diabetes.***

Now, scientists report in ACS' Journal of Natural Products that they have identified two compounds that contribute to this health benefit. Researchers say that this knowledge could someday help them develop new medications to better prevent and treat the disease.

Patients with type 2 diabetes become resistant to insulin, a hormone that helps turn glucose from food into energy. To overcome this resistance, the pancreas makes more insulin, but eventually, it just can't make enough. High blood glucose levels can cause health problems, such as blindness and nerve damage. Several genetic and life style risk factors have been linked to the development of type 2 diabetes, but drinking coffee has been shown to help prevent its onset. Caffeine was thought to be responsible, but studies have shown it has only a short-term effect on glucose and insulin, and decaffeinated coffee has the same effect as the regular version of the drink. To investigate which of coffee's many bioactive components are responsible for diabetes prevention, Søren Gregersen and colleagues tested the effects of different coffee substances in rat cell lines.

The researchers investigated different coffee compounds' effects on cells in the lab. Cafestol and caffeic acid both increased insulin secretion when glucose was added. The team also found that cafestol increased glucose uptake in muscle cells, matching the levels of a currently prescribed antidiabetic drug. They say cafestol's dual benefits make it a good candidate for the prevention and treatment of type 2 diabetes. However, because coffee filters eliminate much of the cafestol in drip coffee, it is likely that other compounds also contribute to these health benefits.

*The authors acknowledge funding from Aarhus University.*

***http://www.eurekalert.org/pub_releases/2015-12/uomh-gmd120215.php***

## Genetic mutations differ within a single tumor, study finds

***Finding adds complexity to targeted therapies for rectal cancer***

ANN ARBOR, Mich. -- When researchers looked at different areas within an individual rectal cancer sample, they found cases in which each area contained different genetic mutations. The findings could have significant implications for treatment recommendations.

Researchers from the University of Michigan Comprehensive Cancer Center used next-generation sequencing techniques to sample the genetic landscape of different geographic areas from tissue samples taken from six patients with rectal cancer. They found that different regions of a single tumor shared as much as 93 percent of genetic mutations and as little as 67 percent.

"Our paper shows that individual parts of a tumor are different. Some tumors have a lot of variation and some don't. This is the first time anyone has shown this in rectal cancer," says lead study author Karin Hardiman, M.D., Ph.D., assistant professor of surgery at the University of Michigan Medical School.

Genetic variation has been found in other types of cancer, including lung cancer, kidney cancer, and some types of leukemia.

Rectal cancer often returns in the area where it was removed, making treatments such as chemotherapy and radiation crucial in addition to surgery. Chemotherapy choices often are determined from the genetic make-up of the tumor.

"When medical oncologists make decisions about targeted chemotherapy, they typically base that off the results of a single biopsy. If they're testing only one biopsy, it may or may not reflect what's in the rest of the tumor," Hardiman says.

The study authors hypothesize that the differences within a tumor might make the cancer more likely to resist targeted therapies. They are studying patient biopsy samples and mouse models to understand why there is variation within a tumor and why that variation is not present in all tumors.

Mouse models of rectal cancer will also allow the researchers to understand whether certain therapies or combinations of therapies can make a tumor more or less likely to respond.

Results of the study appear in the Nature journal Laboratory Investigation.

*Additional authors: Peter J. Ulintz, Rork D. Kuick, Daniel H. Hovelson, Christopher M. Gates, Ashwini Bhasi, Ana Rodrigues Grant, Jianhua Liu, Andi K. Cani, Joel K. Greenson, Scott A. Tomlins, Eric R. Fearon*

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*Reference: Laboratory Investigation, published online Nov. 16, 2015, doi:10.1038/labinvest.2015.131*

http://bit.ly/1TsZCE4

## Are jetpacks about to finally break into the mainstream?

***Jetpacks are back in the news with high-flying stunts and the potential for search and rescue. But we're not as close to the sci-fi dream as we might think***

**Are jetpacks about to finally break into the mainstream?**

**By Hal Hodson**

IN EARLY November, Australian inventor David Mayman took off from the deck of a barge floating in New York Harbour. He rose into the air, circled the Statue of Liberty, then alighted gently back on the boat. He made the trip using two turbines joined to a kerosene-filled backpack – a jetpack, in other words.

One week after his flight, Dubai's firefighting service signed an agreement to buy 20 jetpacks from a New Zealand company called Martin Jetpack. The month before, two men in winged jetpacks had taken to the skies above Dubai, flying in formation next to the world's biggest airliner, the Airbus A380. Are real, functional jetpacks finally arriving for all of us?

Well, not quite. Whether or not a backpack can lift a person into the sky depends on a few fundamentals: being small enough to wear, having fuel that contains enough energy for the flight time to be useful, and being sufficiently reliable so as not to fall out of the sky. Stunt jetpacks seem to meet those goals, but there are huge barriers to wider adoption.

Safety is the biggest hurdle. It takes an experienced pilot to keep themselves upright, balanced and flying on two streams of hot gas. Even the propeller-based Martin Jetpacks require two weeks of training. Gareth Padfield of the University of Liverpool, UK, says automation has a role to play in enabling the average person to pilot a craft that would be inherently unstable without the constant monitoring of an autonomous nanny.

"The Martin Jetpack has got tonnes of control algorithms. If they didn't have this there would be no chance they'd be able to fly it," says mechanical engineer Mathieu Sellier of the University of Canterbury in New Zealand, who has worked on previous models of the Martin Jetpack. "It's always on the verge of instability. You need to correct trajectory many, many times per second."

A jetpack for the masses will also need to be environmentally friendly, says Padfield. "If we've got a constant hum of these vehicles they're not going to be acceptable. If they are strong emitters of pollution they're not going to be acceptable."

His group, along with a consortium of European research institutions, is considering small electric helicopters instead of jet turbines, helping to skirt the environmental issues.

One final barrier is the basic limitations of our fuels – it's hard to find one with a high enough ratio of energy to mass to lift a person off the ground while they are wearing the tank that holds the fuel. Stunt jetpacks may already be pushing the limits of what's possible.

"Lifting a man with a device that you put on your back is probably not far off the limit, short of using nuclear power," says Sellier. Jetpacks might find a use in search and rescue in inaccessible places, but wouldn't be able to carry anyone out.

The answer may be personal air vehicles that transform as soon as they get off the ground – jets or propellers for take-off, with wings for travel that provide lift and efficiency. Padfield's group is looking for ways to integrate wings and helicopter blades to retain the benefits of both systems.

Even so Mayman's Statue of Liberty moment feels like the start of a new chapter. "This definitely looked more like sci-fi," says Sellier.

http://www.eurekalert.org/pub_releases/2015-12/cp-gmt112515.php

## Gut microbes trigger fat loss in response to cold temperatures

***Beneficial health effects of cold exposure are mediated in part by gut microbes***

Exposure to cold temperatures is known to mimic the effects of exercise, protecting against obesity and improving metabolic health. A study published December 3 in Cell now reveals that the beneficial health effects of cold exposure are mediated in part by gut microbes. The researchers found that cold exposure dramatically alters the composition of intestinal bacteria in mice and that this microbial shift is sufficient to burn fat, improve glucose metabolism, and reduce body weight.

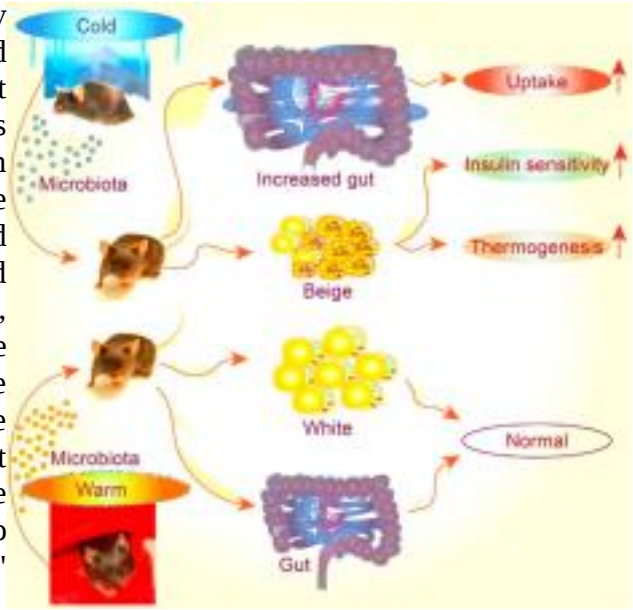
"We provide compelling evidence that gut microbes play a key role in our ability to adapt to the environment by directly regulating our energy balance," says senior study author Mirko Trajkovski of the University of Geneva. "We are excited about exploring the therapeutic potential of these findings and testing whether targeting some of these microbes could be a promising approach for preventing obesity and related metabolic conditions."

One potential therapeutic avenue for obesity centers on promoting the formation of good types of body fat known as brown and beige fat. Human infants have large amounts of heat-generating brown fat to protect them from extreme cold, and scientists recently discovered that adult humans also retain brown fat stores consisting mainly of a subtype known as beige fat. Cold exposure or exercise can

promote the formation of beige fat, thereby burning stored calories and protecting mammals from hypothermia, obesity, and metabolic problems.

Because gut microbes have been implicated in obesity and related metabolic conditions, Trajkovski and his team suspected that they might also play a role in mediating the positive health effects of cold exposure. In support of this idea, they found that exposure to a cold temperature (6° Celsius, 43° Fahrenheit) for up to 10 days caused a major shift in the composition of gut microbes while preventing weight gain in mice.

The researchers next tested the direct impact of these microbes on metabolic health. To do so, they transplanted the cold-induced gut bacteria into other mice that did not harbor gut microbes because they had been raised in a germ-free environment. The transplanted microbes improved glucose metabolism, increased tolerance to cold temperatures, and caused weight loss in the recipient mice by promoting the formation of beige fat. "These findings demonstrate that gut microbes directly regulate the energy balance in response to changes in the environment," Trajkovski says.




***This visual abstract shows how cold exposure markedly shifts the composition of the gut microbiota. This "cold microbiota" mediates remodeling of the fat and intestinal tissues, helping the host to withstand periods of high energy demand.*** **Chevalier and Stojanovi et al./Cell 2015**

However, after three weeks of cold exposure, body weight began to stabilize. The researchers suspected that the intestine was absorbing more nutrients from food, counteracting additional weight loss that would otherwise result from higher overall energy expenditure.

In support of this idea, transplantation experiments showed that gut microbes associated with long-term cold exposure caused the intestine to grow in size and triggered an increase in the surface area of intestinal cells that absorb nutrients. "These findings demonstrate that gut microbes enable mammals to harvest more energy from food as a way to adapt to the increased energy demand associated with long periods of cold exposure, thereby helping to protect against hypothermia," Trajkovski says. "We were surprised to see that gut microbes had such dramatic effects on the structure and function of the intestine."

Moving forward, the researchers plan to study the molecular mechanisms by which gut microbes sense changes in the environment to affect the energy balance of the host. Another avenue of investigation centers on the idea that certain bacteria may prevent obesity by remodeling intestinal tissue and thereby decreasing the absorption of nutrients in the gut.

*The researchers received funding from the European Research Council under the European Union's Seventh Framework Programme; the Louis-Jeantet Foundation; Fondation pour Recherches Médicales; the Novartis Foundation; and the Swiss National Science Foundation Professorship.*

*Cell, Chevalier and Stojanovi? et al.: "Gut Microbiota Orchestrates Energy Homeostasis During Cold"* http://dx.doi.org/10.1016/j.cell.2015.11.004

**http://www.eurekalert.org/pub_releases/2015-12/ats-rib120315.php**

## Researchers identify biomarker of early lung cancer that may increase survival

***Researchers in Taiwan have identified a biomarker that detects the most common lung cancer in its earliest stage. The discovery could one day change how long lung cancer patients live.***

According to theNational Cancer Institute, lung cancer kills about 158,000 Americans each year -- as many as the next 4 most deadly cancers combined. Non-small cell lung cancer (NSCLC) accounts for about 85 percent of all lung cancers.

"When NSCLC is detected early, patients have a 70 percent chance of being alive 5 years later. When NSCLC is detected at an advanced stage, 5-year survival drops to less than 10 percent," said senior investigator Pei-Jung Lu, PhD, professor of medicine at National Cheng-Kung University.

Lu and his colleagues tested Huntingtin interaction protein-1 (HIP1) as a potential new biomarker. They also investigated its role in lung cancer progression and metastasis, the cause of most lung cancer deaths. In addition to serving as a biomarker, the researchers found, HIP1 represses the mobility of lung cancer cells in laboratory studies and suppresses metastasis in a mouse model of the cancer.

Their findings were reported online ahead of print publication in the American Journal of Respiratory and Critical Medicine. Their study is the first to describe HIP1 involvement in the progression of adenocarcinoma, the most common type of NSCLC.

The researchers began by examining lung tissue from 121 patients. They found that those in the earliest stages of the diseases expressed more HIP1 than those in

the later stages of the disease. They also studied the correlation between HIP1 expression in early stages of the disease (stage I-II), and found a significant correlation between those patients who expressed higher levels of HIP1 and longer survival, indicating that HIP1 was a prognostic biomarker.

The researchers also studied the correlation between HIP1 and cellular mobility in vitro and in a mouse model of adenocarcinoma. In the laboratory, they found that HIP1 expression was inversely associated with cancer cell mobility. They confirmed those results in their mouse model. High levels of HIP1 expression were significantly associated with fewer metastatic tumor cells.

The researchers then investigated the mechanisms behind HIP1's ability to suppress cellular mobility and metastasis. They found that HIP1 modulates Akt, a protein kinase that regulates the epithelial-mesenchymal transition, which in turn facilitates cell invasion and the beginning of metastasis.

"If we can restore HIP1 levels and functions, we may be able to stop or prevent human lung cancer metastasis in the early stage," Lu said. "To bring this discovery to clinical care, we now need to identify the regulatory factors of the HIP1 gene that are targetable through gene therapy or small molecule interventions."

***http://www.eurekalert.org/pub_releases/2015-12/sifm-pbm120215.php***

## Potential biochemical mechanism underlying long-term memories identified

***During the holidays, we often remember the past and create new memories. But, why do some memories fade away while others last forever?***

Kansas City, MO - Scientists at the Stowers Institute for Medical Research have identified a possible biochemical mechanism by which the specialized brain cells known as neurons create and maintain a long-term memory from a fleeting experience.

The research, conducted by Stowers Associate Investigator Kausik Si, Ph.D., and his team, is published in the current issue of the journal Cell. Their research builds upon previous studies by Si and Eric Kandel, M.D., of Columbia University and other scientists.

These studies revealed that both short-term and long-term memories are created in synapses, the tiny junctions between neurons. A transient experience -- one source of our memories -- is capable of producing an enduring change in the strength of the synaptic connection, says Si.

For a memory to endure, and not fade away, the synaptic connections must be kept strong.

In a previous study, Kandel and Si identified CPEB as a synaptic protein that is responsible for maintaining the strength of these connections in the sea slug, a model organism used in memory research. In subsequent research at the Stowers Institute, Si and his team identified Orb2 as the fruit fly version of the CPEB synaptic protein.

In their latest study, Mohammed 'Repon' Khan, a predoctoral researcher in the Si Lab and first author of the Cell paper, determined that Orb2 exists in two distinct physical states, monomeric and oligomeric. Monomeric Orb2 is a single molecule capable of binding to other molecules.

Like CPEB, oligomeric Orb2 is prion-like - that is, it's a self-copying cluster. However, unlike disease-causing prions, oligomeric Orb2 and CPEB are not toxic. The paper describes how monomeric Orb2 represses while oligomeric or prion-like Orb2 activates a crucial step in the complex cellular process that leads to protein synthesis. During this crucial step, messenger RNA (mRNA), which is a RNA copy of a gene's recipe for a protein, is translated by the cell's ribosome into the sequence of amino acids that will make up a newly synthesized protein.

"We propose that the monomeric form of Orb2 binds to the target mRNA, and the bound mRNA is kept in a repressed state," explains Khan.

The Stowers scientists also determined that prion-like Orb2 not only activates translation but imparts its translational state to nearby monomer forms of Orb2. As a result, monomeric Orb2 is transformed into prion-like Orb2, and its role in translation switches from repression to activation. Si thinks this switch is the possible mechanism by which fleeting experiences create an enduring memory.

"Because of the self-sustaining nature of the prion-like state, this creates a local and self-sustaining translation activation of Orb2-target mRNA, which maintains the changed state of synaptic activity over time," says Si.

The discovery that the two distinct states of Orb2 have opposing roles in the translation process provides "for the first time a biochemical mechanism of synapse-specific persistent translation and long-lasting memory," he states.

"To our knowledge, this is the first example of a prion-based protein switch that turns a repressor into an activator," Si adds. "The recruitment of distinct protein complexes at the non-prion and prion-like forms to create altered activity states indicates the prion-like behavior is in essence a protein conformation-based switch. Through this switch, a protein can lose or gain a function that can be maintained over time in the absence of the original stimuli. Although such a possibility has been anticipated prior to this study, there was no direct evidence."

*Other Stowers contributors to this work include Liying Li, Consuelo Pérez-Sánchez, Anita Saraf, Ph.D., Laurence Florens, Ph.D., Brian Slaughter, Ph.D., and Jay Unruh, Ph.D.*

http://www.eurekalert.org/pub_releases/2015-12/hms-glb120215.php

# Genetic link between heart and neurodevelopmental disease

## *Researchers show that children with both congenital heart disease and neurodevelopmental delays share certain genetic mutations*

Children with significant congenital heart disease have a far better chance of surviving today than in decades past, thanks to major advances in surgery. But some infants who recover from repairs to their hearts later show the effects of delays in brain development, including impairments to cognitive, language and social functioning. Such impairments can affect how well these children do in school and in the workplace; they can even diminish their overall quality of life.

Epidemiological studies have given numbers to what doctors and families have long observed: The risk of neurodevelopmental delays is tenfold higher for children with moderate to severe congenital heart disease than for other children.

But why?

Over the years, those who study these phenomena have considered several possible reasons. Do the rigors of open-heart surgery so soon after birth play a role? Could heart defects limit nutrients and oxygen needed by the fetus? Or could spontaneous genetic mutations cause congenital problems that affect both the heart and the brain of a child?

Now, the 'why' may have been answered by the efforts of the Pediatric Cardiovascular Genetics Consortium, led by a team of Harvard Medical School scientists. In a recent issue of Science the consortium reported exome sequence analyses of more than 1,200 children and their parents and showed that children with both congenital heart disease and neurodevelopmental delays share certain genetic mutations that thwart the normal development of both the heart and the brain.

Using a mathematical model created by co-authors Kaitlin Samocha and Mark Daly of the Analytical and Translational Genetics Unit at Massachusetts General Hospital, the team analyzed mutations in the protein-coding portion of the genomes of children with congenital heart disease that were not present in their parents' genomes. They found that these children have more of these de novo mutations in genes that are highly expressed in the developing heart, compared to a control cohort of children without congenital heart disease.

The de novo mutations were also found to be more frequent in children with congenital heart disease plus another birth defect, either neurodevelopmental delay or more-subtle abnormalities of finger or ear shape. These findings bolster the case for shared genetic causes of the cardiac and extra-cardiac abnormalities rather than surgeries or environmental factors.

"We're homing in on a set of genes that have multiple different roles in multiple different tissues during development: heart tissue, brain tissue, other developing organs, limb tissue," said Jason Homsy, an HMS LaDue Fellow who trained at Mass General and co-lead author of the Science paper. "Our study shows a common genetic link for the development of these diseases."

According to Homsy and co-senior author Christine Seidman, the HMS Thomas W. Smith Professor of Genetics and Medicine at Brigham and Women's Hospital and a Howard Hughes Medical Institute investigator, these findings could lead to early testing that would help identify newborns with congenital heart disease who are at high risk of neurodevelopmental difficulties.

"We can pretty clearly tell the parents of children with congenital heart disease what's going to happen after the heart surgery, but there's always a big question: Will my kid learn well in school?" Seidman said. "If we could identify children at high risk for neurodevelopmental delays, they could receive increased surveillance and earlier interventions than occur now."

The mutations primarily affected genes involved in three areas: morphogenesis, chromatin modification and transcriptional regulation. If any one of these processes is perturbed even slightly at a critical time in development, the heart is malformed; sometimes another developmental defect occurs, such as a missed connection in the brain. "These genes are not just involved in shaping the heart," Seidman said. "They are master regulators of organ development."

One of the mutated genes is RBFOX2, which encodes a molecule that regulates RNA splicing. Although RBFOX2 has not been previously implicated in congenital heart disease, de novo mutations were identified in multiple affected children.

"There are still many unanswered questions, including why the same mutation can cause very different clinical manifestations," Seidman said. Perhaps additional genetic variants in the multiple layers of transcriptional regulation allow compensation for some mutations but worsen the consequences of others. For now, Seidman said, knowing that a genetic mutation is present is different from knowing the outcome.

"It's a long, long, long way down the road," Seidman said, "but we'd like to believe that if you knew the steps by which these mutations perturbed the regulation of gene expression, there might even be ways to actually treat it."

*This work was supported by grants from the National Heart, Lung, and Blood Institute and the National Human Genome Research Institute of the National Institutes of Health, Howard Hughes Medical Institute, Simons Foundation for Autism Research, John S. LaDue Fellowship at HMS, Medical Scientist Training Program and National Research Science Award, Academy of Medical Sciences, British Heart Foundation, Wellcome Trust, Arthritis*

*Research UK and the NIHR Cardiovascular Biomedical Research Unit at Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, Leducq Foundation, Heart and Stroke Foundation of Ontario, Ted Rogers Centre for Heart Research, Kostin Family Innovation Fund, Aaron Stern Professorship at the University of Michigan, and Braylon's Gift of Hope Fund.*

***http://www.eurekalert.org/pub_releases/2015-12/b-gto120115.php***

## Global toll of injuries down by almost a third since 1990

***'World is becoming a safer place to live in,' say researchers***

The global toll taken by injuries on daily life has fallen by almost a third in the past quarter of a century, reveals research published online in the journal Injury Prevention. The findings prompt the researchers to conclude that "the world is becoming a safer place to live in."

The World Bank commissioned the first Global Burden of Diseases and Injuries, and Risk Factors (GBD) study in the early 1990s. In subsequent updates, injury has emerged as a substantial cause of ill health and death in both the developing and developed world.

As part of a global collaboration, the researchers mined the latest GBD update in 2013 to assess the impact of 26 causes of injury and 47 types of injury, dating back to 1990, for 188 countries in 21 regions of the world.

They used data on the number of injuries, deaths from injuries, and a measure known as disability adjusted life years, or DALYs for short. The DALY is calculated by adding together years of life lost to death, and years of life lived with a disability. They calculated that in 2013 almost a billion people (973 million) sustained injuries that required medical attention/treatment, accounting for 10% of the global toll of disease.

Major causes included car crashes, which made up 29% of the total, followed by self harm, which includes suicide (17.6%); falls (11.6%); and violence (8.5%).

Among those whose injuries warranted some form of healthcare, just under 6% required admission to hospital. The largest category of injury requiring admission was fracture (38.5%).

In almost all regions of the world, injury rates were higher in men than in women, until the age of 80. Almost 5 million people died of their injuries.

Injuries remain an important cause of ill health and death, the calculations show, but between 1990 and 2013, the global DALY, standardised for age, fell by almost a third (31%). This fall was significant for 22 of the 26 causes of injury, including all the major ones. But there were some variations, according to age, gender, geography, and time.

DALYs among the under 15s were lowest in Western Europe and highest in central Sub-Saharan Africa.

Among 15 to 49 year olds, the peak age category for road traffic injuries, there was an eightfold difference in rates between high income Asia Pacific and western Sub-Saharan Africa, while rates were 70% higher in North America than in Western Europe, Australasia and Asia Pacific.

"These decreases in DALY rates for almost all cause of injury categories warrant a general statement that the world is becoming a safer place to live in, although the injury burden remains high in some parts of the world," conclude the researchers.

***http://www.medscape.com/viewarticle/855063***

## Physician Burnout: A Personal Story

***Burnout is not some psychological abnormality too embarrassing to speak about in public***

**Thomas Murphy, MD|December 03, 2015**

***Editor's Note:***

***The following commentary is authored by Thomas Murphy, a rheumatologist living in Boise, Idaho, and practicing medicine in nearby Emmett, Idaho. He recently published a book about physician burnout: Physician Burnout: A Guide to Recognition and Recovery. He also has a website dedicated to the issue of physician burnout. The following article is the first in a series about physician burnout in which Dr Murphy and Medscape seek to bring knowledge and awareness to this topic.***

Time is baffling. It seemed like just yesterday that I sat in a posh auditorium in Chicago, an enthusiastic young adult on my first day of medical school orientation at Northwestern University in 1995. Eighteen years later, I was a 43-year-old burned out physician, practicing in Boise, Idaho, searching Google for the most effective way to end my life. During my time of maximum burnout, I was the type of physician that I never wanted to be: impatient, sarcastic, and occasionally dismissive of my patients. I made caustic jokes about some patients in the lunchroom. In short: I was not happy.

As I learned about the problem of physician burnout, I came to recognize that I was not alone. While researching the subject of burnout for a book I recently wrote on the subject, I learned that burnout is not some psychological abnormality too embarrassing to speak about in public. Quite the contrary. For example, a 2011 survey of over 2000 US physicians found that 87% reported feeling moderately to severely stressed or burned out on an average day.[1] On the extreme spectrum, female physicians have a successful suicide rate of 250%-400% higher than their counterparts in the general population.[2] Something very alarming is going on in the American healthcare system nowadays. Doctors aren't happy, and neither are patients. The proverbial admonition, "Happy doctors make for happy patients" comes to mind with the caveat that the reverse is also true.

## What Does Physician Burnout Look Like?

Three defining symptoms characterize physician burnout: emotional exhaustion, depersonalization, and lack of personal accomplishment. If a physician is suffering from all or even just one of these symptoms, he or she likely is experiencing symptoms of burnout. A physician with burnout may experience all three of these symptoms simultaneously or only one at a time.

Emotional exhaustion. This is manifested by a physician feeling overstretched by the professional responsibilities of the job and having absolutely no reserve left. Emotional exhaustion is somewhat akin to a car that has run out of gas.

As an example, when I was in practice, I came home every day psychologically drained. I had no emotional resilience for response to the normal, mundane hassles of everyday life outside of work. My young daughter becoming sick with a virus felt overwhelming and burdensome.

Physicians suffering from emotional exhaustion have frequently invested so much energy into taking care of their patients and worrying about their patients' problems, as well as dealing with work-related issues, that they simply have nothing left for themselves or their families.

Further compounding the problem of emotional exhaustion are the incessant work-related demands imposed on physicians outside of their daily work schedule. Physicians are frequently on call at night and on weekends. Medical students, residents, and fellows in training have to take call and sleep in the hospital, and they may work up to 30 hours in a row without a break. Additionally, physicians are expected to spend their limited time away from work keeping up to date with the myriad medical advances in their field and to constantly be studying to maintain their board certification status.

Depersonalization. The second telltale sign of burnout is depersonalization, a process of detachment from others. Physicians experiencing this symptom view their patients as objects or things rather than actual human beings. Physicians experiencing depersonalization have described feeling robotic. Their interactions with patients focus primarily on controlling how much time they will be forced to spend with the patient instead of addressing the patient's underlying problem or medical condition. It's as if the names on the physician's daily schedule are no longer people but rather tasks to be checked off a list. Physicians have likened the experience of depersonalization to participating in a movie or TV show, acting out a role that doesn't seem authentic to them. The physician is cognitively present but emotionally absent.

Depersonalization is a coping mechanism, albeit a dysfunctional one, in which physicians try to protect themselves from their patients by distancing and emotionally detaching themselves from them.

Depersonalization is very common in modern medicine. Doctors suffering from burnout can become extremely cynical and jaded in part as a defense mechanism. They don't like it when patients are noncompliant, rude, or needy and seek emotional protection by detaching from them. One could argue that the very process of medical training serves as a fertile training ground for depersonalization. If doctors invest too much psychological energy in patients, then they would be completely overwhelmed every time a patient became severely ill or died.

When a physician loses empathy and is unable to feel compassionately toward his patients or himself, depersonalization is taken to an extreme. Compassion and caring are replaced by caustic jokes and sardonic remarks in the break room. One example that exemplifies depersonalization occurred when I saw a physician speaking on the phone with a patient who had called to thank the physician for his care. After getting off the phone, the doctor shook his head and said, "Senile old joker."

Depersonalization can also be described as "compassion fatigue." A perfect example of compassion fatigue occurred when a burned out physician told me about an encounter he recently had with a patient. The physician stopped by the patient's room and informed him that an MRI had confirmed that the patient had a mild stroke. When the patient tried to elicit more information, the physician grew frustrated because he was behind schedule and felt he had already provided the pertinent information. The patient then began to cry, and the physician became exasperated, frustrated because the matter was taking up a lot of his time. The physician told me he was incapable of putting himself in the patient's position and that his "empathy reserves" were depleted. After this episode, the physician came and talked to me, eventually seeking help.

Lack of personal accomplishment. The final characteristic of burnout is a lack of feelings of personal accomplishment, deriving no personal joy or meaning from work. Many physicians have described losing or shrouding the youthful idealism that characterized their time as medical students as a consequence of the stress and anxiety associated with the practice of modern medicine. They no longer derive any satisfaction from work. The job has become solely a source of income in which a physician attempts to dodge the possibility of potential litigation from any missteps. The physician is no longer proactively looking for solutions and is just trying not to miss anything, checking off the necessary boxes on a computer monitor. He is in survival mode. Physicians in this stage may begin to doubt the quality of the care they are providing in addition to their growing belief that their work lacks meaning. Many physicians report that they went into medicine to help others, but the joy of that ethos was lost during the course of their career.

On a personal level, when I lost my joy in the practice of medicine, going into work literally felt like a prison sentence. While helping other physicians navigate through burnout, I have been amazed at how frequently I hear that exact same analogy. One physician told me, "Driving to the office everyday was a jail sentence, but I told myself at least I have my weekends and nights off. I hope to retire in my mid-fifties so I have about a 14-year sentence left."

**Signs of Physician Burnout**

An obvious change in demeanor or character, or overreactions to seemingly minor provocations resulting in an outburst of temper or crying, may be a sign of burnout. My staff told me they knew I was burned out because things that were relatively insignificant in scope caused me to become extremely agitated and emotional. Changes in sleep habits, appetite, or unintentional weight changes can also be clues to physician burnout.

Sometimes others may be the ones to recognize burnout. A spouse or colleague can be helpful in identifying these signs that we do not see—or perhaps choose not to see. For example, one day when I felt completely overwhelmed by burnout, I went into an exam room to see the friendly face of a psychiatrist who was one of my patients. As I began to ask him about how he was doing and started to go through the details of his case, he politely interrupted me and said, "Wait. I want you to sit down and take several deep breaths. You look terrible. I have been exactly where you are myself. Let's take a minute or two and get you in a better place before we talk about me." We chatted for several minutes, and his recognizing my situation and sharing with me some of his own experiences was invaluable. This kind and helpful gesture was the first wake-up call to me that I was grappling with the issue of burnout.

Burned out physicians also frequently experience anhedonia: a loss of joy from previously pleasurable activities. When my own burnout became extreme, I did not enjoy the things that I used to love to do like running or spending time with my family. Alcohol or illicit drug abuse is another indicator that a physician could possibly be attempting to self-medicate symptoms of burnout.

**Recognizing Burnout in Yourself**

Tragically, many of us choose to ignore the problem of burnout in ourselves, in stark contrast to how we would treat a sick patient. An emergency medicine physician would never tell a 50-year-old man with occasional stabbing substernal chest pain to ignore it. An EKG, cardiac enzymes screen, and notification to the cardiologist on call would all follow—steps to address the emergency. Yet we often convince ourselves that our early warning signs of burnout will just go away or, worse, delude ourselves into believing we can just tough it out.

Burnout is insidious, a creeping tide that slowly and steadily overwhelms a physician's life. It often starts as early as medical school—an environment with a culture of self-reliance and independence. Our self-image as physicians frequently prevents us from showing signs of weakness or suffering. For such reasons, I refused to accept my symptoms of burnout. These symptoms became more extreme, to the point that I felt overwhelmed while driving into work. I felt physically fatigued and exhausted even before the day began! Worse, I had lost empathy for my patients. Once during an office visit, a patient began to cry. Instead of considering what the patient might be feeling, I wondered to myself how long this was going to take and how it would affect my schedule. Was I going to fall behind? I made the appropriate gestures, a hand on the shoulder, an attempt to find a tissue, but I was just going through the motions.

Do you find yourself asking what happened to the passion and enthusiasm you had as a medical student? Do you mock your patients; have you lost all empathy for them? Do you find that you no longer engage with your family; lack focus, energy, and passion; and are just going through the motions robotically?

This should not be surprising to anyone familiar with the system in which we operate. The pressures are unending—overbooked and overburdened in our patient loads, a new electronic health record system to be mastered, patient emails and calls to be answered—and there is no end in sight. Are you beginning to manage your heavy patient load by referring patients out to other specialists and ordering more diagnostic tests, hoping for quick easy answers rather than doing the time-consuming work of performing a thorough history and physical exam? Many of us are just trying to keep our heads above water. If some of this sounds uncomfortably familiar, you are not alone.

During my last several years of practice, each day seemed like a monumental struggle analogous to the Greek mythological character Sisyphus. I tried simply to survive each overscheduled, jam-packed clinical day, a fruitless exercise because I would just have to go through the same ordeal the next day and the day after that. Like Sisyphus, I felt condemned by the burden of rolling a heavy boulder up a monumental hill only to have it roll back down, repeating this process for the rest of eternity. Christina Maslach and Michael Leiter, early pioneers in the field of job burnout, succinctly characterized the problem as "an erosion of the human soul."[3]

**The Consequences of Burnout**

Burnout affects not only the physician experiencing the problem but also their families. It also has dramatic implications for the patients the burned out physician treats. Increasing time constraints, burgeoning bureaucracy, growing patient expectations, and evolving technological advances have made the

profession of medicine even more challenging and stressful. In fact, given the current state and demands of the American healthcare system, I believe that burnout is an almost inevitable response. Something needs to be done.

My journey saw me go from an enthusiastic medical student to a burned-out, middle-aged physician in the span of 19 years. Patients suffer, too, because a disabled doctor can't deliver the type of care they deserve. Sure, he or she can go through the motions, can prescribe the appropriate meds, etc., but that's all he does. And patients intuitively sense this lack of commitment, in contrast to a kind of magical placebo effect that occurs between an engaged doctor and a sick patient. "Hands on" was the way the profession referred to this magic. No visit to a sick patient was complete until the physician placed "hands on the person." The physical touch of a committed physician was thought to promote healing, to give the patient confidence in the care they were receiving. Maybe this practice strikes us as a little hokey today, but the general principle still holds true.

Patients need to believe in their doctor. An empathetic touch can make all the difference and be the key to medical success. Danielle Ofri exemplifies this point in her book,[4] What Doctors Feel: How Emotions Affect the Practice of Medicine, when she describes a study that reported that control of diabetes in patients of doctors who rate high on a standard empathy scale is a remarkable 40% better than those cared for by physicians with low empathy scores.[5] Ofri observes that this difference is comparable "to the benefits seen with the most intensive medical therapy." The tragedy of burnout is that it effaces genuine empathy, spirituality, and commitment. Friedrich Nietzsche put it best: "Physician, heal thyself: then wilt thou also heal thy patient."[6]

**Healing Ourselves**

At some point in almost every physician's career, we have a powerful desire to help others. When suffering burnout, many of us become so disillusioned by our failure to achieve these aspirations that our passion is replaced by a strong contempt, bordering on hatred, for the profession we chose and once loved. My goal is to reignite that flame as I have been able to do for myself and give physicians a chance to rediscover a sense of joy, pleasure, and fulfillment from this noble profession.

In my case, burnout started insidiously like a nagging pain, and I chose to ignore it. I hope others can learn from my example. I am a runner. One time last year while running on a treadmill, I was really pushing myself at a fast pace when I started to notice some mild discomfort in the back part of my right leg. As I kept running, the twinges morphed into severe, agonizing pain, but I pushed through and ignored what my body was trying to tell me, just as we physicians do with burnout. We "tough it out." We "play with the pain." What was the result with my leg? I partially tore my right hamstring and could not run normally for over 3 months.

Don't repeat my mistake with your own burnout, waiting until it is too late to acknowledge the problem. If you feel it creeping up on you insidiously, the time for action is now. If those little twinges you feel are becoming more severe and frequent, stop at this moment. Do something about the problem for yourself, your family, and your patients—before you find yourself in an emergent situation, before something irrevocable happens, before you tear your hamstring.

The best analogy I can think of when it comes to physicians who continue to suffer through burnout in unhappy work environments involves a parable I recently heard about circus elephants. Grown elephants in the circus do not run away because of a small metal chain attached to one of their legs. The chain could not possibly contain these mammoth creatures. What prevents them from trying to break out of their shackle? When the elephant was a baby, a chain was affixed to its leg and connected to a peg hammered into the ground. If a baby elephant tried to break away, the chain and stake were strong enough to hold it. The baby elephant soon learned its lesson and accepted its confinement. It stopped trying to escape. The small chain and stake would never be enough to contain a full-grown animal if it tried to escape, but by the time the animal has reached adulthood, it has relinquished all hope for an escape and freedom.

The adult elephant has grown to accept its fate and is fooled by the little chain around its leg. The same is true for your medical career. You can remain confined by an artificial barricade, or you can experience a newfound freedom. The choice is up to you.

Please join me in my next article in this series—a call to action and the proactive route you can take back to wellness as you recover from burnout.

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http://bit.ly/1XSNLjT

## Here's What Happens When You Age Whisky

***Hint: The barrel really does matter***

**By Danny Lewis**

Technically, it only takes a few days to distil a barrel of whisky, but it takes time for that golden beverage's taste to mature. Although you could drink it straight away, it wouldn't be the peaty, rich liquor that whiskey fans typically relish. So what transpires in the months, years or even decades that a whiskey is left to age?

When whisky is first distilled and sealed up in its barrel, it's more like moonshine than what you'd expect from a spirit like scotch or bourbon. Instead of golden-brown, brand-new whisky is perfectly clear and tastes a lot like the malted barley it's made from. But as soon as it goes into a wooden barrel, things start getting interesting, Camper English writes for Popular Science.

For every batch of whisky, there are two major factors that determine what it will taste like decades into the future: the wooden barrel it's aged in and the environment the barrel is stored in. Traditionally, whisky is aged in oak barrels that are either toasted or charred when they are built, creating a layer of charcoal that filters out the raw spirit's unwanted flavors, English writes. Through a chemical process called adsorption, the molecules that make young whisky so harsh are drawn to the barrel's wall, creating a thin layer of everything you don't want in a drink. At the same time, the wood adds flavor to the whisky, slowly infusing the liquor with lignin and vanillin (for vanilla-like taste), lactones (for a buttery flavor) and tannins or "wood spice" (which makes the whisky dry).

Traditionally, new barrels are used to age bourbon; once they are finished, the bourbon-soaked barrels often go to scotch whisky distillers, who let their product sit for longer to tease out the remaining flavors. And once you start getting into scotch, there's a whole new chemical component to be reckoned with - phenols, introduced when burning peat is used to dry the barley - which gives that type of whiskey its distinctive smoky flavor.

"The longer you age, the more the phenols bond with other things in the solution to form new compounds like phenylated carboxylic esters, which tend to taste like honey," Lost Spirits Distillery's Bryan Davis tells English. "In a way, you trade smoke for honey."

Climate also plays a big role in the whisky's taste. Bourbon distillers often age their whisky in dry environments that help it evaporate and concentrate faster than scotch, which is usually aged in humid climates, Kara Newman reported for Slate.

Most times, the older the whisky, the more complex the taste and the pricier it is. The oldest whiskies available are aged for 50 years and can sell for up to $25,000 a bottle, in the case of Glenlivet's 50-year-old single malt scotch. But while rare half-century old whiskies might draw looks of longing from connoisseurs, there's often a point at which the liquor's age starts to show.

"It is possible for a spirit to get too old," Dave Pickerell, a former master distiller for Maker's Mark, tells Newman. "Sometimes older is better—but sometimes it's just older." Old whiskies might cost a pretty penny, but for the flavor, Pickerell recommends choosing a more middle-aged whisky – 6 to 10 years for bourbon, and about 20 years for scotch. Any older, and you might just be paying for age, not flavorful beauty.

http://www.eurekalert.org/pub_releases/2015-12/su-oth120215.php

## Ocean toxicity hampered the rapid evolution of complex life

***By examining rocks at the bottom of ancient oceans, an international group of researchers have revealed that arsenic concentrations in the oceans have varied greatly over time.***

But also that in the very early oceans, arsenic co-varied with the rise of atmospheric oxygen and coincided with the coming and going of global glaciations. The study was recently published in the Nature Group Journal, Scientific Reports.

"In the article we argue that when we first see the appearance of complex life on Earth, is when life have developed mechanisms to resist catastrophic chemical changes forced by global glaciations. And that this enabled the expansion of complex life in oceans, and paved the way for our own evolution", says Dr Ernest Chi Fru of Stockholm University, who has led the research group.

The first appearance of oxygen in the atmosphere occurred at a time when marine arsenic concentrations were dramatically low, at about after 2.45 billion years ago. This is also a period when Earth experienced its first known global glaciation. At the end of these glaciations, considerable rise in marine arsenic concentrations concurred with rapid demise of atmospheric oxygen. The authors infer -- from the way modern photosynthetic organisms react to changing marine arsenic concentrations -- that this event was due to widespread ocean toxicity resulting from the release of toxic elements into the oceans when the ice melted.

A similar low and high arsenic content accompanied the coming and going of global glaciations at around 0.7 billion years ago, which is when Earth first saw the appearance of complex life. While the low marine arsenic concentrations again coincide with a rapid rise in atmospheric oxygen content to near modern day levels at this time, the subsequent increase when the ice melted is not accompanied by atmospheric oxygen decline.

*The study was performed by an international team of researchers from Sweden, Greece and France, led by Dr Ernest Chi Fru of Stockholm University. It was funded by the European Research Council.*

*The article Arsenic Stress after the Proterozoic Glaciations was recently published in Nature Group Journal, Scientific Reports.*

***http://bit.ly/1TtAq01***

## Asteroid probe conducts 'Earth swing-by' in space quest

***Asteroid probe conducts 'Earth swing-by' in space quest***

TOKYO — A Japanese space probe launched last year passed by Earth on Thursday to harness the planet's gravitational pull to propel it toward a far away asteroid in its quest to study the origin of the solar system, authorities said.

The explorer, named Hayabusa 2, conducted an "Earth swing-by" and came as close as 3,090 kilometers above ground after 7 p.m., before switching its orbit to continue toward tiny Ryugu asteroid, according to simulation data made available on a website managed by Japan Aerospace Exploration Agency (JAXA).

The space agency will now spend about a week analysing whether the probe has gone into the correct orbit, according to local media, including the Mainichi Shimbun daily.

Hayabusa 2 was launched a year ago aboard Japan's main H-IIA rocket from Tanegashima Space Center for its six-year mission to bring back mineral samples from the asteroid. It is expected to reach Ryugu, named after a mythical castle in a Japanese folk tale, in mid-2018 and spend around 18 months in the area. It will also drop rover robots and a "landing package" that includes equipment for surface observation. If all goes well, soil samples will be returned to Earth in late 2020. Analysing the extra-terrestrial materials could help shed light on the birth of the solar system 4.6 billion years ago and offer clues about what gave rise to life on Earth, scientists have said.

The probe is the successor to JAXA's first asteroid explorer, Hayabusa—the Japanese term for falcon—which returned to Earth in 2010 with dust samples after a seven-year mission. The Ryugu asteroid, which is around a kilometer across, is believed to contain significantly more organic matter and water than the potato-shaped rock studied by the original Hayabusa.

***http://bit.ly/1N4HMFH***

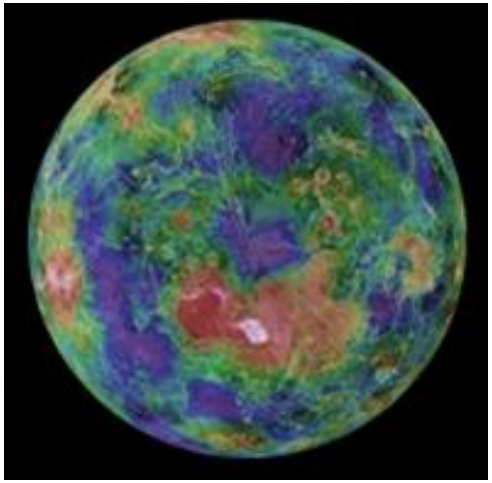
## Japan orbiter seeks second shot at Venus

***Five years after a failed insertion into planet's orbit, Akatsuki tries again.***

- **Alexandra Witze**

Japan's Akatsuki spacecraft, whose name means 'dawn', gets a second chance to rise on 7 December. Exactly five years after it failed to slip into orbit around Venus, Akatsuki will fire its engines and try again.

The spacecraft has spent the past half-decade orbiting the Sun, on its way to catch up with Venus. "It's been quite a long period of waiting," says Masato Nakamura, project manager at the Japan Aerospace Exploration Agency (JAXA) Institute of Space and Astronautical Science in Sagamihara.



***Venus is shown here in a false-colour radar image. NASA/JPL/USGS***

Just before 9 a.m. Japan time on 7 December, engineers will command Akatsuki to fire four of its thrusters simultaneously. The engines will run for around 20 minutes, aiming to nudge the spacecraft onto the correct trajectory for capture by Venus's gravity.

Mission controllers expect to know within a few hours whether the propulsion burn went as expected. It may take a few days after that to confirm whether Akatsuki is indeed orbiting Venus.

If it works, the spacecraft will end up in a highly elliptical orbit, more stretched out and farther from Venus than was originally planned. This would put the orbiter several thousand kilometres away at its closest approach, rather than several hundred. From there, Akatsuki should be able to accomplish most of its original science goals, although data will take longer to accumulate.

"The past five years have been a tough period for us — tracking of a spacecraft which does not yield science data is not fun for scientists," says team member Takeshi Imamura. "Now we are nervous, but at the same time very excited. Venus is a stone's throw from us."

### Dawn breaks

Akatsuki was launched in May 2010 on a mission to study Venus's ever-changing atmosphere, which rotates at up to 100 metres per second — much faster than the planetary surface below it. The spacecraft carries five cameras, ranging from infrared to ultraviolet wavelengths to study different atmospheric features, including the lightning thought to flash through Venus's acidic clouds.

All seemed well until 7 December 2010, when the spacecraft fired its main engine to enter Venus's orbit. Unknown to mission controllers, salt had built up on a valve between a helium tank and a fuel tank, and the blockage caused a ceramic nozzle in the propulsion system to break. Akatsuki went sailing towards the Sun, rather than into orbit around Venus.

JAXA engineers spent years studying whether they could recover the mission[1]. With the main engine dead, the oxidizer fuel was also useless, so mission controllers dumped 65 kilograms of fuel into space in October 2011. This made

the spacecraft lighter and easier to manoeuvre, which should enable it to reach orbit with less thrusting.

The upcoming engine burn will involve four of the spacecraft's eight thrusters. These smaller engines are normally used to make minor adjustments to the probe's orientation, as opposed to major changes to its trajectory. Because the thrusters are lower power than the main engine, they will need to burn for longer than usual. JAXA has tested them several times in deep space, most recently in September. If the thrusters work as well in the upcoming burn as they did in testing, "we are confident that the propulsion will be successful", Imamura says.

**High noon**

But the spacecraft's unexpected detour may still cause problems. Because it has spent more time closer to the Sun than originally designed, Akatsuki is warmer than expected, which may have harmed some of its equipment; this could limit operations at Venus.

During its five years in deep-space wilderness, Akatsuki conducted a little science, such as transmitting radio signals to Earth through the solar corona to measure how the Sun's turbulence scatters radio waves[2]. But the craft's cameras have mostly remained off.

Manoeuvring Akatsuki into Venus's orbit would give scientists their only chance at seeing the planet up close for the foreseeable future. The European Space Agency's Venus Express spacecraft stopped working a year ago, after eight years of circling the planet in a polar orbit. (If Akatsuki succeeds, it will be in an equatorial orbit and so permit different views.) NASA has put two Venus probes on its shortlist of five candidates for the next Discovery-class mission, which would launch no earlier than 2020.

JAXA has a history of nail-biting second chances. The Hayabusa spacecraft survived a number of near-fatal incidents on its way to and from collecting samples of the asteroid Itokawa. But in 2003, after an extended effort to make the mission work, JAXA lost its Mars-bound Nozomi spacecraft, first to a problem with a fuel valve and then to a solar flare that fried its electronics.

Sanjay Limaye, an Akatsuki participating scientist at the University of Wisconsin–Madison, says that the team is ready for something to work for once. "Whatever could go wrong has already gone wrong," he says. "What's left?"

*Nature doi:10.1038/nature.2015.18943*

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## Certain herpes viruses can infect human neurons

***Research suggests viral infection could underlie some symptoms of brain disorders***

PHILADELPHIA - For years, researchers have noted a tantalizing link between some neurologic conditions and certain species of the herpes virus. In patients with Alzheimer's disease, multiple sclerosis, and cerebellar ataxia, among other neuropathies, the cerebrospinal fluid teems with Epstein-Barr virus (EBV). Yet, the nature of that link has remained unclear, as it has been assumed that EBV, as well as other viruses in the same sub-family, called gammaherpesviruses, cannot infect neurons.

Now, thanks to investigators from the Perelman School of Medicine at the University of Pennsylvania, researchers in this field know better. Erle S. Robertson, PhD, a professor of Microbiology and Otorhinolaryngology and Director of the Tumor Virology Training Program at the Abramson Cancer Center, and colleagues published in mBio this week that EBV and a related virus, Kaposi's sarcoma-associated herpesvirus (KSHV), can infect and replicate in both cultured and primary neurons.

Though by no means proving causality, those data do suggest viral infection could underlie at least some of the symptoms of those brain disorders, as well as the potential utility of antiviral drugs as a novel therapeutic strategy.

According to Robertson, several lines of evidence suggested the possibility that gammaherpesviruses could infect brain tissue. First, the viruses are enriched in the cerebrospinal fluid and brain tissue of individuals with such conditions as multiple sclerosis (MS) and Alzheimer's disease. In addition, individuals with a history of infectious mononucleosis caused by EBV are more likely to develop MS, while those who have never been infected with EBV are less likely to do so. Particularly tellingly, the drug acyclovir, which can inhibit EBV and related viruses, has been examined as a potential treatment for MS, with some positive, albeit inconclusive, results.

Still, says Robertson, the ability of gammaherpesviruses to infect neurons has been "controversial." Devan Mehta, a student in Robertson's lab, working with postdoctoral fellow Hem C. Jha, PhD, and Dennis Kolson, MD, PhD, a professor of Neurology, tested the link directly. Using genetically modified viruses that express green fluorescent protein (GFP), Mehta infected human neuroblastoma cells (neurons differentiated from cancer cells) and primary human fetal neurons, monitoring the infection over time by microscopy and protein expression.

In both cell types, infection with either EBV or KSHV resulted in the appearance of a fluorescent signal in the infected cells, as well as the appearance of key viral

proteins. The media in which infected cells were grown also contained functional virus particles capable of infecting other cells, indicating a mode of infection that tears open host cells. On the other hand, treatment of infected cells with acyclovir reduced the production of virus particles.

"I couldn't believe it," Robertson said. "After 50 years of studying EBV, nobody had ever seen the virus in nerve cells. But maybe they just never looked."

According to Robertson, these data suggest that viral infection of neurons could be associated with neuropathology, though he emphasizes that it is not the same as establishing causality. Such proof, if it ever comes, could be years away.

"There's likely to be association of this virus with neurons," he stated. "But more studies will be necessary to know whether it is actually associated with disease pathology.

Why EBV and KSHV infection of neurons results in a specific destructive form of infection will also be explored in future research. In contrast, when these viruses infect other cell types, such as B cells, they enter a latent mode, in which virus particles are relatively dormant. But, when they infect neurons, the particles apparently direct the cells to produce large amounts of virus, burst, and die, which explains why the growth media bathing infected cells could be used to infect other cells. "That's an interesting twist," Robertson said.

If nothing else, the ability of gammaherpesviruses to infect neurons provides a new model system for studying viral life cycles. But these viruses ultimately may also prove useful in studying disease etiology. "If you can infect nerve cells, that's likely to have some sort of pathology," he said.

*Additional authors include Jie Lu, Darine El-Naccache, Sanket K. Shukla and Colleen Kovacsics, all from Penn.*

*The study was funded by the National Cancer Institute (R01-CA- 137894, R01-CA-171979, R01-CA-177423, CA-137894-05, P30-DK- 050306, and P01-CA-174439), the Leukemia & Lymphoma Society, and the Abramson Cancer Center.*

***http://www.bbc.com/news/science-environment-35013190***

## New Horizons: Sharpest images of Pluto's surface

***The New Horizons probe has at last returned some of the super-sharp pictures it took of Pluto during its historic flyby in July.***

**By Jonathan Amos BBC Science Correspondent**

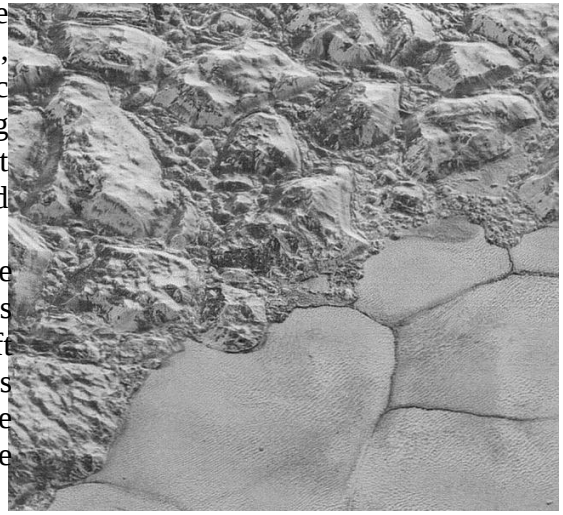
The images released by the US space agency on Friday show details on the surface of the dwarf planet at a resolution better than 80m per pixel.

On Earth at this scale, one could easily discern a city park.

With New Horizons, we see crystal clear views of mountains, craters and smooth ice fields.

"These close-up images, showing the diversity of terrain on Pluto, demonstrate the power of our robotic planetary explorers to return intriguing data to scientists back here on Planet Earth," said John Grunsfeld, the head of Nasa's science directorate.

"New Horizons thrilled us during the July flyby with the first close images of Pluto, and as the spacecraft transmits the treasure trove of images in its onboard memory back to us, we continue to be amazed by what we see."



***The rugged water-ice al-Idrisi mountains meet the smooth nitrogen-rich ices of Sputnik Planum*** **NASA/JPL-JHU/SWRI**

The probe got to about 12,500km from the surface of the dwarf and acquired a mass of pictures and other instrument data.

But because of the vast separation to Earth, and the modest transmitter on New Horizons, the flow of information back home has been extremely slow.

Indeed, it is expected to take until late 2016 to get everything in the probe's memory back on the ground.

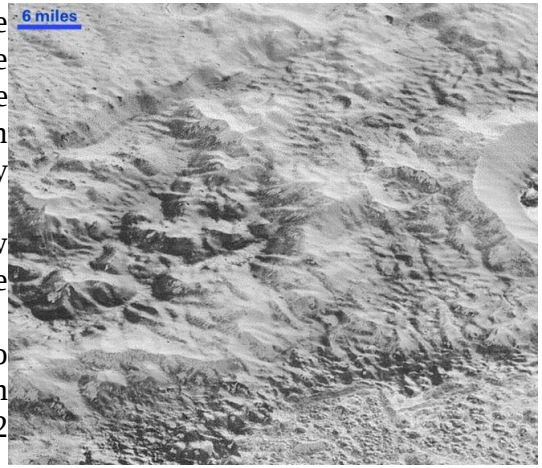
The mission team prioritised what it wanted to see first, which included some general impressions of Pluto - the broad context. Now, nearly five months on from the flyby, we are being treated to some spectacularly detailed offerings.


***Craters seen about 15 minutes before New Horizons' closest approach to Pluto – from a range of just 17,000km*** **NASA/JPL-JHU/SWRI**

Friday's pictures come from a photographic strip that incorporates a segment of its icy flat terrain informally known Sputnik Planum, and the adjacent rugged al-Idrisi mountains.

"These new images give us a breathtaking, super-high resolution window into Pluto's geology," said New Horizons' chief scientist, Alan Stern, of Southwest Research Institute (SwRI) in Boulder, Colorado.

"Nothing of this quality was available for Venus or Mars until decades after their first flybys; yet at Pluto we're there already - down among the craters, ice fields and mountains - less than five months after flyby! The science we can do with these images is simply unbelievable."




All the pictures were acquired by New Horizons' telescopic Long Range Reconnaissance Imager (Lorri).

The probe continues to move deeper into space. It is now about 167 million km beyond the dwarf planet and some 5.2 billion km from Earth.

***The images released by Nasa have a resolution of 77m to 85m per pixel*** **NASA/JPL-JHU/SWRI**

The spacecraft has been put on a course to fly by another object known simply as 2014 MU69. This will occur in just over three years' time.

However, the team does not yet have a budget from the US space agency to operate the probe at the roughly 45km-wide body. The scientists plan to submit a formal request for funding in the next few months.

***http://www.eurekalert.org/pub_releases/2015-12/uorm-ctr120415.php***

## Clinical trial results show new drug is better for CLL patients

***Older adults with chronic lymphocytic leukemia may have an alternative to toxic chemotherapy as their first treatment***

Older adults with chronic lymphocytic leukemia may have an alternative to toxic chemotherapy as their first treatment, according to a national study to be reported online Dec. 6, 2015, in the New England Journal of Medicine and co-authored by a Wilmot Cancer Institute oncologist.

The phase 3 clinical trial compared a newer, targeted drug, ibrutinib, against chlorambucil, a type of chemotherapy usually given to CLL patients as a front-line therapy. Paul Barr, M.D., director of the Clinical Trials Office at Wilmot, which is part of the University of Rochester Medical Center, supervised trial enrollment for patients in the Rochester and Finger Lakes region of upstate New York.

Scientists have been searching for an alternative treatment for CLL because this type of blood cancer often afflicts people in their 70s who have other medical problems and are more likely to be harmed by the toxicity of standard chemo. Ibrutinib is currently approved to treat CLL patients who have already received at least one other drug--but this was the first study to test its use as an initial therapy.

Results showed that among 269 patients with a median age of 73, ibrutinib was superior to chlorambucil in each measured aspect, including progression-free survival, overall response rate, and overall survival. Another key result: ibrutinib appeared to restore bone marrow function, which is relevant since bone marrow failure is a significant problem in CLL.

The risk of death or disease progression was 84 percent lower in the patients who took ibrutinib, compared to chlorambucil. It also extended survival, with about 98 percent of patients still alive two years after starting the targeted drug, versus 85 percent of the chlorambucil patients.

Difficult side effects occurred in about 20 percent of the patients taking ibrutinib, including diarrhea, fatigue, cough, nausea. However, 87 percent of patients were able to continue taking the drug for the median follow-up period of 18.4 months. The chlorambucil patients also experienced similar side effects, although early discontinuation of the chemotherapy drug due to complications was more than twice as frequent, the study said.

*Note: Pharmacyclics LLC, an ABBVie Company, of Sunnyvale, Calif., the maker of ibrutinib, funded the study; and Barr has been a paid consultant for Pharmacyclics.*

***http://nyti.ms/1OPfQX6***

## Penis Transplants Being Planned to Help Wounded Troops

***Within a year, maybe in just a few months, a young soldier with a horrific injury from a bomb blast in Afghanistan will have an operation that has never been performed in the United States: a penis transplant.***

**By DENISE GRADY DEC. 6, 2015**

The organ will come from a deceased donor, and the surgeons, from Johns Hopkins University School of Medicine in Baltimore, say they expect it to start working in a matter of months, developing urinary function, sensation and, eventually, the ability to have sex.

From 2001 to 2013, 1,367 men in military service suffered wounds to the genitals in Iraq or Afghanistan, according to the Department of Defense Trauma Registry. Nearly all were under 35 and were hurt by homemade bombs, commonly called improvised explosive devices, or I.E.D.s. Some lost all or part of their penises or testicles — what doctors call genitourinary injuries.

Missing limbs have become a well-known symbol of these wars, but genital damage is a hidden wound — and, to many, a far worse one — cloaked in shame, stigma and embarrassment.

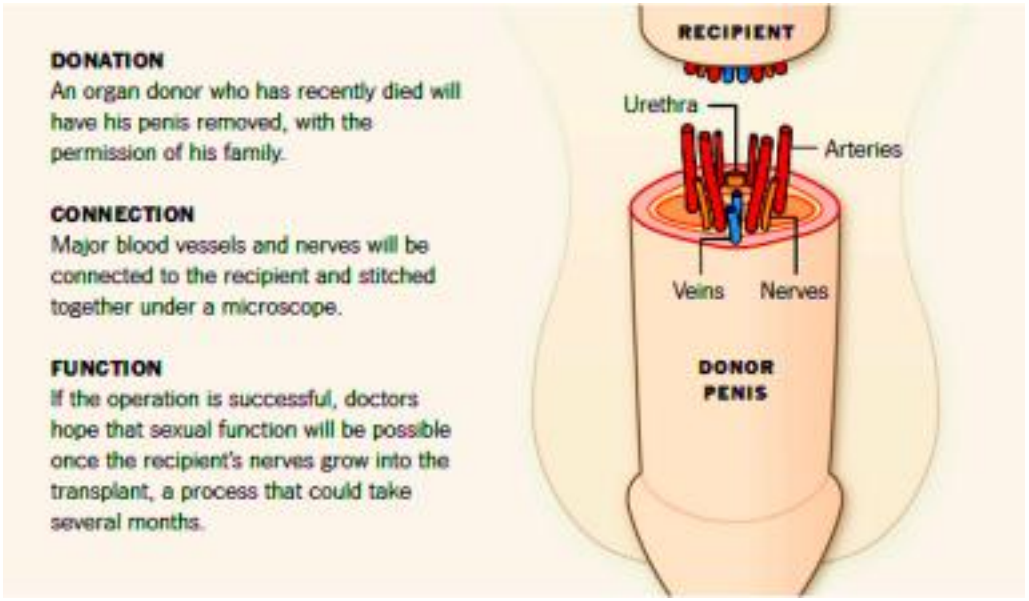
“These genitourinary injuries are not things we hear about or read about very often,” said Dr. W. P. Andrew Lee, the chairman of plastic and reconstructive

surgery at Johns Hopkins. “I think one would agree it is as devastating as anything that our wounded warriors suffer, for a young man to come home in his early 20s with the pelvic area completely destroyed.”

Only two other penis transplants have been reported in medical journals: a failed one in China in 2006 and a successful one in South Africa last year. The surgery is considered experimental, and Johns Hopkins has given the doctors permission to perform 60 transplants. The university will monitor the results and decide whether to make the operation a standard treatment. The risks, like those of any major transplant operation, include bleeding, infection and the possibility that the medicine needed to prevent transplant rejection will increase the odds of cancer.

Dr. Lee cautioned that patients should be realistic and not “think they can regain it all.” But doctors can give the recipients a range of what to expect.

**An Experimental Penis Transplant**




***Surgeons are preparing to perform the first penis transplant in the United States.***

**Sources: Plastic and Reconstructive Surgery; Johns Hopkins University By Jonathan Corum**

“Some hope to father children,” Dr. Lee said. “I think that is a realistic goal.”

Just the penis will be transplanted, not the testes, where sperm are produced. So if a transplant recipient does become a father, the child will be his own genetically, not the offspring of the donor. Men who have lost testicles completely may still be able to have penis transplants, but they will not be able to have biological children.

In the 2006 case in China, the recipient asked that the transplant be removed a few weeks after the operation because of “apparent psychological rejection,” the Johns Hopkins doctors said, adding that in photographs the transplant had patches of dead and peeling skin, possibly from inadequate blood flow.

But the South African recipient, a young man whose penis had been amputated because of a botched circumcision, recently became a father, said Dr. Gerald Brandacher, the scientific director of the reconstructive transplantation program at Johns Hopkins.

Doctors who treat young men wounded in combat say that no matter how bad their other injuries are, the first thing the men ask about when they wake up from surgery is whether their genitals are intact.

“Our young male patients would rather lose both legs and an arm than have a urogenital injury,” said Scott E. Skiles, the polytrauma social work supervisor at the Veterans Affairs Palo Alto Health Care System.

Sgt. First Class Aaron Causey, who lost both legs, one testicle and part of the other from an I.E.D. while in Afghanistan with the Army in 2011, said the testicular damage was the most troubling of his injuries.

“I don’t care who you are — military, civilian, anything — you have an injury like this, it’s more than just a physical injury,” Sergeant Causey said.

Some doctors have criticized the idea of penis transplants, saying they are not needed to save the patient’s life. But Dr. Richard J. Redett, director of pediatric plastic and reconstructive surgery at Johns Hopkins, said, “If you meet these people, you see how important it is.”

“To be missing the penis and parts of the scrotum is devastating,” Dr. Redett said. “That part of the body is so strongly associated with your sense of self and identify as a male. These guys have given everything they have.”

Jeffrey Kahn, a bioethicist at Johns Hopkins, said that at a conference convened last year by the Bob Woodruff Foundation, which aids injured veterans, wives said that genitourinary injuries had eroded their husbands’ sense of manhood and identity. Most telling, Dr. Kahn said, was that the men themselves attended the conference but did not speak about their wounds.

Although surgeons can create a penis from tissue taken from other parts of a patient’s own body — an operation being done more and more on transgender men — erections are not possible without an implant, and the implants too often shift position, cause infection or come out, Dr. Redett said. For that reason, he said, the Johns Hopkins team thinks transplants are the best solution when the penis cannot be repaired or reconstructed. If the transplant fails, he said, it will be removed, leaving the recipient no worse off than before the surgery.

But can men — and their partners — get used to the idea that their most intimate part came from another man’s body?

The best analogy is hand transplants, Dr. Brandacher said, because hands are personal and distinctive — a transplant that the recipient can see, unlike a kidney or liver.

"I can tell you from all the patients — and I've been involved since 1998 — every single one, after surgery, look at the graft, try to move it and they immediately call it 'my hand,' " Dr. Brandacher said. "They immediately incorporate it as part of their body. I would assume, extrapolating, that this is going to be the same for this kind of transplant."

Dr. Kahn said it was essential that the families of organ donors be asked specifically for permission to use the penis, just as special permission was required for face and hand transplants. It is not assumed that people willing to donate kidneys or livers will also consent to having their loved one's genitals removed. The surgeons want a relatively young donor to increase the odds that the transplanted organ will function sexually.

For now, the operation is being offered only to men injured in combat, Dr. Lee said. It is not available to transgender people, though that may change in the future.

"Once this becomes public and there's some sense that this is successful and a good therapy, there will be all sorts of questions about whether you will do it for gender reassignment," Dr. Kahn said. "What do you say to the donor? A 23-year-old wounded in the line of duty has a very different sound than somebody who is seeking gender reassignment."

For a transplant to be possible, certain nerves and blood vessels have to be intact in the recipient, as does the urethra, the tube that carries urine out of the body. The screening process, as for any organ transplant, also involves making sure that the candidate is psychologically ready, understands the risks and benefits, can stick to the regimen of anti-rejection medicine and has a family support network.

A few initial candidates are being evaluated. "We have one that we're moving forward with, and we're very far in the process," Dr. Redett said, adding that he expected the patient to be put on the transplant waiting list soon. "That means you are really only waiting for a donor."

A spokeswoman for Johns Hopkins said the candidates and their families had declined to be interviewed.

The university will pay for the first transplant, Dr. Lee said, adding that he had asked the Defense Department for money to cover more operations. The surgeons are donating their time, he said. Comparing the surgery to hand transplants performed at Johns Hopkins, he estimated the cost at $200,000 to $400,000 per operation. He said the Department of Veterans Affairs would pay for the drug that the men will need to prevent transplant rejection.

The project has been years in the making, the doctors said, with extensive research and practice surgery on cadavers. Some of the work involved injecting brightly colored food dyes into the cadavers to map out the circulatory system in the penis. Dr. Lee said the research had found previously unknown aspects of its blood supply, which will be critical to the transplant's success.

The operation should take about 12 hours, Dr. Lee said. The surgeons will connect two to six nerves, and six or seven veins and arteries, stitching them together under a microscope.

For the first few weeks after the surgery, a catheter will be left in place to drain urine. Sexual function will take longer to develop — probably a few months, Dr. Lee said. He said nerves would grow from the recipient into the transplant at a rate of about one inch per month, so the timing will depend in part on the extent of the recipient's injuries and how far the nerves need to go.

After the transplant, the men will begin taking anti-rejection medication and will need it for the rest of their lives. Such drugs work by suppressing the immune system and can increase the odds of infections and cancer.

To minimize the risks, the Johns Hopkins team has found a way to use just one drug, rather than the three usually needed for other transplants. At the time of the penis transplant, they will treat the recipient with a medication that reduces immune system cells. About two weeks later, he will receive an infusion of stem cells from the donor. The infusion dials back the tendency of the recipient's immune system to attack the transplant, and just one anti-rejection drug, tacrolimus, is then enough to keep it in check. Doctors have used this technique successfully in patients who have had hand transplants.

Ultimately, the goal is to restore function, not just form or appearance, Dr. Brandacher emphasized. That is what the recipients want most.

"They say, 'I want to feel whole again,' " Dr. Brandacher said. "It's very hard to imagine what it means if you don't feel whole. There are very subtle things that we take for granted that this transplant is able to give back."

*Alain Delaquérière contributed research.*

***http://www.eurekalert.org/pub_releases/2015-12/nuos-mhb120415.php***

## Men have better sense of direction than women

***Different approaches to the same navigational tasks underscore sex-linked differences***

It's been well established that men perform better than women when it comes to specific spatial tasks. But how much of that is linked to sex hormones versus cultural conditioning and other factors?

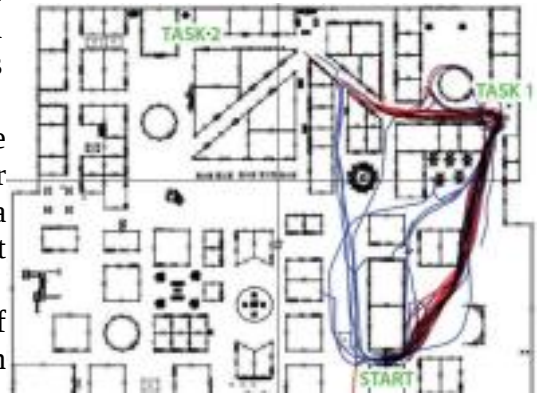
Researchers at the Norwegian University of Science and Technology (NTNU) decided to explore this idea by administering testosterone to women and testing

how they performed in wayfinding tasks in a virtual environment. Using fMRI, the researchers saw that men in the study took several shortcuts, oriented themselves more using cardinal directions and used a different part of the brain than the women in the study.

But when women got a drop of testosterone under their tongue, several of them were able to orient themselves better in the four cardinal directions.

"Men's sense of direction was more effective. They quite simply got to their destination faster," says Carl Pintzka, a medical doctor and PhD candidate at NTNU's Department of Neuroscience.

The directional sense findings are part of his doctoral thesis on how the brain functions differently in men and women.




***The lines show how men and women navigated a route. The blue lines are the women's routes, and the red lines are the men's. The lines show that the men arrived faster and solved more tasks.*** **NTNU**

**Puzzle solving in a 3D maze**

Pintzka used an MRI scanner to see whether there are any differences in brain activity when men and women orient themselves. Using 3D goggles and a joystick, the participants had to orient themselves in a very large virtual maze while functional images of their brains were continuously recorded.

Eighteen men and 18 women first took an hour to learn the layout of the maze before the scanning session. In the MRI scanner, they were given 30 seconds for each of the 45 navigation tasks. One of the tasks, for example, was to "find the yellow car" from different starting points.

**Women often use a route**

The men solved 50 per cent more of the tasks than the women.

According to Pintzka, women and men have different navigational strategies. Men use cardinal directions during navigation to a greater degree.

"If they're going to the Student Society building in Trondheim, for example, men usually go in the general direction where it's located. Women usually orient themselves along a route to get there, for example, 'go past the hairdresser and then up the street and turn right after the store'," he says.

The study shows that using the cardinal directions is more efficient because it is a more flexible strategy. The destination can be reached faster because the strategy depends less on where you start.

**Women have better local memory**

fMRI images of the brain showed that both men and women use large areas of the brain when they navigate, but some areas were different. The men used the hippocampus more, whereas women used their frontal areas to a greater extent.

"That's in sync with the fact that the hippocampus is necessary to make use of cardinal directions," says Pintzka.

He explains the findings in evolutionary terms.

"In ancient times, men were hunters and women were gatherers. Therefore, our brains probably evolved differently. For instance, other researchers have documented that women are better at finding objects locally than men. In simple terms, women are faster at finding things in the house, and men are faster at finding the house," Pintzka says.

**A little testosterone under the tongue**

Step two was to give some women testosterone just before they were going to solve the maze puzzles.

This was a different group of women than the group that was compared to men. In this step, 42 women were divided into two groups. Twenty-one of them received a drop of placebo, and 21 got a drop of testosterone under the tongue. The study was double-blinded so that neither Pintzka nor the women knew who got what.

"We hoped that they would be able to solve more tasks, but they didn't. But they had improved knowledge of the layout of the maze. And . And they used the hippocampus to a greater extent, which tends to be used more by men for navigating," says Pintzka.

Losing one's sense of direction is one of the first symptoms in Alzheimer's disease.

"Almost all brain-related diseases are different in men and women, either in the number of affected individuals or in severity. Therefore, something is likely protecting or harming people of one sex. Since we know that twice as many women as men are diagnosed with Alzheimer's disease, there might be something related to sex hormones that is harmful," says Pintzka.

He hopes that by understanding how men and women use different brain areas and strategies to navigate, researchers will be able to enhance the understanding of the disease's development, and develop coping strategies for those already affected.

*Reference: Changes in spatial cognition and brain activity after a single dose of testosterone in healthy women. Carl W.S. Pintzka et al. Behavioral Brain Research, Vol. 298, Part B, 1 February 2016, Pages 78-90.*

http://www.eurekalert.org/pub_releases/2015-12/aabu-dwf120415.php

# Diabetics with foot complications have impaired cognitive function -- Ben-Gurion University study

***Patients with this diabetes also have significantly impaired cognitive function***

BEER-SHEVA, Israel - In a first-time study, Ben-Gurion University of the Negev (BGU) researchers revealed a new finding in people with diabetes who suffer from "diabetic foot." Patients with this condition also have significantly impaired cognitive function.

"This study shows a clear correlation between diabetes and cognitive deterioration," says Rachel Natovich, a recent BGU Ph.D. graduate. "Diabetes is a multi-system condition that affects the brain, and the risk of a diabetic developing dementia is twice that of a 'normal' person. Diabetic foot is a symptom that the diabetes is causing deterioration of the entire cardiovascular system."

Diabetic foot is one of the most severe but also preventable long-term complications of diabetes mellitus. The symptoms appear as non-healing foot ulcers and necrosis and, if untreated, can lead to multiple amputations. The lifetime risk of a person with diabetes developing a foot ulcer could be as high as 25 percent.

"There is no research focusing on the cognitive functioning of these patients, despite the fact that the micro and macro vascular changes underlying the diabetic foot are systemic, occurring in many different organs, including the brain," says Dr. Natovich, who conducted the study. "Presently, research regarding diabetic foot focuses mainly on epidemiology, prevention and ulcer treatment."

According to the research, those with diabetic foot remember less, have decreased concentration, difficulty with learning, decreased inhibition, slower cognitive and psychomotor responses, and decreased verbal fluency. This implies that diabetic patients with diabetic foot complication suffer cognitive difficulties above and beyond those known in the general diabetic population. The cognitive abilities of the two groups were similar prior to developing the condition. However, the current cognitive status of diabetic foot patients in the study is significantly impaired.

"This new information is an important contribution to the healthcare of patients due to their increased risk for medical complications and the unique challenge that they present to healthcare providers," Natovich says. "Successful adherence to medical recommendations requires considerable cognitive abilities like intact concentration, memory and executive functions."

Natovich proposes practical changes to the treatment strategy, including:

***Patients with diabetic foot must be routinely monitored for cognitive changes. Early detection of cognitive decline will enable initiating proper intervention.***

***Due to difficulties with memory, attention and executive functions, the family and healthcare provider must take a more active role in patient care.***

***Patients with diabetic foot could benefit from participation in group treatment aimed at improving diabetic control, nutrition and physical activity.***

***Diabetic patients should receive psycho-education regarding possible cognitive complications of the disease and the importance of proper disease control for preservation of cognitive abilities.***

Natovich completed her Ph.D. under Prof. Talma Kushnir of BGU's Department of Public Health, Faculty of Health Sciences, and Dr. Ilana Harman-Bahm from Soroka University Medical Center. Dr. Natovich was awarded several prizes for this research, including the Diabetic Foot Best Presentation Award from the American Diabetes Association (ADA). She presented her findings at the ADA Conference earlier this year.