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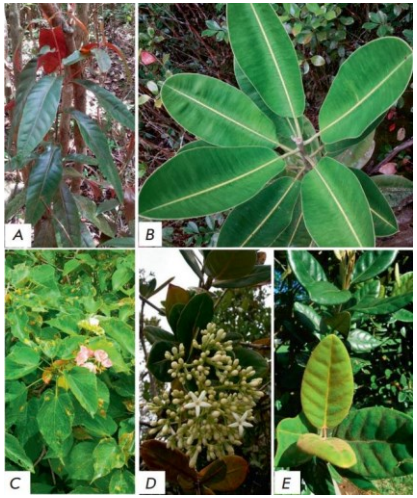
Mauritian medical herbs possess antitumor properties

They contain biologically active substances of these species have shown to contain effective inhibitors of esophageal cancer cells



Far Eastern Federal University (FEFU) scientists teamed up with colleagues from the UK and Mauritius and experimentally demonstrated that extracts of the endemic (i.e. growing only on this island) medicinal herb leaves *Acalypha integrifolia*, *Eugenia tinifolia*, and *Labourdonnaisia glauca* stop the proliferation of oesophageal squamous carcinoma cells, ones of the most deadly cancer type worldwide. A related article is published in the *"Acta Naturae"* journal.

The Mauritius herbarium voucher specimen barcode number is given in brackets ( ). A - A. integrifolia (MAU 0016402); B - L. glauca (MAU 0016430); C - D. acutangula (MAU 0016638); D - G. psychotrioides (MAU 0009450) - E. tinifolia (MAU 0016540) **FEFU press office**

Researchers found out that the extracts contain natural chemical compounds to inhibit the propagation of cancer cells. Namely, they restrain the G2/M stages transition in malignant tumor cells by activating AMPK signaling pathway. Currently, the search for AMPK activators is an urgent problem in molecular oncology. Having studied the medical herbs of Mauritius, scientists may have accomplished an important step, if not a breakthrough in this direction.

"Mauritius Island is a treasure island of the global biodiversity, and the story of continuing tragedy of human greed, barbarian appetite (remember the Dodo bird from the Alice story, RIP) and neglection of true wonders of the planet designed to save human lives. About one-third of the local plants are used in traditional medicine, but there is still a lack of scientific evidence of their therapeutic potential, while genocide of nature is most evident on such small pieces of lost paradise. To date, only 15 percent of the island's plant species have been examined for their medicinal properties, which is still better than in many countries. Ethnobotany combined with modern organic chemistry and cell biology is an extremely fruitful interdisciplinary field for scientific research. We hope to proceed working in this direction, thanks to the growing globally Bio2bio* movement supported by the Global Young Academy**. In particular, further study of the active compounds from the leaves extracts of A. integrifolia, E. tinifolia and L. Glauca promises to reveal prototypes of the future drugs to treat oesophageal cancer, and other deadly diseases" - said Alexander Kagansky, the Head of the Center for Genomic and Regenerative Medicine of the School of Biomedicine FEFU, an expert in the field of cancer epigenetics and chromosome biology.

The lead scientist noted that oesophageal cancer is a growing global concern due to the diets and other detrimental side effects of modern lifestyles, technologies, and culture. At the present time, there is not enough effective means of its treatment, while the existing radiotherapy, chemotherapy resection may prolong lives by few months, usually spent in tremendous suffering. The aggressive disease prevents eating, digestion, and come along with a very negative prognosis. Oesophageal squamous carcinoma together with adenocarcinoma represent the sixth main death cause in the global oncological practice. Less than 15 percent of patients survive for five years from the time of diagnosis. On average, people with such diagnoses live less than a year. These types of cancer are treated with broad-spectrum chemo. The drugs are extremely toxic and evoke a number of side effects worsening the patients' quality

of life. At the same time, the efficacy of current chemotherapy for this disease is not very assuring, to say the least.

More than half of all anti-cancer drugs employing today were developed from natural sources. At the same time, most of the world's population treats cancer by means of thousands of herb species that have been known to traditional medicine for centuries, each of those coming with many different naturally chemistries, evolved for use in nature for millions of years. Taking into the account centuries-old human understanding of nature, modern biomedicine needs to develop new anti-cancer compounds from a wide range of natural sources, such as plants, fungi, bacteria, insects, and marine organisms.

During the study, FEFU scientists in cooperation with foreign colleagues studied in the laboratory carefully isolated and fractionated extracts of five species of Mauritian endemic medicinal plants: *Acalypha integrifolia Willd* (Euphorbiaceae), *Labourdonnaisia glauca Bojer* (family Sapotaceae), *Dombeya acutangula Cav. subsp. rosea Friedmann* (Malvaceae), *Gaertnera psychotrioides (DC.) Baker* (Rubiaceae), *Eugenia tinifolia Lam* (Murtaceae). They were tested on the cell lines from two different types of patients' malignant tumors. Three of the five biologically active substances of these species have shown to contain effective inhibitors of oesophageal cancer cells, stopping their growth and contributing to their death.

Alexander Kagansky emphasized that the future of global medicine depends on the saving of the planet's biodiversity. He reminded that currently the total number of living species is steadily declining. Bringing on the example of medicinal plants of Mauritius, which he and colleagues took an effort to study, the scientist pointed out that they are devastated at an incredible rate at which species are being erased from existence as a result of human 'progressive' activities, such as lumber, energy, and food generation. At the meanwhile, so far these unique species do not grow anywhere else on the planet, a few additional 5-star hotels, bank building, or a golf-course could end up their existence once and for all. Given this, Kagansky became a co-organizer of the Bio2Bio* international consortium thanks to the support of the Global Young Academy and the Interacademy Partnership***. The task of Bio2bio is to protect biodiversity and nature which are sources of valuable biological compounds, as well as to create a database of natural molecules that will provide a basis for drug components elucidation, and for linking traditional medicine systems with each other and modern medicine via integration of other areas such as pharmacognosy, ethnobotany, synthetic and analytic chemistry, immunology, pharmacology, molecular and cell biology, metabolomics, etc.

"Our research should serve the benefit of humanity and show by evidence that on the mechanistic level people depend on natural chemistries, which will reward us by reducing deaths and suffering of ourselves, our parents, and children", the scientist said.

Original article: Mauritian Endemic Medicinal Plant Extracts Induce G2/M Phase Cell Cycle Arrest and Growth Inhibition of Oesophageal Squamous Cell Carcinoma in Vitro.

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Human influence on climate change is traced back to the 19th century

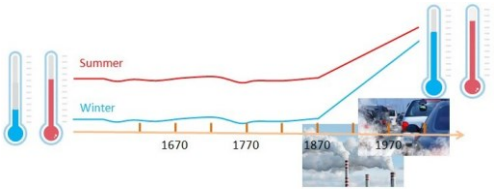
Human influence on climate change can be traced back to the late 19th century

by Chinese Academy of Sciences

Climate change poses a serious challenge to the human society and it is generally believed that humans are themselves to blame. The Intergovernmental Panel on Climate Change has concluded that, with high confidence, human activities are responsible for the continuing rise of global mean surface air temperature since the 1950s.

A recent article published in the journal *Nature Sustainability* by Duan et al. has shown that human influence on climate change can

be traced back to the late 19th century based on summer-winter temperature difference. This research has been carried out by scientists from the Institute of Atmospheric Physics, Chinese Academy of Sciences in collaboration with leading experts on climate research from the UK and Germany.



A graphic illustration for the anthropogenic-induced decrease in the difference of summer and winter temperatures. The thermometers represent the difference between summer and winter temperatures. **Jianping Duan**

"it is well known that humans are driving global warming, but when did this begin?" said the lead author, Dr. Jianping Duan, "Our study has shown that anthropogenic influence on climate change started much earlier than we previously believe."

Anthropogenic climate change is usually focused on the rise of surface air temperature, namely global warming, and the increase of climate extremes. Duan et al. (2019) have found that the amplitude of seasonal temperature fluctuations has been decreasing widely, and this trend can be traced back to the late 19th century. They find that temperature seasonality had been stable until 1860s, from which there have been continuous downward trends across northern hemisphere mid-high latitudes.

A formal detection and attribution analysis using the latest climate model simulations has shown that increased greenhouse gas concentrations and anthropogenic aerosols are the main contributors to the observed downward trends.

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Sugar entering the brain during septic shock causes memory loss

Research gives clear target for drug development and further study into memory loss

TROY, N.Y. -- The loss of memory and cognitive function known to afflict survivors of septic shock is the result of a sugar that is released into the blood stream and enters the brain during the life-threatening condition. This finding, published today in the *Proceedings of the National Academy of Sciences*, explains the premature mental aging that follows septic shock and may shed light on memory loss in other diseases.

"This sugar is getting into the hippocampus, and it shouldn't be in there," said Robert Linhardt, professor of biocatalysis and metabolic engineering at Rensselaer Polytechnic Institute, and lead author of the study. "We actually think this is rewiring memory in the hippocampus, and it's causing memory loss. Neural circuits are being disrupted or broken or connected in the wrong way."

The study is the latest outcome of a six-year partnership between Linhardt and Dr. Eric Schmidt, an expert on sepsis and assistant professor in the Department of Medicine at University of Colorado Denver.

Sepsis is a systemic infection of the body. One-third of patients admitted to hospitals with sepsis go into septic shock. Of those, half will die. In a 2016 study published in the *American Journal of Respiratory and Critical Care Medicine*, a team that included Schmidt and Linhardt developed a simple but accurate test for determining whether patients in septic shock would recover or die.

The test uses a urine sample to check concentrations of a type of sugar - glycosaminoglycans - that ordinarily coat cells lining blood vessels and other surfaces inside the body. In septic shock, the body sheds fragments of these sugars, and the team found that higher concentrations portend death. The test is used in clinical settings, and the insight has helped doctors search for more effective therapies.

Their next step tested whether a link exists between the sugars and mental aging associated with septic shock. Research published in

the February edition of the *Journal of Clinical Investigations* showed that, during septic shock, fragments of the sugar heparan sulfate crossed the blood-brain barrier and entered the hippocampus, a region of the brain critical to memory and cognitive function. Evidence indicated that the heparan sulfate might be binding with brain-derived neurotrophic factor (BDNF), which is critical to hippocampal long-term potentiation, a process responsible for spatial memory formation. The researchers also found that presence of an enriched heparan sulfate in the blood plasma of septic patients upon admission to an intensive care unit predicted cognitive impairment detected 14 days after discharge.

To be sure, the researchers wanted to see the heparan sulfate enter the hippocampus and bind with BDNF. The new study in *PNAS* shows exactly that. To follow heparan sulfate into the brain in a sea of other sugars moving through the bloodstream Linhardt's team had to synthesize heparan sulfate tagged with a stable carbon isotope, which unlike many other labeling methods, is completely safe and was identical to the natural sugar. It took them two years to figure out how to do it.

Then they put their hypothesis to the test. In healthy mice, 100 percent of the tagged heparan sulfated was excreted through the urine within 20 minutes, and none ever entered the brain. But in septic mice, researchers found a small amount of tagged heparan sulfate in the hippocampus region of the brain.

"Now that we know the cause of cognitive damage in septic shock, it gives us a clear target for a drug therapy: something that binds to the sugar and clears it, or an enzyme that converts it to something that won't impair cognitive function," Linhardt said. "This is an important advance, and we're excited about the story that's unfolding."

At Rensselaer, Linhardt is joined in the research by Xing Zhang and Xiaorui Han. At University of Colorado, Schmidt is joined by Yimu Yang, Kaori Oshima, Sarah Haeger, Mario Perez, Sarah McMurtry, Joseph Hippensteel, Joshay Ford, and Paco Herson. The current research also includes Linhardt's former student, Jian Lu, now on the faculty at the University of North Carolina at Chapel Hill, and his colleague, Yongmei Xu, who led in the synthesis of the tagged sugar.

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Soft bedding poses grave danger to sleeping babies, study shows

Bedding caused almost 70% of sleep-related suffocation deaths

Almost 70% of babies who died from sleep-related suffocation between 2011 and 2014 did so because of soft bedding, a new study reveals.

The finding underscores physicians' urgent message to new parents that babies should sleep only in cribs or bassinets free of blankets, toys and other potential hazards.

Unintentional suffocation is the No. 1 cause of injury death in babies less than a year old in the United States, with more than 80% of cases occurring in bed.

The new study, from a University of Virginia Health System physician and her colleagues, sheds light on how that is happening, revealing that soft bedding is responsible for the vast majority of sleep-related infant deaths (69%).

The second most common cause was due to overlay by another person (19%), with 71% of these occurring while sleeping in the same bed with a parent and/or sibling. The third most common was "wedging," in which babies become trapped between two objects, such as a mattress and wall (12%).

"These results are very significant, because these deaths - clearly due to suffocation - were all preventable" said UVA's Fern Hauck, MD. "It is also important to note that the causes of suffocation differed by infant age. So, overlaying is a bigger problem for the youngest infants, soft bedding affects infants most commonly under 4 months, and wedging more a problem when infants are older and can move around in bed."

Unsafe Infant Sleep Practices

Sleep-related suffocation and strangulation was responsible for 14% of all sudden, unexpected infant deaths during the period reviewed, the researchers determined. Death by soft bedding was most likely to occur in an adult bed, with the babies on their backs. Most often, the suffocation or strangulation was caused by a blanket or blankets.

When babies died of overlay, it was most often the mother who overlaid the infants. In wedging deaths, babies were most likely to become trapped between the mattress and a wall.

"Keeping infants safe is a priority for parents, and these types of suffocation deaths can be prevented by following the American Academy of Pediatrics safe sleep guidelines," Hauck said. "These include: placing infants to sleep in a safety-approved bassinet or crib in the caregivers' room; not placing infants alone or with others on adult beds to sleep; keeping all soft objects out of the infant's sleep area, including blankets and pillows (wearable blankets are preferred over loose blankets); and placing infants on their back to sleep."

In conducting the study, the researchers reviewed more than 1,800 infant deaths classified as suffocation in the Centers for Disease Control's national Sudden Unexpected Infant Death Case Registry. The deaths occurred between 2011 and 2014, the most recent year for which data was available. All the *babies were less than a year old.*

Findings Published

The new study has been published in the scientific journal Pediatrics. *The research team consisted of Alexa B. Erck Lambert, Sharyn E. Parks, Carri Cottengim, Meghan Faulkner, Hauck and Carrie K. Shapiro-Mendoza.*

Erck Lambert was supported by a contract between DB Consulting Group and the Division of Reproductive Health at the National Center for Chronic Disease Prevention and Health Promotion, part of the Centers for Disease Control and Prevention. In addition, Faulkner's employer, the Michigan Public Health Institute, received funding from the Centers for Disease Control and Prevention to support the SUID Case Registry.

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Slime mold absorbs substances to memorize them

Slime moulds learn to tolerate a substance by absorbing it

Physarum polycephalum is a complex single-cell organism that has no nervous system. It can learn and transfer its knowledge to its fellow slime moulds via fusion. How it did so was a mystery. Researchers at the Centre de Recherches sur la Cognition Animale (CNRS/UT3 Paul Sabatier)* have recently demonstrated that slime moulds learn to tolerate a substance by absorbing it.

This is a fusion of the venous network of two blobs. **© David Villa / CNRS Photothèque**

This discovery stems from an observation: slime moulds only exchange information when their venous networks fuse. In that case, does knowledge circulate through these veins? Is it the substance that the slime mould gets used to that supports its memory?

First the team of scientists forced the slime moulds to cross salty environments for six days to habituate them to salt. Then they evaluated the salt concentration inside the slime moulds: they contained ten times more salt than "naive" slime moulds. The researchers then placed the habituated slime moulds in a neutral environment and observed that they excreted the salt absorbed within two days, losing the "memory". This experiment therefore seemed to show a link between the salt concentration within the organism and the "memory" of the habituation.

To go further and confirm this hypothesis, the scientists introduced the "memory" into naive blobs by injecting a salt solution directly into the organisms. Two hours later, the slime moulds were no longer naive and behaved like slime moulds that had undergone a six day training

When the environmental conditions deteriorate, slime moulds can enter into a dormant stage. The researchers demonstrated that slime moulds habituated to salt stored the salt absorbed before entering the dormant stage and could store the knowledge for up to a month.

The results of this study prove that the aversive substance could be the support of the slime mould's memory. The researchers are now trying to establish whether if the slime moulds can memorise several aversive substances at the same time and to what extent they can get used to them.

** The Centre de Recherche sur la Cognition Animale is part of the Centre de Biologie Intégrative (CNRS/UT3 Paul Sabatier)*

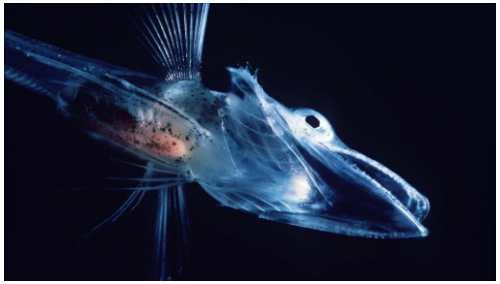
http://bit.ly/2WhUD0U

Icefish Study Adds Another Color to the Story of Blood

The rainbow of pigments that animals use for blood illustrates a central truth about evolution.

John Rennie ***Deputy Editor***

In February, a genomics study appearing in *Nature Ecology & Evolution* drew attention to the bizarre Antarctic blackfin icefish, which swim in the brutally cold waters off the coast of the southernmost continent.



The Antarctic blackfin icefish is the only known vertebrate animal that lacks red blood cells containing hemoglobin. But the use of hemoglobin to transport oxygen through the body is actually a rarity among invertebrates, which rely on a variety of other pigments in their versions of blood. ***Uwe kils***

The icefish of the Channichthyidae family are unusual in several ways — they lack scales and have transparent bones, for example — but what stands out most is their so-called white blood, which is unique among vertebrates. These fish are the only ones known to have neither red blood cells nor hemoglobin pigments for transporting oxygen. Oxygen simply diffuses into their circulating blood plasma from the frigid seawater by way of the fish's enlarged gills and smooth skin.

By looking at the genome of one icefish species, the researchers were able to peek at the evolutionary adaptations that allowed it to survive. Some were common to red-blooded fish that are also native to Antarctic waters, like the presence of extra genes for making blood proteins that act like antifreeze. Some were more distinctive to the icefish's lack of red blood cells, such as a boost in the enzymes that protect tissues from the highly reactive free oxygen in its blood.

Odd as the icefish may seem, what makes it peculiar among vertebrates is the norm across the rest of the animal kingdom. Most invertebrates carry genes for hemoglobins, but they generally use other metalloprotein pigments in their versions of blood. Insects, crustaceans and other arthropods use hemocyanin, a bluish copper-based pigment. Mollusks, ranging from clams to squids and octopuses, use hemocyanin, too, but they seem to have invented their version of it independently. Some worms use purplish hemerythrin; others use greenish chlorocruorin; some use a combination of pigments.

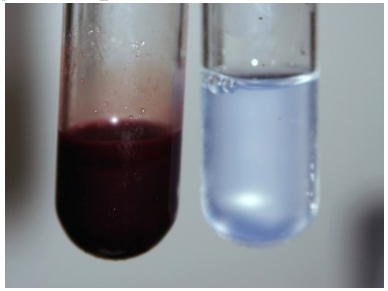
It may seem puzzling that so many varieties of blood exist, and more puzzling still that while invertebrates have experimented wildly, vertebrates — aside from the icefish — have stayed universally loyal to the kind with red cells and hemoglobin. The explanation is deeply entrenched in the history of life, going back to the earliest cells.

An Affinity for Oxygen

From the very beginning of life, cells needed to move electrons around between molecules as part of their metabolism, explained Ross Hardison, a professor of biochemistry and molecular biology at Pennsylvania State University. As controls over these redox (oxidation-reduction) reactions, cells deployed ring-shaped

molecules called porphyrins. When these porphyrins held a metal atom like iron or copper, they had a ferocious affinity for oxygen. "Once you have an iron in that porphyrin ring, it's used throughout the biosphere," Hardison said. He speculated that it "might be one of the earliest molecules that eventually got incorporated into cells."

Hemoglobin arose out of four interlinked globin proteins, each holding a heme, and it rapidly became ubiquitous. "Hemoglobins predate the origin of animals and even predate the common ancestor of animals and plants," said Mark Siddall, a curator in the division of invertebrate biology at the American Museum of Natural History.



Two tubes contrast the opalescent "white" blood of the blackfin icefish with the red blood of a closely related fish. The icefish's blood has no hemoglobin but is cloudy with other proteins and macromolecules, some of which help to keep the blood functional in the cold polar waters. **Bill Detrich, Northeastern**

When respiring animals were only a few cells thick, they could count on diffusion to satisfy their needs for oxygen. But when they grew too bulky for simple diffusion to continue to oxygenate their tissues, hemoglobin was ingeniously ready for the job.

The secret of hemoglobin's success is collaborative bonding: With every oxygen molecule that the pigment binds, it can bind to the next one more easily, until all four vacancies are filled. This makes hemoglobin extremely efficient at collecting oxygen where it's abundant (as in the open air and in lungs) and then releasing it again gradually in oxygen-starved tissues.

Vertebrates typically carry genes for several variant globin proteins with finely tuned uses. For example, fetal mammals have a special hemoglobin in their blood with extra affinity for oxygen, which helps them to draw oxygen out of the maternal blood supply in the placenta. Our skeletal muscles make myoglobin, a single globin protein ancestral to hemoglobin, which helps muscle hang on to a reserve of oxygen to use during exercise.

But as good as hemoglobin is, it's not the ideal molecule for transporting oxygen in all circumstances. Consider hemocyanin, which is so widely used among invertebrates. Hemocyanin is less efficient than hemoglobin at grabbing oxygen because it, like the other hemoglobin alternatives, usually does not bond collaboratively. But the disadvantage of collaborative bonding is that hemoglobin performs worse when oxygen is in short supply. Hemoglobin's effectiveness also drops with temperature. Consequently, for creatures like octopuses and crabs that live on or near the cold ocean floor, hemocyanin may be a more practical choice.

For insects, it's different. Their equivalent to blood is hemolymph, a mostly clear fluid that contains small amounts of hemocyanin. But they generally don't rely on this hemolymph to transport oxygen. Most insects breathe through a network of "tracheal tubes" that pervade their tissues and connect to the air through openings in the exoskeleton. The "open" circulatory system of insects doesn't have vessels like capillaries to direct the hemolymph; instead, the hemolymph sloshes through the body cavity and helps to distribute dissolved nutrients. The hemocyanin may be in the hemolymph just to help insects store oxygen for later use.

Hemerythrin, the blood pigment found in annelids (segmented worms), leeches and certain other worms, has a deceptive name, because it contains no heme at all. However, like hemoglobin, it is an iron-based pigment descended from a family of ancient proteins that early bacteria used to control redox reactions. Hemerythrin has only about one-quarter the oxygen capacity of hemoglobin, though this seems to serve the worms adequately. The pigment also seems to have some immunological functions.

A Toxic Triple Threat

Even if the alternative blood pigments are generally a poor second to hemoglobin at grabbing oxygen, they do have an advantage in terms of simplicity: They usually don't need something like a red blood cell to hold them. In squids, lobsters and the other blue-blooded animals, for example, hemocyanin is dissolved directly in their plasma. This approach works because hemocyanin, hemerythrin and the other pigments are big, frequently polymerized molecules that keep their oxygen-binding metal atoms tucked away from casual interactions. Conversely, hemoglobin is small and its aggressively reactive heme is easily exposed, which makes it highly toxic — so much so that our livers make a protein, haptoglobin, to scavenge stray hemoglobin from broken blood cells out of our blood.

From a toxicity standpoint, hemoglobin is a triple threat, explained Pampee Young, the chief medical officer of biomedical services for the American Red Cross. Heme has even greater affinity for nitric oxide than oxygen, and the body uses nitric oxide as a signaling molecule to control blood pressure. Excess free hemoglobin will therefore rob the blood of nitric oxide, constrict blood vessels and potentially cause hypertension and reduced blood flow to the organs. Compounding the problem is that hemoglobin, when unprotected in blood plasma, decomposes into its component globin subunits. The naked heme molecules then randomly attack the lipid membranes and other structures in the tissues, damaging them. And as a *coup de grâce*, the isolated globin proteins can clog the filtration system of the kidneys and shut them down.

Packaging hemoglobin into red blood cells (erythrocytes) helps to contain the toxicity problems. It also makes the distribution of oxygen more efficient by keeping the hemoglobin inside the blood vessels: The molecule is otherwise so small that some of it would leak out into the tissues and fall out of circulation.

The Perils of Justifying Evolution

Human red blood cells are particularly optimized for the job of oxygen distribution. They are compact, flexible and shaped like biconcave disks, which helps them slip through narrow capillaries and gives them a high volume-to-surface area ration, so they can hold a lot of hemoglobin and oxygen. Moreover, human erythrocytes go a step further than those in most species by ejecting their nucleus and other organelles after stockpiling all the proteins they will need for the balance of their lives — what's left is "basically a bag of hemoglobin," Young said. The cells pay a penalty for that streamlining, however: Because of their limited ability to repair the wear and tear of pushing through capillaries, circulating human red cells have a lifespan of only about 120 days.

When red cells die, the body converts the hemoglobin down into somewhat less toxic compounds including the green pigment biliverdin. (The green color of a healing bruise is from biliverdin.) Too much biliverdin in a human causes jaundice, but biliverdin is normally present in the blood of certain insects and fish, even though it does not transport oxygen. Last year, the herpetologists Christopher Austin and Zachary Rodriguez of Louisiana State University and Susan Perkins, a parasite researcher in the division of invertebrate zoology at the American Museum of Natural History, reported on their genetic analysis of certain skinks from New Guinea that have so much biliverdin in their blood that its green overpowers the hemoglobin's red. ("They have something like 50 times the amount of biliverdin that it would take to kill a human being," Perkins said.) Genetic evidence suggests that this trait evolved four separate times among these lizards, which led researchers to think that the biliverdin might help protect the skinks from malaria or other parasitic infections. Unfortunately for that theory, preliminary evidence suggests that's not the case,

Perkins said, which leaves it mysterious why evolution favors the trait so much in this one small group.

The green blood of the skinks illustrates the perils of trying to justify the variety of blood pigments in nature as purely adaptive. Much of evolution depends on historical contingency, too. The earliest organisms had many oxygen-controlling pigments at their disposal. But once lineages of organisms committed to using certain ones for certain jobs, it may have been difficult if not impossible for them to drastically revise that choice. The reason that vertebrates show less diversity in their blood pigments than invertebrates do is simply that invertebrates are a much more diverse group of organisms overall (all vertebrates fall within a single phylum, Chordata, while invertebrates are in more than 30).

The unusual blood of icefish doesn't contradict this generalization; it actually confirms it. When biologists discovered that icefish had clear blood in the 1950s, they at first assumed it was an adaptation to the cold. Subsequent work, however, pointed to the icefish's loss of hemoglobin genes as more of a lucky accident. In most environments, that mutation would have been fatal. But because the frigid Antarctic waters hold more dissolved oxygen than warmer water does, and because the ancestors of icefish probably already had some adaptations to help them prosper in the cold, the fish survived. It may be true, as Louis Pasteur said, that chance favors the prepared mind, but having a well-prepared genome doesn't hurt.

https://bbc.in/2Wey3GQ

Parkinson's results beyond researchers' wildest dreams

A treatment that has restored the movement of patients with chronic Parkinson's disease has been developed by Canadian researchers.

By Pallab Ghosh Science correspondent, BBC News

Previously housebound patients are now able to walk more freely as a result of electrical stimulation to their spines. A quarter of patients have difficulty walking as the disease wears on, often freezing on the spot and falling. Parkinson's UK hailed its potential impact on an aspect of the disease where there is currently no treatment.

Prof Mandar Jog, of Western University and associate scientific director, Lawson Health Research Institute in London, Ontario, told BBC News the scale of benefit to patients of his new treatment was "beyond his wildest dreams".

"Most of our patients have had the disease for 15 years and have not walked with any confidence for several years," he said. "For them to go from being home-bound, with the risk of falling, to being able to go on trips to the mall and have vacations is remarkable for me to see."

Normal walking involves the brain sending instructions to the legs to move. It then receives signals back when the movement has been completed before sending instructions for the next step.

Prof Jog believes Parkinson's disease reduces the signals coming back to the brain - breaking the loop and causing the patient to freeze.

The implant his team has developed boosts that signal, enabling the patient to walk normally. However, Prof Jog was surprised that the treatment was long-lasting and worked even when the implant was turned off.

He believes the electrical stimulus reawakens the feedback mechanism from legs to brain that is damaged by the disease.

"This is a completely different rehabilitation therapy," he said.

"We had thought that the movement problems occurred in Parkinson's patients because signals from the brain to the legs were not getting through. "But it seems that it's the signals getting back to the brain that are degraded."

Countryside walks

Brain scans showed that before patients received the electrical treatment, the areas that control movement were not working

properly. But a few months into the treatment those areas were restored.

Gail Jardine, 66, is among the patients who has benefited from the treatment. Before she received the implant two months ago, Gail kept freezing on the spot, and she would fall over two or three times a day. She lost her confidence and stopped walking in the countryside in Kitchener, Ontario - something she loved doing with her husband, Stan.

Now she can walk with Stan in the park for the first time in more than two years. "I can walk a lot better," she said. "I haven't fallen since I started the treatment. It's given me more confidence and I'm looking forward to taking more walks with Stan and maybe even go on my own".

Another beneficiary is Guy Alden, 70, a deacon at a catholic church in London, Ontario. He was forced to retire in 2012 because of his Parkinson's disease. His greatest regret was that it curtailed his work in the community, such as his prison visits.

"I was freezing a lot when I was in a crowd or crossing a threshold in a mall. Everyone would be looking at me. It was very embarrassing," he told me.

"Now I can walk in crowds. My wife and I even went on holiday to Maui and I didn't need to use my wheelchair at any point. There were a lot of narrow roads and a lot of (slopes) and I did all of that pretty well."

Dr Beckie Port, research manager at Parkinson's UK, said: "The results seen in this small-scale pilot study are very promising and the therapy certainly warrants further investigation.

"Should future studies show the same level of promise, it has the potential to dramatically improve quality of life, giving people with Parkinson's the freedom to enjoy everyday activities."

http://bit.ly/2GMT4mz

'Longevity gene' responsible for more efficient DNA repair

The key to longevity resides in a gene

Explorers have dreamt for centuries of a Fountain of Youth, with healing waters that rejuvenate the old and extend life indefinitely. Researchers at the University of Rochester, however, have uncovered more evidence that the key to longevity resides instead in a gene.

In a new paper published in the journal Cell, the researchers--including Vera Gorbunova and Andrei Seluanov, professors of biology; Dirk Bohmann, professor of biomedical genetics; and their team of students and postdoctoral researchers--found that the gene sirtuin 6 (SIRT6) is responsible for more efficient DNA repair in species with longer lifespans. The research illuminates new targets for anti-aging interventions and could help prevent age-related diseases.

Inevitable Double-Strand Breaks

As humans and other mammals grow older, their DNA is increasingly prone to breaks, which can lead to gene rearrangements and mutations--hallmarks of cancer and aging. For that reason, researchers have long hypothesized that DNA repair plays an important role in determining an organism's lifespan. While behaviors like smoking can exacerbate double-strand breaks (DSBs) in DNA, the breaks themselves are unavoidable. "They are always going to be there, even if you're super healthy," says Bohmann. "One of the main causes of DSBs is oxidative damage and, since we need oxygen to breathe, the breaks are inevitable."

Organisms like mice have a smaller chance of accumulating double-strand breaks in their comparatively short lives, versus organisms with longer lifespans, Bohmann says. "But, if you want

to live for 50 years or so, there's more of a need to put a system into place to fix these breaks."

The Longevity Gene

SIRT6 is often called the "longevity gene" because of its important role in organizing proteins and recruiting enzymes that repair broken DNA; additionally, mice without the gene age prematurely, while mice with extra copies live longer. The researchers hypothesized that if more efficient DNA repair is required for a longer lifespan, organisms with longer lifespans may have evolved more efficient DNA repair regulators. Is SIRT6 activity therefore enhanced in longer-lived species?

To test this theory, the researchers analyzed DNA repair in 18 rodent species with lifespans ranging from 3 years (mice) to 32 years (naked mole rats and beavers). They found that the rodents with longer lifespans also experience more efficient DNA repair because the products of their SIRT6 genes--the SIRT6 proteins--are more potent. That is, SIRT6 is not the same in every species. Instead, the gene has co-evolved with longevity, becoming more efficient so that species with a stronger SIRT6 live longer. "The SIRT6 protein seems to be the dominant determinant of lifespan," Bohmann says. "We show that at the cell level, the DNA repair works better, and at the organism level, there is an extended lifespan."

The researchers then analyzed the molecular differences between the weaker SIRT6 protein found in mice versus the stronger SIRT6 found in beavers. They identified five amino acids responsible for making the stronger SIRT6 protein "more active in repairing DNA and better at enzyme functions," Gorbunova says. When the researchers inserted beaver and mouse SIRT6 into human cells, the beaver SIRT6 better reduced stress-induced DNA damage compared to when researchers inserted the mouse SIRT6. The beaver SIRT6 also better increased the lifespan of fruit flies versus fruit flies with mouse SIRT6.

Species With Even More Robust SIRT6?

Although it appears that human SIRT6 is already optimized to function, "we have other species that are even longer lived than humans," Seluanov says. Next steps in the research involve analyzing whether species that have longer lifespans than humans--like the bowhead whale, which can live more than 200 years--have evolved even more robust SIRT6 genes.

The ultimate goal is to prevent age-related diseases in humans, Gorbunova says. "If diseases happen because of DNA that becomes disorganized with age, we can use research like this to target interventions that can delay cancer and other degenerative diseases."

http://bit.ly/2VycQub

Anthropogenic global warming kicked off in 1865

New modelling and old records combine to show greenhouse gases and aerosols started to warm things up in the late nineteenth century.

Andrew Masterson reports.

Human-made climate change started to occur much earlier than previously thought, new research reveals.

Current consensus holds that anthropogenic climate warming began to take hold significantly in the 1950s. However, taking the period as a start-point, say a team of researchers led by Jianping Duan of the Chinese Academy of Sciences in Beijing, reflects defects in earlier data quality rather than real-world conditions.

“It has long been speculated that the human influence on the climate may have started much earlier than the recent data-rich period,” the researchers write in a paper published in the journal *Nature Sustainability*.

"Because of the limitations of early instrumental observations and temporal variations in the strength of anthropogenic influence, combined with internal climate variability and changes in natural external forcing factors, it has always been difficult to detect and attribute human influences on earlier climate changes."

One of the main hurdles to assessing climate change at historical distances beyond a few decades, the researchers explain, arise from the practice of using annual mean temperature change as the unit of measure.

Instead, Duan and colleagues turned to a more easily detectable measure known as temperature seasonality, which is simply the difference between average winter and summer temperatures for any given region. The difference, over time, is taken to be a measure of the annual temperature cycle (ATC). A weakening ATC – that is, a smaller difference between summer and winter conditions – is an indication of global warming.

The researchers used a number of verifiable sources of climate proxy records – including Tibetan Plateau tree-ring data and sulfate concentration from glacier ice-cores – and combined them with instrumental observations recorded in four regions within the northern hemisphere.

The numbers were the crunched using European climate records stretching back to the year 1500 CE, the Climatic Research Unit Temperature database compiled by the University of East Anglia in the UK, and the international Coupled Model Intercomparison Project Phase 5 (CMIP5).

The results revealed that anthropogenic warming started to have a significant effect on northern hemisphere climate regions in 1865, and on the Tibetan Plateau in 1872. The changes followed a "weak and insignificant strengthening" of the ATC between 1700 and 1865.

"There is no ATC proxy evidence available that is long enough to identify when the sustained and significant ATC weakening started in northeastern Asia, North America, the northern mid-latitudes, the northern high latitudes and the northern mid–high latitudes," the researchers write.

"However, observations starting in 1851 show discernible weakening in the magnitude of the ATC in all of these regions. These results indicate that although the specific year when the magnitude of the ATC began weakening might not be identical among all regions, prominent ATC weakening has occurred widely since the late nineteenth century."

Although a weakening ATC was recorded across the hemisphere, the human contribution was not consistent. The researchers found evidence to suggest that in the high northern latitudes, the effect was driven by a build-up of greenhouse gas (GHG) production. In lower latitudes the effect was generated by anthropogenic aerosol accumulation.

And although the findings reveal that global warming is a phenomenon that is a lot older, and thus a lot more deeply entrenched, than previously assumed, Duan and colleagues find cause for optimism. "These results imply that a policy of reducing GHG emissions and air pollution can mitigate the anthropogenic weakening of the temperature seasonality," they conclude.

http://bit.ly/2WcF9eW

Distribution of World's First Malaria Vaccine Begins

The World Health Organization and its partners will test the public health effect of immunization in parts of Malawi, Ghana, and Kenya.

Shawna Williams

A program to vaccinate young children in high-risk areas for malaria begins today (April 23) in Malawi, and will soon roll out in Ghana and Kenya, the World Health Organization announced.

WHO plans to pilot the use of the vaccine in conjunction with other preventive measures such as mosquito nets and insecticides.

The immunization requires four doses per child and prevents four in 10 cases of malaria, according to clinical trials.

“This is a bold thing to do, but it’s not a silver bullet,” Thomas Churcher, a malaria expert at Imperial College London, tells the Associated Press. “As long as using the vaccine doesn’t interfere with other efforts, like the urgent need for new insecticides, it is a good thing to do.”

The vaccine, made by GSK, is the first against a parasite, *STAT* notes. While its effectiveness is far lower than that of most vaccines, and delivering the required four doses may present logistical challenges, WHO hopes it will boost efforts to combat malaria, which kills 250,000 children each year in Africa alone. “We have seen tremendous gains from bed nets and other measures to control malaria in the last 15 years, but progress has stalled and even reversed in some areas. We need new solutions to get the malaria response back on track, and this vaccine gives us a promising tool to get there,” says WHO Director-General Tedros Adhanom Ghebreyesus in the agency’s statement. “The malaria vaccine has the potential to save tens of thousands of children’s lives.”

The pilot program aims to reach about 360,000 children each year.

http://bit.ly/2GH97RL

The Moon's Surface Is Totally Cracked

Is the moon all it's cracked up to be? Yes — and then some. New analysis of the lunar surface reveals that it's far more fractured than once thought.

By Mindy Weisberger, Senior Writer

Since the moon formed 4.3 billion years ago, asteroid impacts have scarred its face with pits and craters. But the damage goes far deeper than that, with cracks extending to depths of 12 miles (20 kilometers), researchers recently reported.

Though the moon's craters have been well-documented, scientists previously knew little about the upper region of the moon's crust, the megaregolith, which sustained the bulk of the damage from space rock bombardment. In the new study, computer simulations revealed that impacts from single objects could fragment the lunar crust into blocks about 3 feet (1 meter) wide, opening surface cracks that extend for hundreds of kilometers. This suggests that much of the fracturing in the megaregolith could have come from single, high-speed impacts, leaving the crust "thoroughly fractured" early in the moon's history. These findings helped to address questions raised by NASA's Gravity Recovery and Interior Laboratory (GRAIL), a mission that sent twin spacecraft to the moon in 2011 to create the most detailed lunar gravity map to date.

Data gathered by GRAIL showed that the moon's crust was far less dense than expected, Sean Wiggins, lead author of the new study and a doctoral candidate with the Earth, Environmental and Planetary Sciences Department at Brown University in Rhode Island, told Live Science.

Wiggins and his colleagues suspected that ancient impacts could have substantially fractured the lunar surface, "adding porosity and therefore lowering the density," he said.

Deep impacts

Using simulations, the study authors found that an impact from an object measuring just 0.6 miles (1 km) in diameter could have opened cracks reaching depths of 12 miles (20 km) in the lunar surface. After impacts from objects measuring 6 miles (10 km) in diameter, cracks yawned to similar depths, but also extended laterally to distances up to 186 miles (300 km) from the impact crater.

"There's quite a lot of damage outside of the main crater area," Wiggins said. "Material is still very broken up, farther away than we would have predicted." Over time, networks of cracks grew and

connected, creating a fragmented lunar crust, the researchers reported.

The researchers also used the simulations to explore how similar impacts could affect Earth, which has also been pummeled by asteroids, and they found that gravity played an important role in the quantity and severity of the fractures.

Under conditions with higher gravity — such as on Earth — the surface in simulations suffered less damage from impacts, while lower gravity meant that the surface experienced more damage, the simulations showed. This explains why impacts on the moon created surface cracks that penetrated deeper than cracks from asteroid impacts on Earth.

Piecing together a more detailed picture of the megaregolith will help scientists to better understand how that region conducts heat; this could reveal important clues about the formation of other moons and even planets, Wiggins said.

"It definitely opens doors for further investigation into lots of different processes — not just on the moon, but on other bodies as well, like Mars or Earth," he added. The findings were published online March 12 in the Journal of Geophysical Research: Planets.

http://bit.ly/2ZGnnmo

Computer Program Converts Brain Signals to a Synthetic Voice

A proof-of-principle study raises hopes that technology can give a voice to paralyzed people unable to speak.

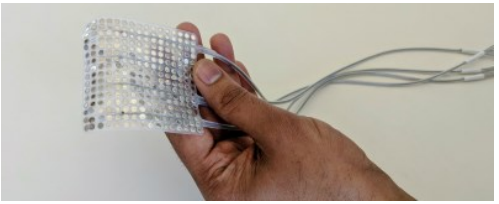
David Adam

A new computer program translates brain signals into language. The technology tracks the electrical messages passed to muscles in and around the mouth to decode what the brain is trying to say. Further tests are needed, but the developers say it could be used to design brain implants to help people who have suffered a stroke or brain disease communicate.

“We want to create technologies that can reproduce speech directly from human brain activity,” Edward Chang, a neurosurgeon at the University of California, San Francisco, who led the research, said during a press conference. “This study provides a proof of principle that this is possible.” He and his colleagues describe the results in *Nature* today (April 24).

The technique is highly invasive and relies on electrodes placed deep in the brain. As such, it has only been tested so far on five people with epilepsy who have had the electrodes fitted as part of their treatment.

These people could—and did—speak during the tests, and this allowed the computer to work out the associated brain signals. The scientists must now check if it works in people who cannot speak.



Coauthor Gopala Anumanchipalli holds the type of intracranial electrode array used in the study. **UCSF**

That will probably be more difficult, says Nick Ramsey, a neuroscientist at the University Medical Center Utrecht in the Netherlands, who works on brain implants to help people with locked-in syndrome communicate, despite widespread paralysis of their muscles. “It’s still an open question whether you will be able to get enough brain data from people who can’t speak to build your decoder,” but he says the study is “elegant and sophisticated” and the results show promise. “I’ve followed their work for a couple of years and they really understand what they’re doing.”

Speech is one of the most complex motor actions in the human body. It requires precise neural control and coordination of muscles across the lips, tongue, jaw, and larynx. To decode this activity, the scientists used the implanted electrodes to track signals sent from the brain when the volunteers read aloud a series of sentences. A

computer algorithm analyzed these instructions using a pre-existing model of how the vocal tract moves to make sounds. A second, processing stage then converted these predicted movements into spoken sentences.

This two-stage approach—translating brain activity to motor movements and then motor movements into words—produces less distortion than trying to directly convert brain signals to speech, Chang says. When the team played 101 synthesized sentences to listeners and asked them to identify the spoken words from a 25-word list, they transcribed 43 percent of them accurately.

Qinwan Rabbani, a graduate student who works on similar systems at Johns Hopkins University, has listened to the synthesized sentences and says they're good, especially as the computer only had a dozen or so minutes of speech to analyze. Algorithms that decode speech typically need "days or weeks" of audio recordings, he says.

Brain signals that control speech are more complicated to decode than those used to, say, move arms and legs, and more easily influenced by emotional state and tiredness. That means a synthetic speech system eventually applied to paralyzed patients would probably be restricted to a limited set of words, Rabbani says.

G.K. Anumanchipalli et al., "Speech synthesis from neural decoding of spoken sentences," Nature, doi:10.1038/s41586-019-1119-1, 2019.

http://bit.ly/2WaSZhM

Chinese-UK project reveals ancient secrets of medicinal mint

The precious chemistry of a plant used for 2000 years in traditional Chinese medicine has been unlocked in a project that raises the prospect of rapid access to a wide array of therapeutic drugs.

Carried out by CEPAMS - a partnership between the Chinese Academy of Sciences and the John Innes Centre - the project has successfully delivered a high-quality reference genome of the mint-family member *Scutellaria baicalensis* Georgi.

The plant, commonly known as Chinese Skullcap, is well-known in Traditional Chinese Medicine (TCM) and is cultivated worldwide for its therapeutic properties. Preparations of its dried roots, 'Huang Qin', show pharmacological activities conferred by novel compounds called flavonoids, including antibacterial, antiviral, antioxidant, anti-cancer, liver-protective and neuroprotective properties. Despite the commercial interest and increasing demand for Scutellaria, improvements through breeding have been limited by a lack of genome information.

***Scutellaria baicalensis* - also known as Chinese Skullcap Botanikfoto, Royalty Free Image**

The team took DNA from a single plant at the Shanghai Chenshan Botanical Garden and used a combination of sequencing strategies to assemble 93% of the genome organised into 9 subsets of information or "pseudo chromosomes." The development means that researchers are now able to identify the genes that produce a wealth of valuable compounds, and then turn them into drug candidates using metabolic engineering techniques in the lab.

The sequencing project outlined in the journal Molecular Plant, also provides a reference gateway for genetic exploration of other valuable members of the Lamiaceae or mint family.

"When I started getting the analysis back on the genome sequence it was like a revelation: it showed at a fundamental level how the pathway to valuable compounds evolved." says Professor Cathie Martin of the John Innes Centre and one of the authors of the study.

"The sequence is so good that it can improve the understanding of all the other genome sequences in the mint family. This is a large

family of plants that is hugely important in Traditional Chinese Medicine and flavourings."

This study highlights the current revival in TCM following the award of the Nobel Prize for Physiology and Medicine in 2015 to Professor You-you Tu for her discovery of artemisinin as a broad spectrum anti-malarial from Artemesia annua (wormwood).

Since then, pharmacology has started examining the healing properties of preparations from plants listed in the traditional texts, such as Shennong Bencaojing (The Divine Farmer's Materia Medica) written between 200 and 250 AD. Such preparations have recently been reported as effective against a variety of complaints including as complementary cancer treatments.

Work on the reference genome and sequences from members of the same family has already started to deliver valuable information that could be applied to development of a wider range of remedies.

"This particular plant makes the bioactive compounds in the root, which means you have to wait three years for the plant to get big enough and of course in taking the root you destroy the plant," said Professor Martin. "We've screened some members of the same family that make similar compounds in the leaves which means you could get more sustainable therapeutics taken in a different way," she added.

The full study: The Reference Genome Sequence of Scutellaria baicalensis *Provides Insights into the Evolution of Wogonin Biosynthesis is published in Molecular Plant journal.*

http://bit.ly/2J0Bkpl

A Common Food Additive Is Linked to Insulin Resistance. Here's What That Means

A common food additive could alter metabolism in ways that could increase the risk of diabetes, a preliminary study suggests.

By Rachael Rettner, Senior Writer

The study, which involved research in humans and mice, investigated a food additive called propionate, which prevents mold growth and is widely used as a preservative in cheeses, baked goods (including bread) and artificial flavorings.

The study found that, in mice, consumption of propionate led to high blood sugar levels in the short term and weight gain and insulin resistance in the long term. (Insulin resistance means the body doesn't respond well to the hormone insulin, which helps cells take in sugar, or glucose. Such resistance can lead to the high blood sugar levels seen in people with diabetes.)

In a small trial involving humans, people who consumed propionate experienced temporary increases in insulin resistance, over the space of a few hours, compared with those who didn't consume the additive.

However, this early research cannot prove that propionate causes diabetes. Larger studies conducted over longer periods are needed to better understand whether propionate contributes to diabetes in people, the authors said.

Still, the findings are concerning given how widely propionate is used, the authors wrote in their paper, published today (April 24) in the journal Science Translational Medicine. They called for more research into the potential metabolic effects of food components like propionate.

"Understanding how ingredients in food affect the body's metabolism at the molecular and cellular level could help us develop simple but effective measures to tackle the dual epidemics of obesity and diabetes," study senior author Dr. Gökhan Hotamisligil, a professor of genetics and metabolism at the Harvard T.H. Chan School of Public Health, said in a statement.

Concerning ingredient

Propionate is "generally recognized as safe" (GRAS) by the U.S. Food and Drug Administration (FDA), meaning the ingredient

doesn't need to be approved by the FDA to be added to food. It's also a naturally occuring fatty acid, produced by our gut bacteria when it breaks down fiber. But no one had investigated the metabolic effects of propionate when it's consumed as a food additive, the authors said.

In the new study, the researchers first gave propionate to mice, finding that the additive led to an increase in levels of several hormones. Those included glucagon (which tells the liver to release sugar into the bloodstream); norepinephrine (which is involved with blood pressure regulation and also raises blood sugar); and fatty acid-binding protein 4, or FABP4 (which is thought to be involved in fatty acid metabolism).

This surge in hormones led to hyperglycemia, or high blood glucose levels, in the mice.

When the researchers gave the mice water with low doses of propionate (similar to the concentrations found in preserved food) for 20 weeks, the animals gained more weight and showed increased insulin resistance, as compared with mice that didn't consume propionate.

Testing in people

To see how these findings translate to people, the researchers conducted a study involving 14 healthy, lean participants who didn't have diabetes. Participants were given a meal that contained either 1 gram of propionate (the amount typically found in a single meal of processed food) or a placebo. The subjects had samples of blood taken once before the meal and then at regular intervals after the meal for 4 hours.

One week later, the participants came back to the lab, and those who had originally received propionate received the placebo, and vice versa. (The study was "double blind," meaning that neither the researchers nor the participants knew which people were getting propionate versus the placebo.)

The study found that when people received propionate, they experienced an increase in hormone levels similar to those seen in the mouse studies. The propionate-receiving participants also showed increased levels of insulin and insulin resistance, compared with when they didn't receive the additive. Both groups had similar peaks blood sugar levels after their meal, but those in the propionate group took slightly longer for their levels to return to baseline.

In a separate analysis, the researchers analyzed data from a previous weight-loss study involving 160 people, finding that blood levels of propionate were linked with insulin resistance. Specifically, the researchers found that larger declines in a person's propionate levels were tied to greater improvement in insulin resistance.

Still, that analysis found only an association and cannot prove that propionate causes insulin resistance or diabetes.

Some previous studies suggested that propionate and other fatty acids have beneficial effects when they are produced in our guts by bacteria as a byproduct of metabolism. But recent research suggests that propionate in foods doesn't have the same beneficial effects, the authors said. This may be because propionate has different effects depending on where it enters the body — when it's consumed in food, it has contact with cells much higher in the gasterointeinal tract than when it's produced by bacteria in the colon, the researchers noted in the study.

Dana Hunnes, a senior dietitian at the Ronald Reagan UCLA Medical Center in Los Angeles, who was not involved with the study, said it was a little challenging to discuss how these findings apply to the general public, given that the study was conducted in mice and a small sample of normal weight people without diabetes. But "I would say the findings are a little concerning if they do in fact mean that eating propionate could both increase blood glucose levels...and decrease the effectiveness of insulin," Hunnes told Live

Science. "Essentially, this could mean, for people with diabetes, that they would need more insulin to effectively deal with the same dose of glucose [or] food" than they would otherwise, she said.

Still, Hunnes said larger studies are needed, particularly ones that involve people with obesity and diabetes. "Especially since over two-thirds of individuals in the United States are overweight or obese, and a growing proportion have diabetes, I think including these groups in a larger study is necessary."

In the meantime, Hunnes recommended to avoid as many food additives as possible, except for those fortified with vitamins and minerals, which are needed in certain circumstances.

"For the most part, I believe that any chemical additive to a food, even with a GRAS designation...could have the potential for unintended negative consequences," Hunnes said.

http://bit.ly/2Lc4zbi

A first in medical robotics: Autonomous navigation inside the body

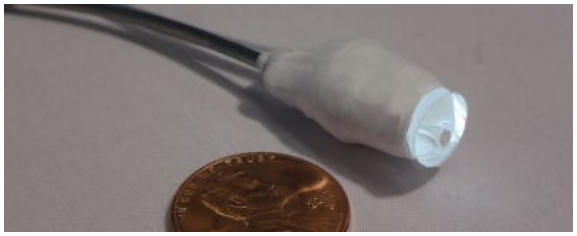
Robotic catheter, using a novel sensor informed by AI and image processing, makes its own way to a leaky heart valve

Bioengineers at Boston Children's Hospital report the first demonstration of a robot able to navigate autonomously inside the body. In an animal model of cardiac valve repair, the team programmed a robotic catheter to find its way along the walls of a beating, blood-filled heart to a leaky valve -- without a surgeon's guidance. They report their work today in *Science Robotics*.

Surgeons have used robots operated by joysticks for more than a decade, and teams have shown that tiny robots can be steered through the body by external forces such as magnetism.

However, senior investigator Pierre Dupont, PhD, chief of Pediatric Cardiac Bioengineering at Boston Children's, says that to his knowledge, this is the first report of the equivalent of a self-driving car navigating to a desired destination inside the body.

Dupont envisions autonomous robots assisting surgeons in complex operations, reducing fatigue and freeing surgeons to focus on the most difficult maneuvers, improving outcomes.



***The robotic cardiac catheter used in the study*. Fagogenis et al., sci. robot. 4 eaaw1977 9 (2019)**

"The right way to think about this is through the analogy of a fighter pilot and a fighter plane," he says. "The fighter plane takes on the routine tasks like flying the plane, so the pilot can focus on the higher-level tasks of the mission."

Touch-guided vision, informed by AI

The team's robotic catheter navigated using an optical touch sensor developed in Dupont's lab, informed by a map of the cardiac anatomy and preoperative scans. The touch sensor uses artificial intelligence (AI) and image processing algorithms to enable the catheter to figure out where it is in the heart and where it needs to go.

For the demo, the team performed a highly technically demanding procedure known as paravalvular aortic leak closure, which repairs replacement heart valves that have begun leaking around the edges. (The team constructed its own valves for the experiments.)

Once the robotic catheter reached the leak location, an experienced cardiac surgeon took control and inserted a plug to close the leak.

In repeated trials, the robotic catheter successfully navigated to heart valve leaks in roughly the same amount of time as the surgeon (using either a hand tool or a joystick-controlled robot).

Biologically inspired navigation

Through a navigational technique called "wall following," the robotic catheter's optical touch sensor sampled its environment at

regular intervals, in much the way insects' antennae or the whiskers of rodents sample their surroundings to build mental maps of unfamiliar, dark environments.

The sensor told the catheter whether it was touching blood, the heart wall or a valve (through images from a tip-mounted camera) and how hard it was pressing (to keep it from damaging the beating heart).

Data from preoperative imaging and machine learning algorithms helped the catheter interpret visual features. In this way, the robotic catheter advanced by itself from the base of the heart, along the wall of the left ventricle and around the leaky valve until it reached the location of the leak.

"The algorithms help the catheter figure out what type of tissue it's touching, where it is in the heart, and how it should choose its next motion to get where we want it to go," Dupont explains.

Though the autonomous robot took a bit longer than the surgeon to reach the leaky valve, its wall-following technique meant that it took the longest path.

"The navigation time was statistically equivalent for all, which we think is pretty impressive given that you're inside the blood-filled beating heart and trying to reach a millimeter-scale target on a specific valve," says Dupont.

He adds that the robot's ability to visualize and sense its environment could eliminate the need for fluoroscopic imaging, which is typically used in this operation and exposes patients to ionizing radiation.

A vision of the future?

Dupont says the project was the most challenging of his career. While the cardiac surgical fellow, who performed the operations on swine, was able to relax while the robot found the valve leaks, the project was taxing for Dupont's engineering fellows, who sometimes had to reprogram the robot mid-operation as they perfected the technology.

"I remember times when the engineers on our team walked out of the OR completely exhausted, but we managed to pull it off," says Dupont. "Now that we've demonstrated autonomous navigation, much more is possible."

Some cardiac interventionalists who are aware of Dupont's work envision using robots for more than navigation, performing routine heart-mapping tasks, for example. Some envision this technology providing guidance during particularly difficult or unusual cases or assisting in operations in parts of the world that lack highly experienced surgeons.

As the Food and Drug Administration begins to develop a regulatory framework for AI-enabled devices, Dupont envisions the possibility of autonomous surgical robots all over the world pooling their data to continuously improve performance over time -- much like self-driving vehicles in the field send their data back to Tesla to refine its algorithms.

"This would not only level the playing field, it would raise it," says Dupont. "Every clinician in the world would be operating at a level of skill and experience equivalent to the best in their field. This has always been the promise of medical robots. Autonomy may be what gets us there."

Georgios Fagogenis, PhD, of Boston Children's Hospital was first author on the paper. Coauthors were Margherita Mencattelli, PhD, Zurab Machaidze, MD, Karl Price, MaSC, Viktoria Weixler, MD, Mossab Saeed, MB, BS, and John Mayer, MD of Boston Children's Hospital; Benoit Rosa, PhD, of ICube, Universite? de Strasbourg (Strasbourg, France); and Fei-Yi Wu, MD, of Taipei Veterans General Hospital, Taipei, Taiwan. For more on the technology, contact TIDO@childrenshospital.org.

The study was funded by the National Institutes of Health (R01HL124020), with partial support from the ANR/Investissement d'avenir program. Dupont and several of his coauthors are inventors on U.S. patent application held by Boston Children's Hospital that covers the optical imaging technique.

http://bit.ly/2DB2rnq

Dengue vaccine fiasco leads to criminal charges for researcher in the Philippines

Indicted over failed introduction of Dengvaxia

By Fatima Arkin

A prominent pediatrician and medical researcher in the Philippines has been indicted over the failed—and many say premature—introduction of Dengvaxia, a vaccine against dengue that was yanked from the Philippine market in 2017 because of safety issues. If convicted of accusations leveled at her by the national Department of Justice (DOJ), Rose Capeding, 63, former head of the dengue department of the Research Institute for Tropical Medicine (RITM) here, could face up to 48 years in prison.

In February, prosecutors concluded there is probable cause to indict Capeding and 19 others for "reckless imprudence resulting [in] homicide," because they "facilitated, with undue haste," Dengvaxia's approval and its rollout among Philippine schoolchildren.

Capeding, through her family, declined to comment, but her son Juhani Capeding says his mother "couldn't have imagined" that submitting research to top medical journals could have led to "this point." Some of Capeding's colleagues agree. "As a scientist, I really feel so disgusted, dismayed, [and] heartbroken about the whole situation," says Lulu Bravo, executive director of the Philippine Foundation for Vaccination here.

Also charged are Capeding's former boss, former RITM head Socorro Lupisan; former Department of Health (DOH) Secretary Janette Garin; other officials at DOH and the Philippines Food and Drug Administration (FDA); and current and former officials of Sanofi Pasteur, the French company producing the shots. The first of eight criminal cases—which could be consolidated—are now pending in five courts throughout the northern island of Luzon, where the vaccination campaign took place.

Dengvaxia consists of an attenuated yellow fever virus that expresses genes of each of the four types of dengue virus. The Philippine FDA greenlighted the vaccine in December 2015, based on research funded by Sanofi Pasteur in which Capeding played an important role. For example, she was the first author on a 2014 paper in *The Lancet* detailing a study among more than 10,000 children in five Asian countries that showed Dengvaxia worked and had a good safety profile. In April 2016, the Philippine government launched a $67 million public school–based immunization program for Dengvaxia.

That alarmed some scientists, because the dengue virus is peculiar: A first infection is rarely fatal, but a second one with a different virus type can lead to much more serious disease, because of what is called antibody-dependent enhancement (ADE), in which the immune response to the first virus amplifies the effect of the second type. Scott Halstead, who studies dengue at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, argued that dengue vaccines could have the same effect, and warned that Dengvaxia should not be given to children never infected with dengue. But a vaccine panel at the World Health Organization (WHO) concluded in 2016 that Dengvaxia was safe for children aged 9 and older.

Halstead's concerns proved valid. In November 2017, Sanofi Pasteur announced that the vaccine could indeed exacerbate cases of dengue in children never previously infected, and the Philippines halted the campaign immediately. (WHO now recommends the vaccine be used only after a test to be sure children have had at least one brush with dengue.)

The news enraged and frightened the parents of some 830,000 schoolchildren who had already received one or more Dengvaxia

shots. Given the high prevalence of dengue in the Philippines, most probably already had the disease at least once, and thus are not at risk of ADE—but some had not. In September 2018, DOH Undersecretary Enrique Domingo told reporters that 130 vaccinated children had died; 19 of those had dengue, meaning ADE possibly played a role. The case triggered "mass hysteria," says Edsel Salvaña, an infectious disease physician at the University of the Philippines here.

"Parents thought their kids were all going to die."

What prosecutors think Capeding—or any of the other accused—is responsible for remains unclear, because the full report about the case has not yet been released. But other scientists have come to Capeding's defense. "[If] you're going to say that a scientist doing a clinical trial is actually liable for anything bad that happens once the product is approved, then that's just crazy," Salvaña says. "The indictment of Rose Capeding is an egregious, unjust, and highly disturbing act," adds Tikki Pangestu, a Singapore-based adviser to the Asia Dengue Vaccine Advocacy Group who has written policy and advocacy papers with Capeding.

But Halstead says the trials Capeding helped conduct were not well designed; if the researchers had looked separately at outcomes for children who did and didn't have dengue before the shot, they would have identified the ADE risk, he says. He notes that Sanofi and WHO committees designed the trials, however, not Capeding. He declined to say whether criminal charges are warranted: "This is a very complex ethical and scientific question that needs to be handled carefully."

Sanofi, in a statement to *Science*, says the company "strongly disagrees with the DOJ's findings made against its officials (current and past) and we will vigorously defend them." It's not yet clear when the criminal trials will start.

https://wb.md/2vsyam6

Cancers, Infectious Diseases Get Large Portion of New Drugs

Stubbornly low levels of success rates and long durations for bringing scientific innovation through the R&D process and to patients

Marcia Frellick

A record number of new drugs — 59 in the United States alone — were approved in 2018, according to "The Changing Landscape of Research and Development" report, released Tuesday by the IQVIA Institute for Human Data Science.

Of those new active substances (NASs), 27% are new therapies for cancer, and 20% are for the treatment of infectious diseases.

Murray Aitken, MBA, director of the institute, described to reporters in a press teleconference on Monday "positive momentum" from the amount of investment and research that has resulted in new drug launches. However, he also pointed to a disappointing 27% drop in productivity over 5 years, broadly defined as "success divided by effort."

"We continue to see stubbornly low levels of success rates and long durations for bringing scientific innovation through the R&D [research and development] process and to patients," Aitken said.

Cancer Drugs Were 40% of the 5-Year Pipeline Increase

The number of new drugs for cancers increased 63% during the past 5 years; new cancer drugs made up 40% of the total pipeline increase. Conversely, the number of vaccines declined during that period by 4%.

In the past year, other areas of therapy that have seen a large boost in new drug options are amyotrophic lateral sclerosis (ALS) and other degenerative musculoskeletal conditions, rare gastrointestinal diseases, and nonnarcotic pain treatments, the report indicates.

Fewer Participants in Studies

In 2018, almost half of new drugs (46%) were approved on the basis of trials that included fewer than 500 persons, reflecting the growing need for specialty, niche, and orphan drugs.

The report also indicated that the drug development process remains slow and risky: 2018 NASs in the United States required an average 13.7 years from patent filing to market. However, that was 2 years faster than drugs launched in the 2 years before and 6 months faster than the average over 5 years.

Number of Clinical Trials Up 9%

The total number of clinical trials that started in 2018 was up 9% from the year before and 35% during the past 5 years. Most of the growth comes from phase 2 trials, the report authors write, up 26% over the prior year and 61% over 5 years. The increase has been fueled by oncology and neurology trials.

The number of trials for gastrointestinal diseases and nonalcoholic steatohepatitis was up 42%, and oncology trials were up 27% during those 5 years. The number of trials of drugs to treat respiratory and endocrine diseases declined.

One Drug Approved in 10 Years for Alzheimer Disease

One of the notable areas of frustration has been in treatments for Alzheimer disease. Since 2008, for Alzheimer disease, "only one product received regulator approval, while 86 other development projects were discontinued, including four in 2018," according to the report. However, new treatments are in development.

The report states, "Treatments for nervous system disorders like MS [multiple sclerosis], Parkinson's, ALS, Alzheimer's and other neuromuscular disorders account for 18 next-generation biotherapeutics treatments, up from just five in 2009. Gene therapies are also under investigation for Parkinson's disease, Alzheimer's disease and spinal muscular atrophy."

5-Year Drop in Productivity

According to the report, productivity dropped overall by 27% from 2013 to 2018, largely because of a decrease in productivity in phase 1 trials.

"This speaks to what we recognize are ongoing challenges," Aitken said. "Those are particularly acute in oncology, which has a relatively low level of productivity, in part because it has a high level of complexity. And with the growing share of clinical trial activity being in the oncology space, that's been one factor that has brought the overall level of productivity down in 2018."

Many factors may lift productivity in the next 5 years, Aitken said, including improvement in digital health technologies to enable capture of drug efficacy and safety data remotely and to relieve work burden on trial sites, and an increase in focusing on patient-reported outcomes and use of artificial intelligence.

Databases consisting of data regarding people who agree to make their data available for research, such as those involved in 23andMe, and the Precision Medicine Initiative, are expected to help ensure that trials don't fail because of lack of recruitment, which can lead to shorter trials and faster times to market, the report authors predict.

"We're optimistic that we can foresee some sizeable and measurable improvements in productivity over the next 5 years," Aitken said.

Investment in Research Strong

The report adds that financial support for research is strong and growing. Venture capital firms invested more than $23 billion in new treatments 2018, and the 15 largest pharma companies reported spending more than $100 billion on research and development for the first time, up 32% during the past 5 years.

The report also highlights the importance of emerging biopharma companies, which the authors define as those that spend less than $200 million a year on research and development or have less than $500 million a year in revenue.

Emerging biopharma companies produced 72% of the drugs launched in 2018, and those companies registered almost half of them, Aitken said.

http://bit.ly/2J3NTAj

Lung cancer under-recognized in people who have never smoked

A group of respiratory medicine and public health experts are calling for lung cancer in never-smokers to be given greater recognition.

**** Lung cancer in people who have never smoked is more common than most people think, and on the rise***

**** Historically strong, and correct, messaging on smoking and lung cancer has inadvertently contributed to lung cancer receiving much less attention than breast, prostate and ovarian cancers***

**** Increasing awareness could help lead to earlier diagnosis, reduce the blame culture around lung cancer and re-balance research funding***

A group of respiratory medicine and public health experts are calling for lung cancer in never-smokers to be given greater recognition. Writing in the *Journal of the Royal Society of Medicine*, they say that lung cancer in people who have never smoked is under recognised and presents a diagnostic challenge, particularly for GPs seeking to balance over-investigation with early diagnosis and high quality care.

It is estimated that around 6,000 people in the UK who have never smoked die of lung cancer every year, greater than the numbers of people who die of cervical cancer (900), lymphoma (5,200), leukaemia (4,500) and ovarian cancer (4,200).

Major contributors to lung cancers in never-smokers include second-hand smoke, occupational carcinogen exposure and outdoor pollution. Globally, the use of solid fuels for indoor cooking and second-hand smoke exposure are important contributions to lung cancer in never-smokers and disproportionately affect women.

Lead author, Professor Paul Cosford, Director for Health Protection & Medical Director, Public Health England, said: "This paper demonstrates an estimated 6,000 people who have never smoked die each year from lung cancer in the UK. This makes it, by itself, the eighth most common cause of cancer related death in the UK.

"For too long having lung cancer has only been thought of as a smoking related disease. This remains an important association but, as this this work shows, the scale of the challenge means there is a need to raise awareness with clinicians and policy makers of the other risk factors including indoor and outdoor air pollution.

"This is one reason why PHE published its review of the evidence and recommended specific actions local authorities can take to improve their air quality. By delivering on the promise of a clean air generation we can reduce the number of lung cancers among those who have never smoked."

Co-author Professor Mick Peake, clinical director of the Centre for Cancer Outcomes, University College London Hospitals Cancer Collaborative, said: "Despite advances in our understanding, most people who have never smoked do not believe they are at risk and often experience long delays in diagnosis, reducing their chances of receiving curative treatment."

Prof Peake added: "The stigma of smoking has been the major factor behind the lack of interest in, knowledge of and research into lung cancer. Therefore, in many ways, never-smokers who develop lung cancer are, as a result, disadvantaged.

"Drawing attention to the contribution of underlying risk factors to lung cancer in never-smokers presents opportunities to reinforce efforts to tackle other major public health challenges. For example, the impact of passive smoking and air pollution on lung cancers adds weight to the government's ambitions to improve air quality and the public, clinicians and policy makers must all be aware of this relationship."

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Alcohol relapse rate among liver transplant recipients identical regardless of sobriety period

Growing number of researchers are questioning the six-month waiting period for a liver transplant

For decades, patients with liver disease related to alcohol use have been told they must be sober for six months before they can get a liver transplant. Many die before that six-month wait period is up. Now, a growing number of researchers are questioning that six-month waiting period.

In two published review papers, Johns Hopkins researchers outline the case for giving liver transplants to selected patients with alcoholic hepatitis. Their argument is backed by data from a six-year pilot study at Johns Hopkins, and they've now received an $8.4 million grant from the National Institutes of Health to expand the study to even more patients with alcoholic hepatitis.

"Alcoholic hepatitis patients have previously been stigmatized, and told that they don't deserve this treatment that could save their life. Now, we're trying to move forward and modernize our approach," says Andrew Cameron, M.D., Ph.D., professor of surgery and chief of the division of transplantation at the Johns Hopkins University School of Medicine.

Alcoholic hepatitis is inflammation of the liver caused by drinking excessive amounts of alcohol. As many as 50 percent of patients with severe forms of the disease die in just 28 days without treatment. While drugs such as steroids, as well as abstinence from drinking, can help resolve some cases of hepatitis, the only treatment for more advanced cases is liver transplant. However, due to concerns about patients returning to alcohol after their transplant, most liver transplant centers require six months of sobriety before allocating a liver to a person with alcoholic hepatitis. Relapsing alcoholism can cause problems with a new liver or a recurrence of hepatitis, and may also be associated with noncompliance in taking necessary post-transplant medications.

In 2012, however, a small study from France and Belgium published in the *New England Journal of Medicine* showed good outcomes in patients with alcoholic hepatitis who received liver transplants without a sobriety waiting period. In the wake of these results, Johns Hopkins launched a pilot study to waive the transplant waiting period for a selected group of patients with alcoholic hepatitis -- those who are otherwise healthy, have a strong support network and good insight into the role that alcohol played in their disease.

Last year, the Johns Hopkins team reported on the outcomes of the first 46 patients who underwent liver transplantation under the pilot program, receiving livers between October 2012 and July 2017. Patients were followed for an average of 532 days after transplant. Psychiatric care was determined on an individual basis. During the follow-up period, the alcohol relapse rate among patients who did not have a wait period was identical to that seen in a group of 34 patients who received transplants under the standard six months of sobriety rule -- in both cases, 28 percent relapsed at one point, but 98 percent of all patients were sober at the end of the study period. According to the National Institute on Alcohol Abuse and Alcoholism, around 90 percent of people in the general public with alcoholism relapse within four years of beginning a treatment. In addition, the rates of overall transplant functioning and patient survival were statistically identical between the groups and were what the researchers consider to be high, "better than that seen with other indications for liver transplant, such as hepatitis C," adds Cameron.

Now, Cameron and his colleagues are calling for more transplant centers to follow Johns Hopkins' lead. In review papers published this month and earlier this year in *Journal of Intensive Care*

Medicine and *Journal of Hepatology*, they outline data seen in the patients at Johns Hopkins as well as a handful of other transplant centers with similar, smaller, pilot programs.

"I think what the field is looking for at this point is published results based on careful scientific research that help us answer who to transplant in a nonjudgmental and nonstigmatized way," says Cameron. The Johns Hopkins group, he adds, with the largest existing cohort of patients with alcoholic hepatitis who have received transplanted livers, is in a position to provide this research. But more data is still needed on the long-term outcomes of these patients, what psychiatric interventions can help decrease relapse rates, as well as the underlying mechanisms of alcoholic hepatitis.

Many factors can increase a person's risk for alcohol use disorder, says Mary E. McCaul, Ph.D., a Johns Hopkins professor of psychiatry and behavioral sciences who is collaborating with Cameron. "These factors generally are not under an individual's control, and people do not choose to develop a drinking problem," she says. "Importantly, people with an alcohol disorder can stop drinking and achieve a strong recovery; they should have equal access to lifesaving liver transplants."

To answer some of the researchers' outstanding questions, the National Institutes of Health awarded Cameron and his colleagues at Johns Hopkins an $8.4 million P50 grant to establish a new alcohol research center. Over the next five years, the researchers plan to continue with liver transplants in patients with alcoholic hepatitis when appropriate and compare these results with those transplanted after a six-month wait. Additionally, the center will help expand a liver tissue bank that researchers around the country can use to study alcoholic hepatitis, study why some people can drink more than others without getting liver disease, and answer ethical questions about transplanting livers in patients with alcoholic hepatitis.

"We used to view liver transplants in this population as a reward for what you've already done, for your sobriety in the past," says Cameron. "Now, we're looking at how we can allocate this limited resource based instead on what you can do in the future if you get a second chance."

In addition to Andrew Cameron, other authors on the Journal of Hepatology *paper are Gene Im of Icahn School of Medicine at Mount Sinai and Michael Lucey of University of Wisconsin. Other authors on the* Journal of Intensive Care Medicine *paper are Michelle Ma, Katie Falloon, Po-Hung Chen, Behnam Saberi, Aliaksei Pustavoitau, Elif Ozdogan, Zhiping Li, Benjamin Philosophe and Ahmet Gurakar, all from Johns Hopkins.*

The authors received no financial support for the research or authorship of the review articles.

http://bit.ly/2GKJ1qp

Creativity is not just for the young, study finds

Two career paths revealed for Nobel laureates in economics

COLUMBUS, Ohio - If you believe that great scientists are most creative when they're young, you are missing part of the story.

A new study of winners of the Nobel Prize in economics finds that there are two different life cycles of creativity, one that hits some people early in their career and another that more often strikes later in life.

In this study, the early peak was found for laureates in their mid-20s and the later peak for those in their mid-50s.

The research supports previous work by the authors that found similar patterns in the arts and other sciences.

"We believe what we found in this study isn't limited to economics, but could apply to creativity more generally," said Bruce Weinberg, lead author of the study and professor of economics at The Ohio State University. "Many people believe that creativity is exclusively associated with youth, but it really depends on what kind of creativity you're talking about."

Weinberg did the study with David Galenson, professor of economics at the University of Chicago. Their study appears in a special issue of the journal *De Economist*.

In the study, the Nobel Prize winners who did their most groundbreaking work early in their career tended to be "conceptual" innovators.

These type of innovators "think outside the box," challenging conventional wisdom and tend to come up with new ideas suddenly. Conceptual innovators tend to peak early in their careers, before they become immersed in the already accepted theories of the field, Weinberg said.

But there is another kind of creativity, he said, which is found among "experimental" innovators. These innovators accumulate knowledge through their careers and find groundbreaking ways to analyze, interpret and synthesize that information into new ways of understanding.

The long periods of trial and error required for important experimental innovations make them tend to occur late in a Nobel laureate's career.

"Whether you hit your creative peak early or late in your career depends on whether you have a conceptual or experimental approach," Weinberg said.

The researchers took a novel, empirical approach to the study, which involved 31 laureates. They arranged the laureates on a list from the most experimental to most conceptual.

This ranking was based on specific, objective characteristics of the laureates' single most important work that are indicative of a conceptual or experimental approach.

For example, conceptual economists tend to use assumptions, proofs and equations and have a mathematical appendix or introduction to their papers.

Experimental economists rely on direct inference from facts, so their papers tended to have more references to specific items, such as places, time periods and industries or commodities.

After classifying the laureates, the researchers determined the age at which each laureate made his most important contribution to economics and could be considered at his creative peak.

They did this through a convention of how academics rate the value and influence of a research paper. A paper is more influential in the field when other scientists mention - or cite - the paper in their own work. So the more citations a paper accumulates, the more influential it is.

Weinberg and Galenson used two different methods to calculate at which age the laureates were cited most often and thus were at the height of their creativity. The two methods found that conceptual laureates peaked at about either 29 or 25 years of age. Experimental laureates peaked when they were roughly twice as old - at about 57 in one method or the mid-50s in the other.

Most other research in this area has studied differences in peak ages of creativity between disciplines, such as physics versus medical sciences. These studies generally find small variations across disciplines, with creativity peaking in the mid-30s to early 40s in most scientific fields.

"These studies attribute differences in creative peaks to the nature of the scientific fields themselves, not to the scientists doing the work," Weinberg said. "Our research suggests than when you're most creative is less a product of the scientific field that you're in and is more about how you approach the work you do."

The researchers were supported by grants from the National Science Foundation, the National Institute on Aging, the National Institutes of Health's Office of Behavioral and Social Sciences Research and the Ewing Marion Kauffman and Alfred P. Sloan foundations.

The special issue of De Economist *that includes this study commemorates the first Nobel Prize in economics given in 1969. One of the recipients was the Dutch economist Jan Tinbergen.*

http://bit.ly/2vudBGa

A spoonful of peppermint helps the meal go down

A pilot study at the Medical University of South has found that peppermint oil improved symptoms, including difficulty swallowing and non-cardiac chest pain, in patients with certain disorders of the esophagus.

Imagine that while eating a delicious meal at your favorite restaurant, your joy is cut short because of difficulty swallowing your food, followed by chest pain.

If you go see a doctor about these symptoms, and there is no evidence of a cardiac cause of the chest pain, you could be diagnosed as having some sort of disorder of the esophagus.

Peppermint can help with the difficulty swallowing and non-cardiac chest pain experienced by some patients with disorders of the esophagus, report investigators at the Medical University of South Carolina (MUSC) in Digestive Diseases & Sciences. Of the 38 patients enrolled in the MUSC pilot study, 63 percent overall reported improvement of symptoms. Patients were recruited from the Esophageal Disorders Clinic at the MUSC Health Digestive Disease Center.

"Peppermint oil is an established agent in the treatment of irritable bowel syndrome. We tried to examine its effect on patients with swallowing and chest pain issues with no apparent cause," says Mohamed Khalaf, M.D., an esophageal disorders research fellow at the MUSC Health Digestive Disease Center and first author on the article.

"Our findings suggest that peppermint may help prevent these symptoms by relaxing the smooth muscle in the lower esophagus," says Donald O. Castell, M.D., a professor emeritus in the MUSC College of Medicine, a nationally recognized gastroenterologist, and senior author on the article.

Peppermint oil has been known to have therapeutic effects in multiple disorders due to its muscle-relaxing properties. However, only two previous studies have investigated its role in the upper digestive tract.

The MUSC study found that patients who took peppermint oil tablets before eating felt better after meals than those who did not. Those with both non-cardiac chest pain and unobstructed difficulty swallowing saw the most benefits: 73 percent of them reported feeling better. Of patients with just one of the symptoms, those with non-cardiac chest pain had a more positive response from the peppermint oil (63 percent) than those with difficulty swallowing (53 percent).

The results were even better among patients with spastic disorders of the esophagus: 83 percent reported feeling better or slightly better. Although less well-known than esophageal disorders such as acid reflux, spastic disorders of the esophagus can also disrupt a patient's life. In these disorders, the esophagus undergoes painful spasms that can interfere with eating. Because the spasms occur only from time to time, these disorders are difficult to diagnose and treat.

Current standard of care calls for these disorders involves trying multiple drugs, including tricyclic antidepressants and calcium channel blockers, and hoping that one works.

Peppermint offers an attractive first line of defense for these patients, who experience intermittent symptoms, because they can take it freely as symptoms occur.

"In this study, patients who had experienced difficulty swallowing took two pieces of a commercially available peppermint right before meals. Those with chest pain took the peppermint tablets as needed," says Khalaf.

This study highlights the effects of the so-called Charleston Approach, which advocates a "start low and go slow" treatment

strategy. The Charleston Approach differs from current standard of care in that it uses peppermint oil as a first attempt to relieve symptoms.

Castell and Khalaf caution that patients must first be examined by a doctor to rule out heart disease and undergo a procedure known as an endoscopy to rule out obstruction before they are offered peppermint as a first-line treatment. Endoscopy involves inserting a flexible tube fitted with a light and camera into the esophagus.

One of the drawbacks of the study was that researchers did not know the precise dosage of peppermint being given since it was a commercial candy (only one type of which was effective) with a proprietary recipe. Another was the study relied on self-reporting by patients to determine whether symptoms improved.

Although the preliminary findings of this study are promising, they need to be confirmed in a trial that compares outcomes in patients who receive a specific dose of peppermint oil and those who receive only a placebo.

In the meantime, however, patients who have been diagnosed as having spastic disorders of the esophagus and who have no heart disease or obstruction can try using peppermint to see if it relieves their symptoms. "Given the safety profile, low cost, and widespread availability, there are no risks from empirical use of peppermint oil," says Khalaf.

http://bit.ly/2PzCqSN

African populations crossbred with other extinct humans

First use of AI to demonstrate that African populations hybridized with other extinct humans.

by Centre for Genomic Regulation

A new international study led by David Comas, principal investigator at UPFand at the Institute of Evolutionary Biology (IBE: CSIC-UPF), demonstrates for the first time using artificial intelligence that African populations hybridized with other extinct humans. The study is published today, 26 April, in the journal *Genome Biology*.

Until now it was known that some extinct populations, such as Neanderthals or Denisovans, had mixed with modern humans outside Africa. However, in African populations no crossbreeding had been consistently demonstrated. Now, they have identified the introgression of an extinct line of humans in the DNA of present-day African populations. "This totally unknown archaic population mixed with the ancestors of Africans and their genes have been conserved in their genome until the present," explains David Comas, full professor of Biological Anthropology at the Department of Experimental and Health Sciences (DCEXS) at UPF.

This totally unknown archaic population mixed with the ancestors of Africans and their genes have been conserved in their genome until the present.

Belén Lorente-Galdos, one of the authors of the article says "the scenario we know in Africa of societies that mixed in a complex way during its recent history is just the tip of the iceberg of the evolutionary history of humans, and so it would appear complex from the beginning."

Artificial intelligence to study the DNA of African populations

The researchers conducted a study of modern genomes of different populations with a broad diversity of lifestyles, languages or geography in the African continent. By sequencing these current genomes they have demonstrated that some of them come from introgression. "By using artificial intelligence tools and complete genomes we have been able to infer the general history of the evolution of African populations," saysÒscar Lao, principal investigator at the National Centre for Genome Analysis (CNAG-CRG), from the Centre for Genomic Regulation (CRG), also one of the authors of the study.

"What has surprised us is that in order to describe the genetic diversity found in African populations today, the presence must be taken into account of an extinct archaic African population, with whom anatomically modern humans would have mixed," he adds. This result indicates that not only were there archaic populations different from the sapiens lineage outside Africa (such as Neanderthals or Denisovans), but that within this continent there were sub-populations with which anatomically modern humans who remained in Africa had offspring.

By using artificial intelligence tools and complete genomes we have been able to infer the general history of the evolution of African populations.

"This finding challenges the observations made previously on the crossbreeding of Neanderthals or Denisovans with European or Asian ancestors because Africans have always been taken as a model of population without introgression," explains David Comas, head of the Human Genome Diversity group at the IBE. "Our research leads one to question some assumptions established today based on the premise that the African population did not have introgressions," he adds.

Belén Lorente-Galdos concludes, "our method has enabled clearly ruling out the prevalent model that does not consider archaic introgression in Africa. The new model we present has forced us, furthermore, to review the amount of DNA in people of Eurasian origin that comes from Neanderthals, which could be up to three times higher than had been estimated to date using the previous models."

The study involved researchers from the Yale School of Medicine, the University of Taibah (Saudi Arabia), the University of Jendouba (Tunisia), IDIBELL, the University of Helsinki (Finland), the University of Witwatersrand (South to Africa) and the Lebanese American University.

http://bit.ly/2J1s6ZP

Placental function linked to brain injuries associated with autism

Disrupting supply of a potent neurosteriod can leave the developing fetus vulnerable to brain injuries associated with ASD

BALTIMORE - Allopregnanolone (ALLO), a hormone made by the placenta late in pregnancy, is such a potent neurosteroid that disrupting its steady supply to the developing fetus can leave it vulnerable to brain injuries associated with autism spectrum disorder (ASD), according to Children's research presented during the Pediatric Academic Societies 2019 Annual Meeting.

In order to more effectively treat vulnerable babies, the Children's research team first had to tease out what goes wrong in the careful choreography that is pregnancy. According to the Centers for Disease Control and Prevention, about 1 in 10 babies is born preterm, before 37 weeks of gestation. Premature birth is a major risk factor for ASD.

The placenta is an essential and understudied organ that is shared by the developing fetus and the pregnant mother, delivering oxygen, glucose and nutrients and ferrying out waste products. The placenta also delivers ALLO, a progesterone derivative, needed to ready the developing fetal brain for life outside the womb.

ALLO ramps up late in gestation. When babies are born prematurely, their supply of ALLO stops abruptly. That occurs at the same time the cerebellum - a brain region essential for motor coordination, posture, balance and social cognition- typically undergoes a dramatic growth spurt.

"Our experimental model demonstrates that losing placental ALLO alters cerebellar development, including white matter development," says Anna Penn, M.D., Ph.D., a neonatologist in the divisions of Neonatology and Fetal Medicine, and a developmental neuroscientist at Children's National. "Cerebellar white matter

development occurs primarily after babies are born, so connecting a change in placental function during pregnancy with lingering impacts on later brain development is a particularly striking result."

The research team created a novel experimental model in which the gene encoding the enzyme responsible for producing ALLO is deleted in the placenta. They compared these preclinical models with a control group and performed whole brain imaging and RNAseq gene expression analyses for both groups.

"We saw long-term cerebellar white matter alterations in male experimental models, and behavioral testing revealed social impairments and increased repetitive behaviors, two hallmark features of ASD," says Claire-Marie Vacher, Ph.D., lead study author. "These male-specific outcomes parallel the increased risk of brain injury and ASD we see in human babies born prematurely."

ALLO binds to specific GABA receptors, which control most inhibitory signaling in the nervous system.

"Our findings provide a new way to frame poor placental function: Subtle but significant changes in utero may set in motion neurodevelopmental disorders that children experience later in life," adds Dr. Penn, the study's senior author. "Future directions for our research could include identifying new targets in the placenta or brain that could be amenable to hormone supplementation, opening the potential for earlier treatment for high-risk fetuses."

Pediatric Academic Societies 2019 Annual Meeting presentation

"Placental allopregnanolone loss alters postnatal cerebellar development and function." Sunday, April 28, 2019, 5:15 p.m. to 5:30 p.m. (EST)

Claire-Marie Vacher, Ph.D., lead author; Jackie Salzbank, co-author; Helene Lacaille, co-author; Dana Bakalar, co-author; Jiaqi O'Reilly, co-author; and Anna Penn, M.D., Ph.D., a neonatologist in the divisions of Neonatology and Fetal Medicine, developmental neuroscientist and senior study author.