http://www.eurekalert.org/pub_releases/2016-04/tes-cfr040216.php

Common flame retardant chemical disrupts a hormone that is essential to life

PBDEs used in many consumer products overstimulates an adrenal gland hormone in a way that may lead to the development of cardiovascular disease

Boston, MA-- Brominated fire retardants, used in many consumer products and known to cause hormonal irregularities, overstimulates an adrenal gland hormone in a way that may lead to the development of cardiovascular disease, new research in human cells finds. Researchers will present their study results Saturday at the Endocrine Society's 98th annual meeting in Boston.

Flame retardants such as polybrominated diphenyl ethers (PBDEs) have been widely used in furniture foam cushions, clothes, building materials and electronics to slow the rate of ignition and fire growth. The United States is phasing out use of these industrial chemicals because they are endocrine disruptors, substances that can impair hormone-controlled processes, and mounting scientific evidence shows they can affect neurologic development in infants and children as well as reproductive, thyroid, and metabolic functions.

"However, these chemicals leach into the environment and bioaccumulate, and have appeared in our environment, including house dust, the food supply and breast milk samples in the U.S.," said the study's principal investigator, Phillip Kopf, PhD, an assistant professor at Midwestern University in Downers Grove, IL.

Kopf and his co-workers wanted to know whether PBDEs affect aldosterone. This important hormone, made in the adrenal gland, regulates salt and water balance in the body's circulation and participates in blood pressure stability by acting on the kidneys.

The investigators studied application of various doses of a common PBDE flame retardant on human adrenal cells in culture dishes and compared the effects with those of only the vehicle, the inactive substance used to deliver the chemical. The PBDE doses were higher than those found in the blood of most humans tested, according to Kopf, but these chemicals accumulate in the adrenal gland, where their concentrations are higher. In addition, the exposure duration in this study was much shorter than in real life--only three days.

Cells exposed to the PBDE showed elevated secretion, or release, of aldosterone from the cell. Too much secretion of this hormone typically results in an elevated level of aldosterone in the blood. Past research, Kopf said, shows the elevating circulating aldosterone levels are associated with high blood pressure, blood clot formation, thickening of the heart muscle (called cardiac hypertrophy) and congestive heart failure.

Kopf said they plan to further examine the cardiovascular effects of brominated flame retardants in an animal model of high blood pressure.

http://www.eurekalert.org/pub_releases/2016-04/uons-asd033116.php

Australian scientists develop 'game changing' stem cell repair system

Stem cell therapies capable of regenerating any human tissue damaged by injury, disease or ageing could be available within a few years

Stem cell therapies capable of regenerating any human tissue damaged by injury, disease or ageing could be available within a few years, following landmark research led by UNSW Australia researchers.

The repair system, similar to the method used by salamanders to regenerate limbs, could be used to repair everything from spinal discs to bone fractures, and has the potential to transform current treatment approaches to regenerative medicine.

The UNSW-led research has been published today in the Proceedings of the National Academy of Sciences journal.

Study lead author, haematologist and UNSW Associate Professor John Pimanda, said the new technique, which reprograms bone and fat cells into induced multipotent stem cells (iMS), has been successfully demonstrated in mice.

"This technique is a significant advance on many of the current unproven stem cell therapies, which have shown little or no objective evidence they contribute directly to new tissue formation," Associate Professor Pimanda said.

"We are currently assessing whether adult human fat cells reprogrammed into iMS cells can safely repair damaged tissue in mice, with human trials expected to begin in late 2017."

There are different types of stem cells including embryonic stem (ES) cells, which during embryonic development generate every type of cell in the human body, and adult stem cells, which are tissue-specific. There are no adult stem cells that regenerate multiple tissue types. "This technique is ground-breaking because iMS cells regenerate multiple tissue types," Associate Professor Pimanda said.

"We have taken bone and fat cells, switched off their memory and converted them into stem cells so they can repair different cell types once they are put back inside the body."

The technique developed by UNSW researchers involves extracting adult human fat cells and treating them with the compound 5-Azacytidine (AZA), along with platelet-derived growth factor-AB (PDGF-AB) for approximately two days. The cells are then treated with the growth factor alone for a further two-three weeks.

AZA is known to induce cell plasticity, which is crucial for reprogramming cells. The AZA compound relaxes the hard-wiring of the cell, which is expanded by the

growth factor, transforming the bone and fat cells into iMS cells. When the stem cells are inserted into the damaged tissue site, they multiply, promoting growth and healing. The new technique is similar to salamander limb regeneration, which is also dependent on the plasticity of differentiated cells, which can repair multiple tissue types, depending on which body part needs replacing.

The study's first author, Dr Vashe Chandrakanthan, who developed the technology, said the new technique is an advance on other stem cell therapies being investigated, which have a number of deficiencies.

"Embryonic stem cells cannot be used to treat damaged tissues because of their tumour forming capacity. The other problem when generating stem cells is the requirement to use viruses to transform cells into stem cells, which is clinically unacceptable," Dr Chandrakanthan said.

"We believe we've overcome these issues with this new technique."

Neurosurgeon and Conjoint Lecturer with UNSW's Prince of Wales Clinical School, Dr Ralph Mobbs, will lead the human trials, once the safety and effectiveness of the technique using human cells in mice has been demonstrated.

"The therapy has enormous potential for treating back and neck pain, spinal disc injury, joint and muscle degeneration and could also speed up recovery following complex surgeries where bones and joints need to integrate with the body," Dr Mobbs said.

Research shows that up to 20% of spinal implants either don't heal or there is delayed healing. The rates are higher for smokers, older people and patients with diseases such diabetes or kidney disease.

"Spinal implants currently used to replace damaged or troubled discs don't always weld with the adjacent bones, so by transplanting these reprogrammed stem cells, we hope to be able to better fuse these implants to the host bone," Dr Mobbs said.

"This represents a potential huge leap forward for spinal and orthopaedic procedures."

Along with confirming that human adult fat cells reprogrammed into iMS stem cells can safely repair damaged tissue in mice, the researchers said further work is required to establish whether iMS cells remain dormant at the sites of transplantation and retain their capacity to proliferate on demand.

http://www.eurekalert.org/pub_releases/2016-04/arh-aci040416.php

A chink in the armor of breast cancer cells

Scientists succeed in killing aggressive form of breast cancer in lab experiments

Working with human breast cancer cells, a team of scientists from Ann & Robert H. Lurie Children's Hospital of Chicago have successfully turned off a misbehaving protein that fuels the growth of a particularly aggressive, drug-resistant form of the disease known as triple-negative breast cancer.

In a set of lab experiments, the team managed to neutralize the protein, called Nodal, a growth factor already known for its role in early embryonic development. A description of the work is published in the March 23 issue of the journal Cell Cycle.

The team's work demonstrates that in addition to its role in promoting embryonic growth, Nodal also appears to play a role in instigating malignant cell changes that culminate in the development of triple-negative breast cancer.

The findings, researchers say, reveal a key player in the development of a disease that has long mystified scientists.

The so-called triple-negative breast cancer is not caused by any of three hormones and growth factors known to drive the development of other forms of disease. Thus, triple-negative breast cancer does not respond to traditional therapies that "starve" cancer cells of their fuel. As a result, patients diagnosed with this disease are treated with more toxic forms of chemotherapy, rather than with precision-targeted treatments that spare healthy cells and tissues. If reaffirmed in further experiments, the results can pave the way to much-needed new therapies for a form of the disease that accounts for 20 percent of all breast cancers.

"While clearly preliminary, our results reveal a pivotal catalyst in the development of a disease for which we lack precision-targeted, effective treatments," says study author Thomas Bodenstine, Ph.D. "Our results also indicate one possible way to improve the accuracy and efficacy of current treatments by delivering an antibody that can neutralize the influential tumor-promoting effects of this gene."

Building on earlier observations that the protein Nodal is found in higher levels in many aggressive forms of cancer, the team homed in on human breast cancer cells obtained from patients with the triple-negative form of the disease. The scientists pre-treated cancer cells with doxorubicin, a commonly used breast-cancer drug, then added an antibody known to disable, or inactivate, Nodal. Cancer cells treated with combination therapy were weaker and died off faster than breast cancer cells that received only standard drug treatment, the researchers found.

To understand why that was, researchers used a form of protein analysis to track minute shifts in proteins inside the cancer cells. The proteins of cancer cells treated with the dual therapy, the research team found, were less capable of repairing themselves. In other words, the researchers say, adding the antibody somehow made the cells weaker, less capable of repair and survival and thus rendered them more vulnerable to the effects of the standard chemotherapy drug.

"The antibody appears to create vulnerability in the cells' armor, exposing them to the effects of the standard drug," says Mary J.C. Hendrix, Ph.D., principal investigator on the study.

"The new study establishes several key findings with great potential for future clinical application that can also help pave the way to less toxic chemotherapy treatments," writes Danny Welch, Ph.D., in an accompanying editorial by a team of breast-cancer specialists not involved in the research. Welch is professor and chair of the Department of Cancer Biology at the University of Kansas.

Bodenstine, now an assistant professor of biochemistry at Midwestern University, completed the work while completing a post-doctoral research fellowship at the Hendrix Lab at the Stanley Manne Children's Research Institute.

Hendrix, formerly president and chief scientific officer of Stanley Manne Children's Research Institute, is now president of Shepherd University in Shepherdstown, West Virginia.

Co-authors on the study included Naira Margaryan, DVM, PhD, Elisabeth Seftor and Luigi Strizzi, MD, PhD, and former research institute students Grace Chandler and David Reed, all members of the Manne Research Institute; Alina Gilgur, AbbVie, Inc.; Janis Atkinson, Nida Ahmed and Matthew Hyser, of Presence Saint Francis Hospital in Evanston, Illinois.

This study was supported by a grant from the National Institutes of Health (NIH) and the Northwestern Memorial Foundation Dixon Translational Research Grant. Additional support came from the Brinson Foundation and from the Kennedy Foundation at Presence Saint Francis Hospital. Hendrix and Seftor hold a patent for targeting Nodal.

http://www.eurekalert.org/pub_releases/2016-04/cmaj-fpp033016.php

Fentanyl patch prescribing still not safe in 50 percent of prescriptions

Half of new prescriptions being written for people who have not had the required previous opioid exposure

Although prescribing of the fentanyl patch has improved, physicians are still failing to adhere to safe prescribing guidelines, with half of new prescriptions being written for people who have not had the required previous opioid exposure, found new research from the University of Manitoba, Winnipeg, Canada, in CMAJ (Canadian Medical Association Journal) (pre-embargo link only). http://www.cmaj.ca/site/press/cmaj.150961.pdf

Fentanyl is a highly potent opioid with potential adverse effects such as central nervous system depression, dangerously low blood pressure, impaired breathing and death. Between 1996 and 2015 in Canada, there were 284 reported deaths linked to fentanyl patches, many during the drug's initiation phase. The fentanyl patch is recommended for people who have already used an opioid equivalent to 60 mg of morphine daily for at least a week before starting the 25 µg/h patch.

"One important safety issue, and a factor under the control of prescribers, is the recommendation that first-time users of the fentanyl patch have adequate prior exposure to opioids," writes Dr. Shawn Bugden, Associate Professor, College of Pharmacy, Faculty of Health Sciences at the University of Manitoba, with coauthors. With the rising use of fentanyl and associated adverse events, the authors suggest it is time to look at safety issues related to the fentanyl patch.

The study examined fentanyl patch prescribing over 12 years in Manitoba, Canada, and included 11 063 people who received prescriptions for the patch. The researchers found that 74% of fentanyl prescriptions were not safe because users had not had adequate previous exposure to opioids. In 18% of cases, first-time patients started on the 50 µg/h dose or higher, rather than the 25 µg/h dose. Prescribing did improve over the study period, from 87% unsafe prescribing at the start of the study to 50%, and it was safer in women and people younger than 65 years of age.

"Of particular concern, patients 65 and older, who may be at the greatest risk, had higher levels of unsafe fentanyl initiation than younger patients," write the authors. "There was considerable improvement, with a 37.0% decrease in unsafe prescribing over the study period." However, half of all fentanyl patch prescriptions are still unsafe. The researchers noted that although these patients had not had previous opioid exposure, most did not receive lethal doses.

The authors note several limitations to the study. They assessed safety based on product monograph recommendations and safety warnings, and could not include prescriptions obtained in other provinces.

"Considerable attention and effort have been placed into making prescribers aware of the need to ensure adequate opioid tolerance before prescribing fentanyl patches," write the authors. "Special attention should be paid to older patients, who are at greatest risk of adverse outcomes but had the lowest level of safe prescribing."

A related commentary http://www.cmaj.ca/site/press/cmaj.160291.pdf, "Consequences of unsafe prescribing of transdermal fentanyl," discusses fentanyl patch prescribing, adverse events and potential for abuse.

http://www.eurekalert.org/pub_releases/2016-04/uoc--tta040416.php

To treat a leading cause of osteoporosis, surgery is better than widely used medications

UCLA study finds that using drugs to combat hyperparathyroidism is worse than doing nothing at all

While most cases of osteoporosis are caused by normal aging, another leading cause of the bone-loss disease is a condition called hyperparathyroidism, in which the parathyroid glands release an excessive amount of a hormone that regulates the body's calcium levels.

Doctors commonly treat hyperparathyroidism using a class of prescription drugs called bisphosphonates, including alendronate (marketed under the brand name Fosamax) and ibandronate (Boniva), which are supposed to strengthen bones.

Now, a study led by scientists at UCLA found that those drugs actually increase the risk of fracture, meaning that taking them is worse than doing nothing at all to treat the condition. The research also revealed that patients who have surgery to remove the overactive parathyroid glands have fewer subsequent bone fractures.

The report appears in the April 5 issue of the Annals of Internal Medicine.

About 400,000 people in the U.S. -- 1 in 400 women and 1 in 1,200 men -- have hyperparathyroidism; and osteoporotic fractures are a major public health and economic burden, said Dr. Michael Yeh, an associate professor of surgery and medicine, and the study's first author.

"Hip fractures in particular are associated with significant rates of mortality, disability and loss of independence," said Yeh, who also is the chief of endocrine surgery at the UCLA David Geffen School of Medicine. "Before this study, there was no data that compared parathyroid surgery with prescribing medication on the risk for fractures in people with hyperparathyroidism."

The researchers analyzed data from more than 6,000 people who had been diagnosed with hyperparathyroidism between 1995 and 2010. All had health care coverage through Kaiser Permanente Southern California, and their demographic and socioeconomic profiles mirrored those of the greater Los Angeles population.

Yeh described the findings as "startling."

Among study participants who were not treated for hyperparathyroidism, there were 56 hip fractures per 1,000 people after 10 years.

Among those who had parathyroid surgery, there were just 20 fractures per 1,000 people.

For those taking bisphosphonate medications, the rate of hip fractures was 86 per 1,000 patients -- higher than the combined rate for those who underwent surgery or did nothing at all.

The researchers also reviewed the number of bone fractures of all types (including hip fractures), and the results were similar: For people who did not receive treatment, there were 206 fractures per 1,000; for those who had surgery, 157 fractures per 1,000; and for those taking bisphosphonate medications, 303 fractures per 1,000.

Yeh said it was also surprising that people taking medications had a higher risk for fractures, even though X-rays showed that they had similar gains in bone density to the people who had undergone surgery.

"The drugs make the bones look dense on scans, but that is deceptive," Yeh said. "We must presume there is a defect in the quality of the bone. But we don't know why."

Researchers also found that the risk for fractures among people taking bisphosphonates was higher whether people had osteopenia, or early bone loss, or full-blown osteoporosis, which Yeh said could suggest that either the drugs themselves are harmful or that the people taking them had other risk factors.

"Regardless, we were unable to demonstrate any benefit associated with this class of drugs, which have been around and routinely prescribed for more than 20 years," he said. "These findings should make bisphosphonates less attractive as an alternative to parathyroid surgery in patients with primary hyperparathyroidism."

Yeh said more research is needed to see if bisphosphonates also increase the risk for fractures for people with underlying causes of osteoporosis other than hyperparathyroidism. Women are more likely to have osteoporosis; other key risk factors are a lack of vitamin D, calcium or estrogen. Osteoporosis afflicts some 54 million people over age 50 in the U.S. and is responsible for 2 million bone fractures a year.

The study's other authors were Ning Li and Dr. Philip Ituarte of UCLA, and Hui Zhou, Annette Adams, In-Lu Amy Liu and Dr. Philip Haigh of Kaiser Permanente Southern California. Funding was provided by the National Institutes of Health (RFA-AG-11-007).

http://bit.ly/1SMTo2T

Planet Nine might be an exoplanet stolen by the sun

The hypothetical ninth planet at the fringes of our solar system might have been captured from a star passing by long ago

Our solar system might harbour an alien interloper. The proposed Planet Nine lurking at the edge of the solar system could have been stolen from a passing star.

In January, Konstantin Batygin and Michael Brown announced evidence for an unseen planet around 10 times Earth's mass lurking in the fringes of the solar system. Other astronomers immediately came forward with suggestions for how so-called Planet Nine might have migrated from the inner solar system towards its outer edges.

The Pleiades star cluster: it might once have been the sun's nursery, with planets ripe for the taking **NASA**

But one team now suggests just the opposite: that it was captured from a nearby star.

The idea isn't all that far-fetched. The sun was born in a reasonably large stellar cluster with roughly 1000 or maybe even 10,000 stars, says Alexandar Mustill from the Lund Observatory in Sweden. In such a dense cluster, the sun would have had quite a few close encounters with other stars, potentially letting them swap planets from time to time.

"It would be pretty wild – to pick up an alien planet and bring it along for the ride," says Greg Laughlin at the Lick Observatory in California.

Good odds

To check just how wild, Mustill and his colleagues ran simulations of encounters between the solar system and any passing planetary systems. They found that if that a system happened to have a wide-orbit planet, the likelihood it would be captured by the sun is about 50 per cent.

Those are pretty good odds, but they dropped when the team took into account whether the passing planetary system would have a wide-orbit planet in the first place. Also, it wasn't enough to just capture a planet – their simulations only worked if they captured one that was exactly like Planet Nine. Overall, Mustill and his colleagues think the chance that Planet Nine is an exoplanet ranges from 0.1 to 2 per cent.

"Although these probabilities seem low, you have to compare them to each other, and not absolutely," says Mustill. "Because ultimately any very specific outcome is very unlikely." The probability that evidence for Planet Nine's existence is random chance is just 0.007 per cent at present, so the fact that the odds of it being an exoplanet are 15 to 300 times higher than that actually bodes well for the exoplanet scenario.

Capture or exile?

A fugitive on the run is just one way to explain Planet Nine, however. Batygin and Brown initially thought it was likely to be the core of a gas giant ejected from the inner solar system early in its formation. "My pet theory is it happened early and there was a lot of gas around in the solar nebula and that gas sort of slowed it down and kept it from being completely removed," Brown says.

This theory is relatively straightforward, says Scott Kenyon of the Harvard-Smithsonian Center for Astrophysics in Cambridge, Massachusetts. The array of Jupiter-like exoplanets that orbit dangerously close to their host stars suggest that massive planets regularly migrate inward. "Whenever you scatter something inward, to conserve energy, you're likely to scatter something else outward," Kenyon says.

And there's one final option: the planet could have formed where we find it now. Although some have speculated that there wouldn't be enough material to form a planet in the outer fringes of the solar system, Kenyon found that there could be enough icy pebbles to form something as small as Planet Nine in a couple of hundred million years.

"I think it's premature to say what's most likely," says Kenyon. A definitive answer will likely hinge on actually finding the unseen planet.

References: http://arxiv.org/abs/1603.07247, http://arxiv.org/abs/1603.08008

http://bit.ly/1oxoJeV

Why did early human societies practice violent human sacrifice?

Human sacrifice was practiced in many early human societies throughout the world. In China and Egypt the tombs of rulers were accompanied by pits containing hundreds of human bodies, whose spirits were believed to provide assistance in the afterlife.

Joseph Watts

Ritually slaughtered bodies are found buried next to rings of crucibles, brass cauldrons and wooden idols in the peat bogs of Europe and the British Isles. Early explorers and missionaries documented the importance of human sacrifice in Austronesian cultures, and occasionally became human sacrifices themselves. In Central America, the ancient Mayans and Aztecs extracted the beating hearts of victims on elevated temple altars.

It is no surprise, then, that many of the oldest religious texts, including the Quran, Bible, Torah and Vedas, make reference to human sacrifice.

This raises some key questions: how and why could something as horrifying and costly as human sacrifice have been so common in early human societies?

Is is possible that human sacrifice might have served some social function, and actually benefited at least some members of a society?

Illustration of ritualised human sacrifice in traditional Hawaiian culture, as documented by the French explorer and artists Jaques Arago in 1819. **Arago, Jacques. (1822). Promenade autour du monde: pendant les années 1817, 1818, 1819 et 1820, sur les corvettes du roi l'Uranie et la Physicienne, commandées par M. Freycinet**

Social control?

According to one theory, human sacrifice actually did serve a function in early human societies. The Social Control Hypothesis suggests human sacrifice was used by social elites to terrorise underclasses, punish disobedience and display authority. This, in turn, functioned to build and maintain class systems within societies.

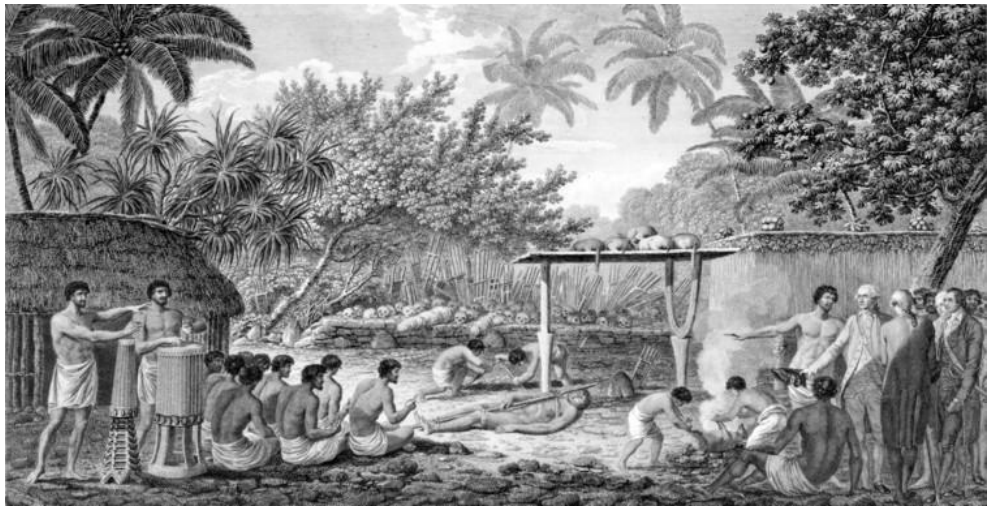
My colleagues and I were interested in testing whether the Social Control Hypothesis might be true, particularly among cultures around the Pacific.

So we gathered information on 93 traditional Austronesian cultures and used methods from evolutionary biology to test how human sacrifice affected the evolution of social class systems in human prehistory.

The ancestors of the Austronesian peoples were excellent ocean voyagers, originating in Taiwan and migrating west as far as Madagascar, east as far as Easter Island and south as far as New Zealand. This is an area covering more than half the world's longitude.

These cultures ranged in scale from the Isneg, who lived in small, egalitarian, family-based communities, to the Hawaiians, who lived in complex states with royal families, slaves and hundreds of thousands of people.

Human sacrifice was performed in 43% of the cultures we studied. Events that called for human sacrifice included the death of chiefs, the construction of houses and canoes, preparation for wars, epidemic outbreaks and the violation of major social taboos.



Captain James Cook witnessed human sacrifice in Taihiti during his visit around 1773.
1815 edition of Cook's 'Voyages'/Wikimedia Commons

The physical act of sacrifice took a wide range of forms, including strangulation, bludgeoning, burning, burial, drowning, being crushed under a newly-built canoe, and even being rolled off a roof and then decapitated.

In Austronesia human sacrifice was common in cultures with strict class systems but scarce in egalitarian cultures. While an interesting correlation, this doesn't tell us whether human sacrifice functioned to build social class systems, or whether social class systems led to human sacrifice.

Good for the elites

Using what is known about the family tree of Austronesian languages and the data we collected on 93 traditional Austronesian cultures, we were able to reconstruct Austronesian prehistory and test how human sacrifice and social structures co-evolved through time.

This enabled us to not only test whether human sacrifice is related to social class systems, but also get at the direction of causality based on whether human sacrifice tends to arise before or after social class systems.

Our results show that human sacrifice tended to come before strict class systems and helped to build them. What's more, human sacrifice made it difficult for cultures to become egalitarian again.

This provides strong support for the Social Control Hypothesis of human sacrifice. In Austronesia, the victims of human sacrifice were often of lower status, such as slaves, and the perpetrators of high status, such as chiefs or priests. There was a great deal of overlap between religious and political systems and in many cases the chiefs and kings themselves were believed to be descended from the gods.

As such, the religious systems favoured social elites, and those who offended them had a habit of becoming human sacrifices. Even when a broken taboo strictly required human sacrifice, there was flexibility in the system and punishment was not even-handed.

For example, in Hawaii, a person who broke a major taboo could substitute the life of a slave for their own, providing they could afford a slave.

Human sacrifice could have provided a particularly effective means of social control because it provided a supernatural justification for punishment, its graphic and painful nature served as a deterrent to others, and because it demonstrated the ultimate power of elites.

The overlap between religious and secular systems in early human societies meant that religion was vulnerable to being exploited by those in power. The use of human sacrifice as a means of social control provides a grisly illustration of just how far this can go.

This research was funded by grants from The John Templeton Foundation and The Marsden Fund of New Zealand.

http://www.eurekalert.org/pub_releases/2016-04/fm-hts033116.php

How to survive extinction: Live fast, die young

Field Museum examines life history of ancient mammal

Two hundred and fifty-two million years ago, a series of Siberian volcanoes erupted and sent the Earth into the greatest mass extinction of all time. Billions of tons of carbon were propelled into the atmosphere, radically altering the Earth's climate. Yet, some animals thrived in the aftermath and scientists now know why.

This is an early Triassic Lystrosaurus murrayi specimen, National Museum Bloemfontein, South Africa. **Jennifer Botha-Brink**

In a new study published in Scientific Reports, paleontologists from The Field Museum and their collaborators demonstrate that some ancient mammal relatives, known as therapsids, were suited to the drastic climate change by having shorter life expectancies. When combined with results from survivorship models, this observation leads the team to suggest that these animals bred at younger ages than their predecessors.

"Before the Permo-Triassic extinction, the therapsid Lystrosaurus had a life span of about 13 or 14 years based on the record of growth preserved in their bones," said Field Museum paleontologist Ken Angielczyk, one of the paper's authors. "Yet, nearly all of the Lystrosaurus specimens we find from after the extinction are only 2¬-3 years old. This implies that they must have been breeding when they were still juveniles themselves."

This adjustment in life history also meant a physical change for Lystrosaurus. Before the mass extinction, this creature would have been a couple meters long and have weighed hundreds of pounds--About the size of a pygmy hippo. Post-extinction, its size dropped to that of a large dog, in large part due to its altered lifespan. Yet, these adaptations seemed to pay off for Lystrosaurus. Ecological simulations show that by breeding younger, Lystrosaurus could have increased its chance of survival by 40% in the unpredictable environments that existed in the aftermath of the extinction.

This change in breeding behavior is not isolated to ancient animals either. In the past century, the Atlantic cod has undergone a similar effect due to human interference. Industrial fishing has removed most large individuals from the population, shifting the average size of cod significantly downward. Likewise, the remaining individuals are forced to breed as early in their lives as possible. Similar shifts have also been demonstrated in African monitor lizards.

"With the world currently facing its sixth mass extinction, paleontological research helps us understand the world around us today," said Angielczyk. "By studying how animals like Lystrosaurus adapted in the face of disaster, we can better predict how looming environmental changes may affect modern species."

Summary of Major Findings

1. Study of bone microstructure and body size distributions in the forerunners of mammals (therapsids) reveals distinct life history changes during the Permo-Triassic Mass Extinction (252 Mya).

2. Our results show that post-extinction species took less time to reach adult size, had shortened life expectancies, high mortality rates, and were at great risk of extinction.

3. Simulations using ecological modelling show that breeding earlier, which would have led to shortened generation times, could have helped therapsids survive in the unpredictable, resource-limited post-extinction environment, and explains body size distributions observed in earliest Triassic species like Lystrosaurus.

4. The results help explain how the "disaster taxon" Lystrosaurus, not only survived, but spread to all areas of the globe and became the most abundant vertebrate after the Permo-Triassic Mass Extinction.

Background Facts

There have been five major mass extinctions in Earth's history.

The Permo-Triassic Mass Extinction (252 Mya) was the most catastrophic extinction in Phanerozoic history.

It killed 80-96% of all marine species and 70% of all terrestrial species.

Post-extinction ecosystems did not fully recover until some 5 million years after the event.

Therapsids include animals like Lystrosaurus, and another group called the cynodonts, which includes mammals and their immediate ancestors. Their body sizes ranged from a tiny mouse to a massive rhino. South Africa contains the best fossil record of early therapsids in the world.

Our paper does NOT say

We do not demonstrate behavioral or physical evidence of early reproduction. Rather, our main empirical dataset comes from body size distributions and bone histology, which show direct evidence of shorter life expectancies in Triassic therapsids. Our inference of earlier breeding is then based on size distributions and expectations of survivorship models that we pursued based on our histologic findings.

Funding

To Dr. Jennifer Botha-Brink: National Research Foundation (South Africa): Early Triassic Recovery Project NRF-65244

To Dr. Adam Huttenlocker: National Science Foundation Doctoral Dissertation Improvement Grant 1209018; National Science Foundation Postdoctoral Fellowship in Biology NSF DBI-1309040

http://www.bbc.com/news/health-35959556

Vitamin D 'heals damaged hearts'

Vitamin D supplements may help people with diseased hearts, a study suggests.

By James Gallagher Health editor, BBC News website

A trial on 163 heart failure patients found supplements of the vitamin, which is made in the skin when exposed to sunlight, improved their hearts' ability to pump blood around the body.

The Leeds Teaching Hospitals team, who presented at a meeting of the American College of Cardiology, described the results as "stunning".

The British Heart Foundation called for longer trials to assess the pills.

Vitamin D is vital for healthy bones and teeth and may have important health benefits throughout the body but many people are deficient.

No safe way to suntan - warning

The average age of people in the study was 70 and, like many people that age, they had low levels of vitamin D even in summer.

"They do spend less time outside, but the skin's ability to manufacture vitamin D also gets less effective [with age] and we don't really understand why that is," said consultant cardiologist Dr Klaus Witte.

Patients were given either a 100 microgram vitamin D tablet or a sugar pill placebo each day for a year. And researchers measured the impact on heart failure - a condition in which the heart becomes too weak to pump blood properly.

The key measure was the ejection fraction, the amount of blood pumped out of the chambers of the heart with each beat.

In a healthy adult, the figure is between 60% and 70%, but only a quarter of the blood in the heart was being successfully pumped out in the heart failure patients.

But in those taking the vitamin pills, the ejection fraction increased from 26% to 34%.

Dr Witte told the BBC News website: "It's quite a big deal, that's as big as you'd expect from other more expensive treatments that we use, it's a stunning effect. "It's as cheap as chips, has no side effects and a stunning improvement on people already on optimal medical therapy, it is the first time anyone has shown something like this in the last 15 years."

The study also showed the patients' hearts became smaller - a suggestion they are becoming more powerful and efficient.

In the UK, people over 65 are advised to take 10 microgram supplements of the vitamin.

However, Dr Witte does not think high-dose vitamin D should be routine prescribed just yet. He told the BBC: "We're a little bit off that yet, not because I don't believe it, but data have shown improvements in heart function, they may show improvements in symptoms and we now need a large study."

It is also not clear exactly how vitamin D is improving heart function, but it is thought every cell in the body responds to the vitamin.

Most vitamin D comes from sunlight, although it is also found in oily fish, eggs and is added to some foods such as breakfast cereals.

Prof Peter Weissberg, from the British Heart Foundation, cautioned that the patients seemed no better at exercise. And added: "A much bigger study over a longer period of time is now needed to determine whether these changes in cardiac function can translate into fewer symptoms and longer lives for heart failure patients."

http://bit.ly/1YijYT1

Polish Scientists Dig Up 240-Million-Year-Old Fossilized Blood Vessels--the Oldest Ever Found

Polish scientists say fossilized blood vessels with preserved chemical traces of proteins are the oldest in the world. **Edward Baran reports.**

Polish scientists say they've discovered the world's oldest preserved fossils of blood vessels and fragments of fossilised animal proteins.

The discovery was made inside bones that are 240 million years old.

They report their findings in PLOS ONE.

At that time southern Poland was partially covered by a warm sea, allowing reptiles such as Nothosauria to live there.

The remains of some of these reptiles were found during excavation work by a team of scientists who noticed well-preserved bone structures.

University of Silesia Scientist, Professor Jacek Szade:

"By using various spectroscopic methods we succeeded in acquiring very interesting information about the chemical structure and molecular remnants of blood vessels in these very, very old fossilised bones."

Researchers were soon able to show that there was organic matter from prehistoric animals present in the bones.

Scientists confirmed the tested samples contained fragments of amino acids which are typical components of collagen.

Scientist at University of Silesia and Science and Human Evolution Park in Krasiejow, Dr. Andrzej Boczarowski:

"Among other proteins, we managed to find collagen, one of the most important proteins in the bodies of animals in general, and in vertebrates in particular."

The world's oldest protein fragments of fossilised soft tissue to date were discovered by American scientists, and dated back 80 million years.

This latest discovery goes back three times further.

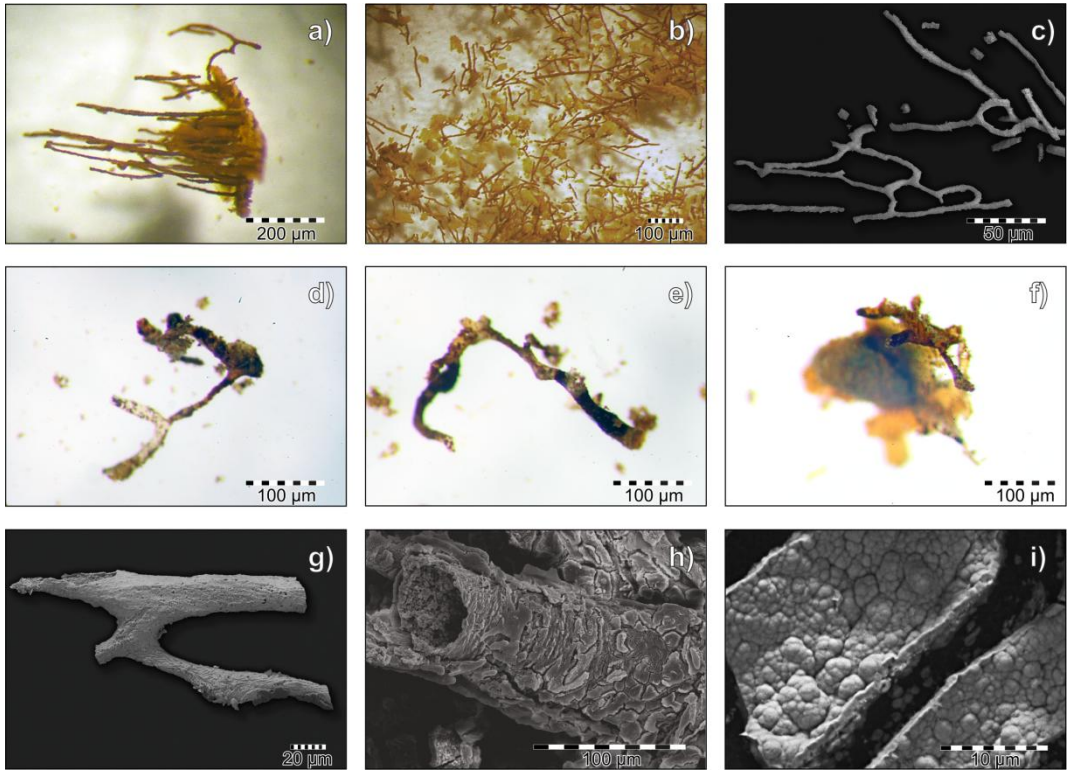


Fig 1. Demineralized blood vessel from fossil samples. Stereoscopic and ESEM microscope images of blood vessels: a) partially demineralized bone sample from the near-cortical region shows parallel-oriented fossilized blood vessels (SUT-MG/F/Tvert/2 sample) in stereoscopic microscope image; b) fossilized "floating" blood vessels from sample SUT-MG/F/Tvert/2 during the demineralization (decalcification) process in EDTA solution in stereoscopic microscope image; c) ESEM image of bifurcated blood vessels mounted on a carbon conductive tab (WNoZ/s/7/166 sample); d-f) isolated branch-like-shaped blood vessels (WNoZ/s/7/166 sample) in stereoscopic microscope images; g) ESEM image of fossilized blood vessel mounted on carbon conductive tab; h) ESEM images of magnified fragment of a mineralized blood vessel with preserved tubular morphology from a demineralized part of bone from specimen WNoZ/s/7/166; i) ESEM image of heavily mineralized, damaged walls of a blood vessel (SUT-MG/F/Tvert/2) with nodular-form goethite crystals, mounted on a carbon conductive tab.

Dawid Surmik Andrzej Boczarowski Katarzyna Balin Mateusz Dulski Jacek Szade Barbara Kremer Roman Pawlicki

http://www.eurekalert.org/pub_releases/2016-04/uoca-csa040416.php

CU study: Ancient Mars bombardment likely enhanced life-supporting habitat

Giant impacts would have created Yellowstone-like hydrothermal vents on Mars conducive to extreme life 4 billion years ago

The bombardment of Mars some 4 billion years ago by comets and asteroids as large as West Virginia likely enhanced climate conditions enough to make the planet more conducive to life, at least for a time, says a new University of Colorado Boulder study.

CU-Boulder Professor Stephen Mojzsis said if early Mars was as barren and cold as it is today, massive asteroid and comet impacts would have produced enough heat to melt subsurface ice. The impacts would have produced regional hydrothermal systems on Mars similar to those in Yellowstone National Park, which today harbor chemically powered microbes, some of which can survive boiling in hot springs or inhabiting water acidic enough to dissolve nails.

Scientists have long known there was once running water on Mars, as evidenced by ancient river valleys, deltas and parts of lake beds, said Mojzsis. In addition to producing hydrothermal regions in portions of Mars' fractured and melted crust, a massive impact could have temporarily increased the planet's atmospheric pressure, periodically heating Mars up enough to "re-start" a dormant water cycle.

"This study shows the ancient bombardment of Mars by comets and asteroids would have been greatly beneficial to life there, if life was present," said Mojzsis, a professor in the geological sciences department. "But up to now we have no convincing evidence life ever existed there, so we don't know if early Mars was a crucible of life or a haven for life."

Published in Earth and Planetary Science Letters, the study was conducted by Mojzsis and Oleg Abramov, a researcher at the U.S. Geological Survey in Flagstaff, Arizona and a former CU-Boulder research scientist under Mojzsis.

Much of the action on Mars occurred during a period known as the Late Heavy Bombardment about 3.9 billion years ago when the developing solar system was a shooting gallery of comets, asteroids, moons and planets. Unlike Earth, which has been "resurfaced" time and again by erosion and plate tectonics, heavy cratering is still evident on Mercury, Earth's moon and Mars, Mojzsis said.

Mojzsis and Abramov used the Janus supercomputer cluster at the University of Colorado Computing facility for some of the 3-D modeling used in the study. They looked at temperatures beneath millions of individual craters in their computer simulations to assess heating and cooling, as well as the effects of impacts on Mars from different angles and velocities. A single model comprising

the whole surface of Mars took up to two weeks to run on the supercomputer cluster, said Mojzsis.

The study showed the heating of ancient Mars caused by individual asteroid collisions would likely have lasted only a few million years before the Red Planet - about one and one-half times the distance to the sun than Earth - defaulted to today's cold and inhospitable conditions. "None of the models we ran could keep Mars consistently warm over long periods," said Mojzsis.

While Mars is believed to have spent most of its history in a cold state, Earth was likely habitable over almost its entire existence. A 2009 study by Mojzsis and Abramov showed that the Late Heavy Bombardment period in the inner solar system nearly 4 billion years ago did not have the firepower to extinguish potential early life on Earth and may have even given it a boost if it was present.

"What really saved the day for Earth was its oceans," Mojzsis said. "In order to wipe out life here, the oceans would have had to have been boiled away. Those extreme conditions in that time period are beyond the realm of scientific possibility."

The new Mars study was funded by NASA and the John Templeton Foundation. Mojzsis recently received an $800,000 grant from the Foundation for Applied Molecular Evolution in Alachua, Florida made possible by the Templeton Foundation to better understand early Earth and the beginning of life before about 4 billion years ago.

"Studies of Mars provide us with valuable information about our own place in the solar system," he said. "Our next steps are to model similar bombardment on Mercury and Venus to better understand the evolution of the inner solar system and apply that knowledge to studies of planets around other stars."

Mojzsis will meet with scientists from the California Institute of Technology and NASA's Jet Propulsion Laboratory in Pasadena next month to discuss possible landing sites and research targets for the upcoming Mars 2020 rover mission. Mars 2020 will carry instruments to seek out past life or present life, hunt for habitable areas and demonstrate technologies for use on future robotic and human missions to Mars.

http://bit.ly/1UMvQ1s

Collecting Positive Foreign Words That Lack English Equivalents

English lacks some felicitous words it could really use

By Steve Mirsky on April 1, 2016

When I was in grade school, we were fed the now disputed notion that Eskimo languages, reflecting local concerns, had an unusually large number of words for snow. But nobody told us about the Inuit word *iktsuarpok*, which would have come in handy to describe one's behavior after putting in a call for a pizza delivery. *Iktsuarpok* "refers to the anticipation one feels when waiting for someone, whereby one keeps going outside to check if they have arrived." So writes University of East London psychologist Tim Lomas in a cross-cultural linguistics study for the *Journal of Positive Psychology*.

Lomas's paper is entitled "Towards a Positive Cross-Cultural Lexicography: Enriching Our Emotional Landscape through 216 'Untranslatable' Words Pertaining to Well-Being." The 216 words in question, the first cull of Lomas's mostly Web-based searches, can of course be at least loosely translated, which explains the qualifying quotation marks around untranslatable. Lomas explains that the words "are deemed 'untranslatable' to the extent that other languages lack a single word/phrase for the phenomenon." And let me tell you, his parents must be kvelling over his publication. The Yiddish word *kvell*, to use the many English words required in the paper, means "to glow with pride and happiness at the successes of others (often family members)." So much easier to simply kvell.

But can any mom and dad truly kvell without access to the word? Or is their emotional experience limited by the words available in their native language? "The existence of 'untranslatable' words pertaining to well-being implies that there are positive emotional states which have hitherto only been explicitly recognised by particular cultures," Lomas writes. "However, this does not mean that people in other cultures may not have had a comparable experience. Yet, lacking a specific term for it, such people have arguably not had the opportunity to specifically identify that particular state, which instead thus becomes just another un-conceptualised ripple in the on-going flux of subjective experience."

In other words, his parents could indeed probably kvell even if they don't speak Yiddish. (Whether they got all the *nachas* they had coming is another question.) "However," he writes, "the value of exploring 'untranslatable' words is that, if people are introduced to a foreign term, this may then be used to give voice to these hitherto unlabelled states."

So let's give voice, using some of Lomas's excavated non-English words, to some hitherto unlabeled states and possibly enrich our emotional landscape.

Ever keep eating even when full because to do so was just so damn enjoyable? The Georgian word *shemomedjamo* describes this phenomenon. It's also the sound that comes out of you a few hours later. Portuguese has *desbundar* to capture becoming uninhibited while having fun. Bantu's even more specific *mbuki-mvuki* involves whipping off your clothes to dance. Hey, it's tough to dance in tight pants.

One of life's great pleasures (memorably captured in the movie *The Shawshank Redemption*) is drinking beer outside on a hot day, which is *utepils* in Norwegian. Drink too much and thereby come up with an ingenious plan, and you've committed the German *Schnapsidee*. Try to realize that plan, and your enemies

will no doubt be filled with *Schadenfreude*, an example of a word so good that English simply imported it. Yes, we English speakers are word *banditos*.

I had no idea until I read Lomas that I had many times engaged in *gökotta*. That's Swedish for waking up early to go outside to hear the morning's first birds sing. In the right setting, *gökotta* can help fulfill your *prostor*. That's the Russian word Lomas's paper cites as capturing "a desire for spaciousness, roaming free in limitless expanses, not only physically, but creatively and spiritually." You might concurrently achieve *Waldeinsamkeit*, German for the mysterious, and possibly slightly creepy, solitude available when alone in the woods.

Once your *Wanderlust* is quenched, you can contribute to Lomas's research. Just go to www.drtimlomas.com/lexicography to add any "untranslatable" words he has yet to uncover. It might even be good for your *karma*.

http://bit.ly/22hPAsU

Calls for pharma to follow GSK and make drugs more accessible

Other pharma companies are under pressure to follow GSK's example

By Andy Coghlan

Poor countries will soon be able to make their own versions of GlaxoSmithKline's drugs without paying royalties, the UK-based pharma giant has announced.

Building on concessions announced in 2009, GSK has now said it will not file patents for its drugs in countries deemed to be low income and least developed. In lower middle income countries, it will offer 10-year licences on generous terms to firms seeking to make generic copies of its drugs. Around 85 countries could potentially benefit, covering 2 billion of the world's 7.4 billion people.

GSK will also explore putting its experimental anti-cancer drugs into a UN-backed "patent pool" so that they can be made available cheaply to certain countries if and when they are approved. This will become increasingly important as life expectancy, and therefore the prevalence of cancer, rises around the world.

Knowledge Ecology International, an NGO in Washington DC, described the move as welcome and impressive. It urged others to follow GSK's lead, especially with regard to cancer drugs.

"Companies, such as Roche, Novartis, Bayer, Astellas and BMS, with important oncology drugs should begin to engage on expanding access to their patented medicines," it said.

Of five major multinationals contacted by New Scientist, only Pfizer responded. "We are committed to providing broad access to our medicines through a variety of ways including partnerships, flexible access arrangements, and in certain less developed countries, donations," a spokesperson said.

GSK itself said that it was up to other companies how to proceed. "We think what we've done is the right thing for us, and if other companies want to follow suit, great," said a spokeswoman. "The aim is just to make a further contribution to widening access, particularly in the poorest countries."

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Mysterious Gravitational Tug on Orbiter May Help Find Planet Nine

Astronomers are homing in on the whereabouts of a hidden giant planet in our solar system, and could discover the unseen beast in roughly a year

By Shannon Hall on April 5, 2016

The hunt is on to find "Planet Nine"—a large undiscovered world, perhaps 10 times as massive as Earth and four times its size—that scientists think could be lurking in the outer solar system. After Konstantin Batygin and Mike Brown, two planetary scientists from the California Institute of Technology, presented evidence for its existence this January, other teams have searched for further proof by analyzing archived images and proposing new observations to find it with the world's largest telescopes.

Just this month, evidence from the Cassini spacecraft orbiting Saturn helped close in on the missing planet. Many experts suspect that within as little as a year someone will spot the unseen world, which would be a monumental discovery that changes the way we view our solar system and our place in the cosmos. "Evidence is mounting that something unusual is out there—there's a story that's hard to explain with just the standard picture," says David Gerdes, a cosmologist at the University of Michigan who never expected to find himself working on Planet Nine. He is just one of many scientists who leapt at the chance to prove—or disprove—the team's careful calculations.

Batygin and Brown made the case for Planet Nine's existence based on its gravitational effect on several Kuiper Belt objects—icy bodies that circle the sun beyond Neptune's orbit. Theoretically, though, its gravity should also tug slightly on the planets, moons and even any orbiting spacecraft. With this in mind, Agnès Fienga at the Côte d'Azur Observatory in France and her colleagues checked whether a theoretical model (one that they have been perfecting for over a decade) with the new addition of Planet Nine could better explain slight perturbations seen in Cassini's orbit. Without it, the eight planets in the solar system, 200 asteroids and five of the most massive Kuiper Belt objects cannot perfectly account for it. The missing puzzle piece might just be a ninth planet.

So Fienga and her colleagues compared the updated model, which placed Planet Nine at various points in its hypothetical orbit, with the data. They found a sweet spot—with Planet Nine 600 astronomical units (about 90 billion kilometers) away

toward the constellation Cetus—that can explain Cassini's orbit quite well. Although Fienga is not yet convinced that she has found the culprit for the probe's odd movements, most outside experts are blown away. "It's a brilliant analysis," says Greg Laughlin, an astronomer at Lick Observatory, who was not involved in the study. "It's completely amazing that they were able to do that so quickly." Gerdes agrees: "That's a beautiful paper."

The good news does not end there. If Planet Nine is located toward the constellation Cetus, then it could be picked up by the Dark Energy Survey, a Southern Hemisphere observation project designed to probe the acceleration of the universe. "It turns out fortuitously that the favored region from Cassini is smack dab in the middle of our survey footprint," says Gerdes, who is working on the cosmology survey. "We could not have designed our survey any better." Although the survey was not planned to search for solar system objects, Gerdes has discovered some (including one of the icy objects that led Batygin and Brown to conclude Planet Nine exists in the first place).

Laughlin thinks this survey has the best immediate chance of success. He is also excited by the fact that Planet Nine could be so close. Although 600 AUs—roughly 15 times the average distance to Pluto—does sound far, Planet Nine could theoretically hide as far away as 1,200 AUs. "That makes it twice as easy to get to, twice as soon," Laughlin says. "And not just twice as bright but 16 times as bright."

And the Dark Energy Survey is not the only chance to catch the faint world. It should be possible to look for the millimeter-wavelength light the planet radiates from its own internal heat. Such a search was proposed by Nicolas Cowan, an exoplanet astronomer at McGill University in Montreal, who thinks that Planet Nine might show up in surveys of the cosmic microwave background (CMB), the pervasive afterglow of the big bang. "CMB experiments have historically used solar system giant planets to calibrate their instruments, so we know that current and planned CMB experiments are sensitive enough to measure the flux from Planet Nine if it is as bright as we think it is," Cowan says.

Already, cosmologists have started to comb through data from existing experiments, and astronomers with many different specialties have also joined in on the search. "I love that we can take this four-meter telescope and find a rock 100 kilometers in diameter that is a billion kilometers past Neptune with the same instrument that we are using to do extragalactic stuff and understand the acceleration of the universe," Gerdes says.

In the meantime Batygin and Brown are proposing a dedicated survey of their own. In a recent study they searched through various sky maps to determine where Planet Nine cannot be. "We dumpster-dived into the existing observational data to search for Planet Nine, and because we didn't find it we were able to rule out parts of the orbit," Batygin says. The zone where the planet makes its farthest swing from the sun as well as the small slice of sky where Fienga thinks the planet could be now, for example, have not been canvassed by previous observations. To search the unmapped zones, Batygin and Brown have asked for roughly 20 observing nights on the Subaru Telescope on Mauna Kea in Hawaii. "It's a pretty big request compared to what other people generally get on the telescope," Brown says. "We'll see if they bite." If they do, Brown is convinced he will have his planet within a year.

"I really want to see what it looks like," says Batygin, who adds that his aspiration drives him to search for the unseen world. But Laughlin takes it a step further: "I think [the discovery] would provide amazing inspiration for the next stage of planetary exploration," he says. We now have another opportunity to see one of the worlds of our own solar system for the first time. "If Planet Nine isn't out there, we won't have that experience again."

http://bit.ly/1TG6Fwm

Think Fast! Caffeine Speeds Up Older Adults' Reaction Time

Coffee has been linked to a slew of health benefits, and now, a new study suggests that it may improve reaction time in older adults.

by Sara G. Miller, Staff Writer | April 05, 2016 04:49pm ET

NEW YORK - In the study, presented today (April 5) here at the Cognitive Neuroscience Society's annual meeting, researchers set out to examine the effects of caffeine on a number of cognitive abilities in healthy, older adults.

Ultimately, their goal is to see what role caffeine may play in treating dementia, said Kanchan Sharma, a neurology researcher at the University of Bristol in England and the lead researcher on the new study.

Currently, some treatments for dementia work by boosting attention, Sharma told Live Science. Caffeine is also thought to boost attention, but interestingly, this hasn't been proven in research, he said.

To study the effects of caffeine on attention, Sharma and his colleagues tested 38 healthy adults who ranged in age from 55 to 91, Sharma said.

The participants first took a series of tests that measured different aspects of attention. Then, the participants were asked to stop drinking caffeine for one week. After one week, one group was given 100 milligrams (1 cup) of caffeinated coffee, and the other group was given decaffeinated coffee, and they were asked to perform the tests again. The next day, the drinks were switched. This way, the participants could serve as their own controls, Sharma said.

The researchers found that drinking the caffeinated coffee improved the participants' average reaction time. They also found that the caffeine improved

participants' accuracy on a test called the "Stroop test," which measures skills such as planning and focusing.

In the Stroop test, participants are shown the name of a color, but the name is written in a different color. For example, the word "blue" may be written in red text. The participants are then asked to identify either the name of the color, or the color of the text.

Drinking caffeine had no effect, however, on the participants' motor speed, or how quickly they could press a button when prompted.

Sharma noted that the improvements the researchers observed in the study were small. However, in people with cognitive impairment, caffeine could have a much greater effect because their baseline would be lower, Sharma said. In future studies, Sharma plans to look at the effects of caffeine on people who have cognitive impairments, such as dementia, he said.

The findings have not been published in a peer-reviewed journal.

http://www.eurekalert.org/pub_releases/2016-04/uot-yat040616.php

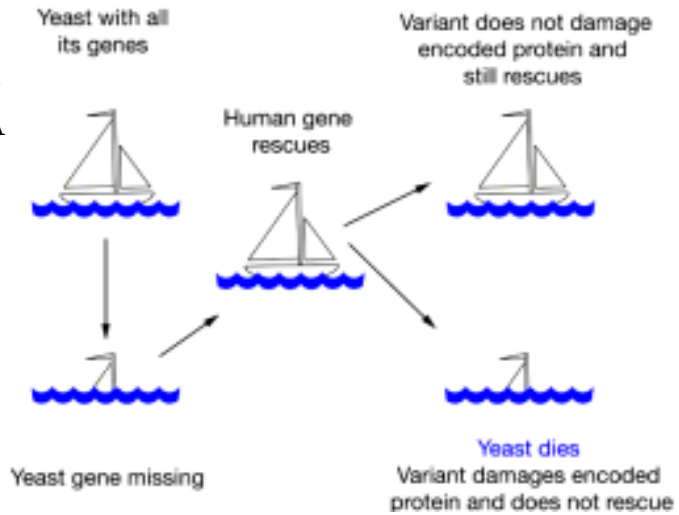
Yeast against the machine: Bakers' yeast could improve diagnosis

How our billion-year-old cousin, baker's yeast, can reveal -- more reliably than leading algorithms -- whether a genetic mutation is actually harmful

It's easier than ever to sequence our DNA, but doctors still can't exactly tell from our genomes which diseases might befall us. Professor Fritz Roth is setting out to change this by going to basics -- to our billion-year-old cousin, baker's yeast.

By testing the effects of human mutations in yeast, Roth's research team at the University of Toronto's Donnelly Centre for Cellular and Biomolecular Research and the Lunenfeld-Tanenbaum Research Institute was able to identify harmful changes in the DNA better than leading algorithms.

The ultimate goal of his approach, detailed in the latest issue of Genome Research is to create "look-up tables" of damaging mutations to help clinicians diagnose patients more accurately.



The basic concept of testing human gene variants in yeast. **University of Toronto**

The reason our genomes remain impenetrable is the vast amount of genetic diversity among us. Of the three billion DNA letters in the genome, three million are different between any two people. The vast majority of these differences, also called genetic variants, have no bearing on our lives. But some variants change proteins, the molecular machines that do much of the work in our cells -- and this could lead to disease.

"If we want to interpret people's personal genomes, then we need a way of knowing whether variants are damaging the gene they are in," says Roth, who is also a professor in the Department of Molecular Genetics and co-director of the Canadian Institute for Advanced Research Genetic Networks Program.

Currently the only way to predict damaging mutations, for most genes, is through computational methods. For some genes, however, damaging mutations can be detected using yeast. The international team led by Roth did a head-on comparison of yeast against the machine to see which approach fared better at finding disease-causing mutations.

Yeast cells are simple, yet their basic architecture is similar to human cells. Because almost half of our genes have a shared ancestry with a yeast gene, it is often possible to study human genes in this easy-to-manipulate living organism.

One way to test a human gene's function is to see whether it can replace a yeast counterpart gene. Think of yeast as a ship -- taking a gene out leaves a hole in the bottom. Scientists then try to stop the leak by plugging the hole with the matching human gene to prevent the ship from sinking. If the normal human gene can rescue the yeast but a mutated one cannot, Roth predicts that the mutation is damaging. Thanks to yeast's fast rate of growth, it is possible to know within days which versions of human genes fail to keep the yeast afloat. These same variants are also likely to be damaging for human cells and could matter for our health.

Roth's team focused on 22 genes, linked to conditions such as autism, mental retardation and heart disease, and whose intact copies were able to replace their yeast counterparts. Previous work found these genes to be present in hundreds of variations among people. Roth's group tested 179 variants, roughly half of which are reported to cause disease.

To test variant function, the researchers inserted each human variant, one by one, in place of a matching yeast gene, using a comprehensive library of yeast strains created by Professors Brenda Andrews and Charlie Boone's groups at the Donnelly Centre. They then watched how well the yeast grew and this allowed them to predict whether or not a variant was harmful. Importantly, this simple test in a billion-year old machinery outperformed the best available computational methods. Based on cell-growth data, the researchers were able to identify 62 per

cent of disease variants as damaging. By contrast, the best current computational method could confidently identify only 23 per cent of disease variants.

"By every measure we are beating the computational predictions. Some might say it's obvious that an experiment beats a computational prediction, but many clinicians would not accept evidence about human variants based on how they perform in baker's yeast. Our paper highlights the important and direct role that model organisms can play in interpreting individual human genomes," says Roth.

For the subset of human disease genes that will be able to fill in for their yeast counterparts, Roth believes it is possible to test all variants this way. For other genes, similar assays could be done in other model organisms or using other tests in yeast. The goal is to create lists of experimentally tested mutations before they are detected in the genomes of affected patients.

"I think the way to go forward is to do all of the experiments up front before you've even seen the variants in the clinic. Organized networks of researchers could test the variants in a common way so that we can build a resource so that clinicians can go immediately to the look-up table," says Roth.

Sometimes you need to turn to the basics -- in this case a simple organism like yeast -- in order to tackle some of our most complex medical challenges.

http://www.eurekalert.org/pub_releases/2016-04/uob-rsh040616.php

Ring-shaped sugar helps in cases of atherosclerosis

Researchers at the University of Bonn show that cyclodextrin promotes the breakdown of dreaded plaques

Hardened and inflamed arteries, atherosclerosis, can be very dangerous. The consequences of atherosclerosis are among the most common causes of death in industrialized nations; in particular heart attacks and strokes. Crystalline cholesterol can contribute to this life-threatening inflammation in the arteries. An international research team of immunologists and cardiologists from the University of Bonn has now discovered that the ring-shaped sugar known as "cyclodextrin" can prevent and even reduce these dangerous cholesterol deposits. The results are now being published in the journal "*Science Translational Medicine*."

It is always a challenge for researchers to find the right approach for tackling a scientific issue. Yet sometimes people without any particular medical expertise also provide important clues which then lead to real breakthroughs. This was the case with Chris Hempel from the USA whose twin daughters suffer from the rare "Niemann-Pick type C" disease. In this disease, gene mutations cause the dysfunction of cholesterol transport in the cells. Those affected initially develop normally, but then in childhood there is a rapid worsening of neurological function, with cognitive and motor impairment. Until Chris Hempel became active, there was no treatment for Niemann-Pick C. With the aid of scientists, the mother developed a novel therapy with the ring-shaped sugar "cyclodextrin" which leads to better elimination of excess cholesterol from brain cells. Clinical studies on this are currently being conducted in the USA.

Prof. Dr. Eicke Latz from the Institute of Innate Immunity at the University of Bonn is studying how crystalline cholesterol causes massive immune responses and leads to life-threatening inflammation in arterial walls. In 2010, he published a study in the renowned journal "Nature" on the connection between atherosclerosis and the immune system. In this study, the team of researchers working with Prof. Latz demonstrated that cholesterol crystals can activate an important receptor complex of the innate immune system and thus increase the inflammatory response in atherosclerosis. This caught Chris Hempel's attention and she reported her experiences with cyclodextrin to the immunologist.

High-cholesterol diet for mice

With an international team of researchers from Germany, the USA, Norway, Australia and Sweden, the scientists from a variety of fields from the University Hospital Bonn, under the direction of Prof. Latz, investigated whether cyclodextrin also has an effect on atherosclerosis. The researchers fed a particularly cholesterol-rich diet to mice for eight weeks and subcutaneously injected the animals with cyclodextrin. "They were far less affected by plaques in their blood vessels than a control group who did not receive any cyclodextrin," says Dr. Sebastian Zimmer from the Department of Medicine II of the University Hospital Bonn. The ring-shaped sugars apparently program the cells in a way that leads to better elimination of excess crystalline cholesterol and also to a reduction in the inflammation in blood vessels at the same time.

Cyclodextrin increases the natural breakdown of cholesterol in the cells

The transcription factor "liver-X-receptor" (LXR) is a key regulator of cholesterol metabolism and thus plays an important role in connection atherosclerosis. "If too much cholesterol is present, LXR gives a signal. As a result, genes responsible for the efflux from the cell are activated," reports Alena Grebe, doctoral student in Prof. Latz's team. "In addition, this factor downregulates inflammation." If the gene for LXR was muted absent in mice, this signal cascade did not function and cyclodextrin did not show any effect. The ring-shaped sugar evidently fulfills the function of an intermediary which increases the natural mechanisms of cholesterol breakdown in the cells and additionally reduces the inflammatory response.

Using human atherosclerotic vessels, the team also investigated whether cyclodextrin has the same effect in humans as in mice. The researchers cultivated plaques which had been surgically removed from the carotid arteries of atherosclerosis patients in order to improve their blood flow. If cyclodextrin was

mixed into the nutrient solution, the cells showed the same reprogramming as those of the rodents: the mechanisms for plaque reduction started up and the inflammatory response subsided.

The active substance is already on the market

Prof. Latz hopes that cyclodextrin can be further developed as a drug for the treatment of atherosclerosis. "It is already on the market as a pharmaceutical solubilizing agent. However, costly clinical studies are needed for the new application," says the immunologist from the University of Bonn. Chris Hempel who pointed out the active substance cyclodextrin is incidentally listed as a co-author in the journal publication.

Publication: Cyclodextrin promotes atherosclerosis regression via macrophage reprogramming, "Science Translational Medicine"*, DOI: 10.1126/scitranslmed.aad6100*

http://www.eurekalert.org/pub_releases/2016-04/uoc--sbh040416.php

Supermassive black holes may be lurking everywhere in the universe

Surprise discovery of 17-billion-solar-mass black hole in sparse area of local universe

A near-record supermassive black hole discovered in a sparse area of the local universe indicates that these monster objects - this one equal to 17 billion suns - may be more common than once thought, according to University of California, Berkeley, astronomers.

Until now, the biggest supermassive black holes - those with masses around 10 billion times that of our sun - have been found at the cores of very large galaxies in regions loaded with other large galaxies. The current record holder, discovered in the Coma Cluster by the UC Berkeley team in 2011, tips the scale at 21 billion solar masses and is listed in the Guinness Book of World Records.

The newly discovered black hole is in a galaxy, NGC 1600, in the opposite part of the sky from the Coma Cluster in a relative desert, said the leader of the discovery team, Chung-Pei Ma, a UC Berkeley professor of astronomy and head of the MASSIVE Survey, a study of the most massive galaxies and black holes in the local universe with the goal of understanding how they form and grow supermassive.

While finding a gigantic black hole in a massive galaxy in a crowded area of the universe is to be expected - like running across a skyscraper in Manhattan - it seemed less likely they could be found in the universe's small towns.

"Rich groups of galaxies like the Coma Cluster are very, very rare, but there are quite a few galaxies the size of NGC 1600 that reside in average-size galaxy groups," Ma said. "So the question now is, 'Is this the tip of an iceberg?' Maybe there are a lot more monster black holes out there that don't live in a skyscraper in Manhattan, but in a tall building somewhere in the Midwestern plains."

While the black hole discovered in 2011 in the galaxy NGC 4889 in the Coma Cluster was estimated to have an upper limit of 21 billion solar masses, its range of possible masses was large: between 3 billion and 21 billion suns. The 17-billion-solar-mass estimate for the central black hole in NGC 1600 is much more precise, with a range (standard deviation) of 15.5 to 18.5 billion solar masses.

Interestingly, the stars around the center of NGC 1600 are moving as if the black hole were a binary. Binary black holes are expected to be common in large galaxies, since galaxies are thought to grow by merging with other galaxies, each of which would presumably bring a central black hole with it. These black holes would likely sink to the core of the new and larger galaxy and, after an orbital dance, merge with the emission of gravitational waves. The proposed Evolved Laser Interferometer Space Antenna, or eLISA, is designed to detect gravitational waves produced by the merger of massive black holes, while other groups are looking for evidence of gravitational waves from massive black hole mergers in nanosecond glitches in the precisely timed flashes of millisecond pulsars.

Ma and her colleagues will report the discovery of the black hole, which is located about 200 million light-years from Earth in the direction of the constellation Eridanus, in the April 6 issue of the journal Nature.

In search of quasar remnants

Black holes form when matter becomes so dense that not even light can escape its gravitational pull. In the early universe, when gas was abundant, a handful of voracious black holes grew to become extremely massive by swallowing it up, emitting immense amounts of energy. Looking back in time at the distant universe, these supermassive black holes appear as very bright quasars. As astronomers look closer to Earth, however, they see galaxies with little gas - it's already turned into stars - and no quasars. The most massive of these local galaxies may, however, house old quasars at their cores. Ma says that the monster black holes her team discovered in 2011 in NGC 4889 and NGC 3842, each weighing about 10 billion solar masses, may be quiescent quasars.

Because NGC 1600 is an old galaxy with little new star formation, Ma suspects that it, too, may harbor an ancient quasar that once blazed brightly but is now asleep. It would be the first discovered in a sparsely populated region of the local universe, she said.

"The brightest quasars, probably hosting the most massive black holes, don't necessarily have to live in the densest regions of the universe," she said. "NGC 1600 is the first very massive black hole that lives outside a rich environment in

the local universe, and could be the first example of a descendent of a very luminous quasar that also didn't live in a privileged site."

The MASSIVE Survey was funded in 2014 by the National Science Foundation to weigh the stars, dark matter and central black holes of the 100 most massive, nearby galaxies: those larger than 300 billion solar masses and within 350 million light-years of Earth, a region that contains millions of galaxies. Among its goals is to find the descendants of luminous quasars that may be sleeping unsuspected in large nearby galaxies.

The supermassive black hole found in NGC 1600 is one of the first successes of the project, proving the value of a systematic search of the night sky rather than looking only in dense areas like those occupied by large clusters of galaxies, such as the Coma and Virgo clusters. The new findings combine image data from the Hubble Space Telescope and spectra taken by the Gemini Telescope in Hawaii and the McDonald Observatory in Texas.

Based on the Gemini spectra of the center of NGC 1600, most stars inside the sphere of influence of the black hole - a region about 3,000 light-years in radius - are traveling on circular orbits around the black hole, with very few moving radially inward or outward. It is as if the stars on radial orbits towards the black hole have been slung away, Ma said.

This would be the case only if the closest stars were scattering off a black hole pair and slingshotted away, just as NASA slingshots space probes around other planets to move them more quickly through the solar system.

The black hole's sphere of influence - the region within which the gravity due to the black hole wins out over that due to visible stars - is much larger than the event horizon, the point of no return, which would be about eight times the size of Pluto's orbit for the NGC1600 black hole.

"Somehow the stars have been scared away from the center of very massive galaxies, and either were afraid to come in, or came in and got kicked out," Ma said. The stellar orbits around the center of NGC 1600 indicate the latter, which "may be support for a binary black hole formed by a merger."

Binary black holes and core scouring

Because stars flung out by a binary black hole sap energy from the orbiting pair, the two move closer together and eventually merge. If NGC 1600 does contain a binary black hole with a combined mass of 17 billion suns, orbiting a fraction of a light-year apart, the ongoing pulsar timing arrays have a chance of picking up the emitted gravitational waves, Ma said.

NGC 1600 suggests that a key characteristic of a galaxy with binary black holes at its core is that the central, star-depleted region is the same size as the sphere of influence of the central black hole pair, Ma said. Images taken by the Hubble Space Telescope revealed that the center of NGC 1600 is unusually faint, indicating a lack of stars close to the black hole. A lack of stars close to the galactic center distinguishes massive galaxies from standard elliptical galaxies, which are much brighter in their cores.

"One dynamical footprint of a binary black hole is core scouring," Ma said.

This signature will help Ma and her colleagues refine the MASSIVE Survey and more quickly find the supermassive black holes in Earth's vicinity.

Ma's co-authors are first-author Jens Thomas of the Max Planck Institute for Extraterrestrial Physics in Garching, Germany; former UC Berkeley doctoral student Nicholas McConnell and John Blakeslee of the Dominion Astrophysical Observatory in Victoria, British Columbia; former Miller Visiting Professor Jenny Greene of Princeton University; and Ryan Janish of UC Berkeley's Department of Physics.

http://www.eurekalert.org/pub_releases/2016-04/uoc--hlo040616.php

Higher levels of vitamin D correspond to lower cancer risk, researchers say

Higher levels of serum 25-hydroxyvitamin D are associated with a reduced risk of cancer

Researchers at University of California, San Diego School of Medicine report that higher levels of vitamin D - specifically serum 25-hydroxyvitamin D - are associated with a correspondingly reduced risk of cancer. The findings are published in the April 6, online issue of PLOS ONE.

"We have quantitated the ability of adequate amounts of vitamin D to prevent all types of invasive cancer combined, which had been terra incognita until publication of this paper," said Cedric Garland, DrPH, adjunct professor in the UC San Diego School of Medicine Department of Family Medicine and Public Health and member of Moores Cancer Center at UC San Diego Health.

Garland and his late brother, Frank, made the first connection between vitamin D deficiency and some cancers in 1980 when they noted populations at higher latitudes (with less available sunlight) were more likely to be deficient in vitamin D, which is produced by the body through exposure to sunshine, and experience higher rates of colon cancer. Subsequent studies by the Garlands and others found vitamin D links to other cancers, such as breast, lung and bladder.

The new PLOS ONE study sought to determine what blood level of vitamin D was required to effectively reduce cancer risk. The marker of vitamin D was 25-hydroxyvitamin D, the main form in the blood. The researchers employed a non-traditional approach, pooling analyses of two previous studies of different types: a randomized clinical trial of 1,169 women and a prospective cohort study of 1,135 women. A clinical trial focuses upon whether a specific test or treatment is safe

and effective. A prospective study looks for outcomes during the study period, in this case incidence of cancer among participants.

By combining the two studies, the researchers obtained a larger sample size and a greater range of blood serum levels of 25-hydroxyvitamin D or 25(OH)D.

The only accurate measure of vitamin D levels in a person is a blood test. In the Lappe trial cohort, the median blood serum level of 25(OH)D was 30 nanograms per milliliter. In the GrassrootsHealth prospective cohort, it was higher: 48 ng/ml.

The researchers found that the age-adjusted cancer incidence was 1,020 cases per 100,000 person-years in the Lappe cohort and 722 per 100,000 person-years in the GrassrootsHealth cohort. Cancer incidence declined with increased 25(OH)D. Women with 25(OH)D concentrations of 40 ng/ml or greater had a 67 percent lower risk of cancer than women with levels of 20 ng/ml or less.

Recommended blood serum levels of vitamin D have been a source of vigorous debate in recent years. In 2010, the Institute of Medicine (IOM) concluded that levels lower than 12 ng/ml represented a vitamin D deficiency and recommended a target of 20 ng/ml, which could be met in most healthy adults (ages 19 to 70) with the equivalent of 600 International Units of vitamin D each day.

Subsequently, other groups have argued for higher blood serum levels: 50 ng/ml or more. Above 125 ng/ml, there may be side effects. Many vitamin D supporters now advocate 800 to 1,000 IUs daily; more for persons older than 70 and pregnant or lactating women.

Garland does not identify a singular, optimum daily intake of vitamin D or the manner of intake, which may be sunlight exposure, diet and/or supplementation. He said the current study simply clarifies that reduced cancer risk becomes measurable at 40 ng/ml, with additional benefit at higher levels.

"These findings support an inverse association between 25(OH)D and risk of cancer," he said, "and highlight the importance for cancer prevention of achieving a vitamin D blood serum concentration above 20 ng/ml, the concentration recommended by the IOM for bone health."

Garland said a broad effort to increase 25(OH)D concentrations to a minimum of 40 ng/ml in the general population would likely and substantially reduce cancer incidence and associated mortality.

"Primary prevention of cancer, rather than expanding early detection or improving treatment, will be essential to reversing the current upward trend of cancer incidence worldwide," the researchers wrote. "This analysis suggests that improving vitamin D status is a key prevention tool."

Co-authors include S.L. McDonnell, C. Baggerly, C.B. French, L.L. Baggerly, GrassrootsHealth, California; E.D. Gorham, UC San Diego; and J.M. Lappe and R.P. Heaney, Creighton University.

Funding for this study came, in part, from Bio-Tech Pharmacal, Pure North S'Energy Foundation and the Vitamin D Society. Funding for the Lappe study came from Department of Health and Human Services grant AG14683-01A2. Funding for the GrassrootsHealth study was through self-sponsorship by participants and donations from the funders listed above.

http://www.bbc.com/news/science-environment-35976498

Exploding stars left recent, radioactive mark on Earth

Two new studies confirm that multiple exploding stars, called supernovae, have showered the Earth with radiation within the last few million years.

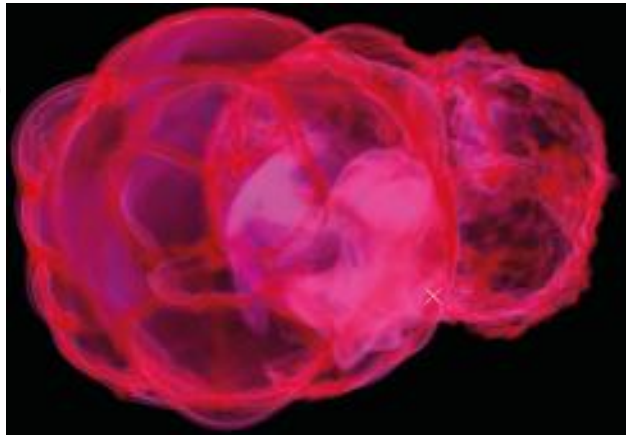
By Jonathan Webb Science reporter, BBC News

One study reports traces of radioactive iron-60, a strong indicator of supernova debris, found buried in the sea floor right across the globe. A second paper models which specific supernovae are most likely to have splattered this isotope across our historic, galactic neighbourhood. Both appear in the journal Nature.

The periods of bombardment highlighted by the two teams do not coincide with any mass extinction events - and indeed, the predicted locations of the culprit supernovae are not quite close enough to unleash that level of destruction.

But the blasts may nonetheless have affected the Earth's climate and thus, the evolution of life. Importantly, the two sets of results are entirely consistent, according to Dieter Breitschwerdt from the Berlin Institute of Technology, Germany, who led the modelling research.

His team has spent years studying the "local bubble": a ballooning region of hot gas, 600 light-years across, that surrounds the Solar System and dominates our stellar neighbourhood. It was formed, Prof Breitschwerdt and his colleagues have found, by upwards of a dozen supernovae all blowing up within a nearby, moving clump of stars. Their new paper pinpoints those explosions.



Modelling the distribution of iron-60 in the local bubble; "X" marks the Solar System

Michael Schulreich

"We now can make a table of the stars - what mass they had, when they exploded, and where they were," he told the BBC News website.

Specifically, his team calculated how much iron-60 those supernovae would have sprayed into space - and how much the Earth could have swept up, based on the Solar System's path as it orbits around the Milky Way.

The tiny quantities of this isotope found in the Earth's crust - first detected in samples from the bottom of the Pacific Ocean in 1999 - show a peak at about two million years ago. So, do the closest explosions in Prof Breitschwerdt's table match that peak?

The short answer is yes. The nearest blast in the simulation took place 2.3 million years ago, and the second-nearest 1.5 million years ago.

That is quite a spread - but a prolonged, recent scattering of iron-60 is precisely what the other Nature paper reports, based on atom-counting measurements from 120 sea-bed samples spanning the Indian, Pacific and Atlantic Oceans.

Together, these new samples cover 11 million years of Earth's geological history - and they reveal an increased smattering of iron-60 between 1.5 and 3.2 million years ago. "We were very surprised that there was debris clearly spread across 1.5 million years," said that study's lead author Anton Wallner, a nuclear physicist at the Australian National University in Canberra.

"It suggests there were a series of supernovae, one after another."

Coincidental cooling?

Dr Wallner and his colleagues also detect a spike in iron-60 a little earlier, between 6.5 and 8.7 million years ago - but it is the more recent deposit that aligns remarkably well with Prof Breitschwerdt's simulation.

Even the teams' predicted distances match: the simulations and the ocean-floor data both place the recent explosions 300 light-years away, or less.

The timing of the supernovae also has some fascinating implications: "It's an interesting coincidence that they correspond with when the Earth cooled and moved from the Pliocene into the Pleistocene period," Dr Wallner adds, referring to the epoch of regular ice ages that took hold some 2.5 million years ago.

The idea that nearby stellar explosions could have triggered key transitions in our planet's natural history is not a new one. But it has found little scientific support over the years. Adrian Melott from the University of Kansas, US, specialises in studying those possible effects. He was not involved in either of the new studies but wrote a commentary for Nature on their implications. "The events [described in the new findings] weren't close enough to cause a big mass extinction or severe effects, but not so far away that we can ignore them either," he said.

Prof Melott's own research team will be following up on the results, he added - particularly the new, precise estimates for when the two nearest supernovae flung their debris in our direction. "We're trying to decide if we should expect to have seen any effects on the ground on the Earth."

http://www.eurekalert.org/pub_releases/2016-04/ul-dib040716.php

Drop in body temperature linked to aging aggravates manifestations of Alzheimer's disease

Drop in body temperature linked to aging aggravates manifestations of Alzheimer's disease

Québec City - The drop in body temperature associated with aging could aggravate the main manifestations of Alzheimer's, suggests a study published in the latest issue of Neurobiology of Aging by Université Laval researchers. Although the phenomenon was demonstrated using transgenic mice, researchers believe that the findings are convincing enough to warrant further investigation in humans.

"We know that the incidence of Alzheimer's is low before age 65, but doubles every 5 to 6 years afterward," explains the study's lead author Frédéric Calon, professor at the Université Laval Faculty of Pharmacy and researcher at Centre de recherche du CHU de Québec-Université Laval. "We also know that metabolism and body temperature decrease as people get older. We therefore tested the hypothesis that the changes in the body's thermoregulation that occur with age amplify the main manifestations of Alzheimer's and that a vicious circle can even set in because the disease expresses itself in certain areas of the brain involved in temperature regulation."

To test this hypothesis, the researchers used a type of transgenic mice that express the main manifestations of Alzheimer's disease as they age: They produce beta-amyloid, which leads to the formation of senile plaque in the brain; they are affected by a pathology that renders neurons non-functional; and they lose synaptic proteins. In these mice, memory problems begin to arise at the age of 6 months.

By comparing these transgenic mice with normal ones, researchers first established that the transgenic mice were less able to effectively maintain their body temperature as they aged. The difference reached almost 1° Celsius by the age of 12 months. The researchers also observed that the manifestations of Alzheimer's were markedly more pronounced in transgenic mice when they were exposed to low temperatures: "The abnormal tau proteins responsible for neuron deterioration increase more in transgenic mice than normal mice, and the loss of synaptic proteins is more pronounced," explains Professor Calon.

Conversely, researchers observed that exposure to a high ambient temperature mitigated some manifestations of Alzheimer's disease. After one week in a 28°C environment, the transgenic mice's body temperature had increased by 1°C, beta-amyloid production had dropped substantially, and memory test results were comparable to those of normal mice.

"Our findings suggest that it is worth exploring the treatment of thermoregulation among seniors suffering from Alzheimer's," says Professor Calon. "If our conclusions are confirmed, it would be a relatively easy therapeutic option to implement because body temperature can be increased through physical activity, diet, drugs, or simply by increasing the ambient temperature."

The study published in Neurobiology of Aging was authored by Milène Vandal, Phillip White, Marine Tournissac, Cyntia Tremblay, Isabelle St-Amour, Janelle Drouin-Ouellet, Mélanie Bousquet, Marie-Thérèse Traversy, Emmanuel Planel, André Marette, and Frédéric Calon.

http://www.eurekalert.org/pub_releases/2016-04/muhc-tst040716.php

Traditional skin tests used to predict allergies to antibiotics are useless say Montreal researchers

Skin tests traditionally used to predict allergies to amoxicillin, one of the most commonly prescribed antibiotics in children are ineffective

Montreal, - Skin tests traditionally used to predict allergies to amoxicillin, one of the most commonly prescribed antibiotics in children, are ineffective according to a new study led by a team at the Research Institute of the McGill University Health Centre (RI-MUHC) in Montreal. The findings, published in the journal JAMA Pediatrics this week, determined that oral provocation or challenge test, with appropriate follow up, was a more efficient and safer screening method for diagnosing non-life threatening reactions to amoxicillin in children.

"Our study suggests that skin tests are essentially useless as diagnostic tests, and that we should go directly to the graded provocation test that is highly sensitive and specific," says study's lead author Dr. Moshe Ben-Shoshan, who is an allergist at the Montreal Children's Hospital at the MUHC (MCH-MUHC) and an assistant professor of Pediatrics at McGill University. "This is a game changer in the way physicians assess amoxicillin allergy in children given the fact that skin tests are still the recommended screening method in hospitals."

Provocation or challenge (PC) tests are performed with the suspected allergen (for example pollen, food or drug) which involves gradual introduction of the allergen to the patient. Challenge tests are performed in a hospital or clinic, where any serious reactions can be safely managed.

Up to 10 per cent of children develop rashes while on antibiotics. "The majority are diagnosed without further evaluation as allergic to the implicated antibiotic," explains Dr. Ben-Shoshan who is also a researcher from the Infectious Diseases and Immunity in Global Health Program of the RI-MUHC. "Most of the patients continue to avoid the suspect antibiotic in favor of alternatives which may be less effective, more toxic, and more expensive."

The researchers conducted the largest study of its kind to assess the use of a graded PC in children who presented with a rash due to suspected amoxicillin allergy. They assessed 818 children who presented to the MCH-MUHC Allergy clinic from March 2012 to April 2015. Unlike previous studies all children had to undergo a graded PC. Researchers observed that 94.1 per cent were tolerant to the graded PC for amoxicillin. From all the study's participants, only 17 had an immediate positive reaction to amoxicillin, and only one within this group had a positive skin test. Indeed for many antibiotics (including amoxicillin), skin tests can have a high false-negative rate. Thirty one had non-immediate reactions developing more than one hour after challenge. All non-immediate reactions were mild and manifested mainly as skin eruptions. "Our study is the first to determine the percentage of immediate and non-immediate amoxicillin allergy in all children presenting with a suspected amoxicillin induced rash through a graded PC," says Dr. Ben-Shoshan. "Further, we showed that in children with a negative PC, amoxicillin can be safely used in the future, although under 10 per cent may develop mild cutaneous symptoms upon subsequent exposure."

According to the researchers, future studies are required to assess factors associated with specific PC outcomes, and in particular researchers should investigate specific association with genetic markers to accurately determine future risk for antibiotic allergic reactions.

About the study

The study Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Non immediate Reactions to Amoxicillin in Children was co-authored by Christopher Mill, Marie-Noël Primeau, Elaine Medoff, Christine Lejtenyi, Elena Netchiporouk, Alizee Dery, and Moshe Ben-Shoshan from the McGill University Health Centre, Montreal, Quebec, Canada; and by Andrew O'Keefe from the Memorial University, St John's, Newfoundland and Labrador, Canada.

http://www.eurekalert.org/pub_releases/2016-04/sumc-mml033116.php

Modern men lack Y chromosome genes from Neanderthals, Stanford researchers say

Study suggests that Neanderthal Y-chromosome genes disappeared from the human genome long ago

Although it's widely known that modern humans carry traces of Neanderthal DNA, a new international study led by researchers at the Stanford University School of Medicine suggests that Neanderthal Y-chromosome genes disappeared from the human genome long ago.

The study will be published April 7 in The American Journal of Human Genetics, in English and in Spanish, and will be available to view for free. The senior author is Carlos Bustamante, PhD, professor of biomedical data science and of genetics

at the School of Medicine, and the lead author is Fernando Mendez, PhD, a postdoctoral scholar at Stanford.

The Y chromosome is one of two human sex chromosomes. Unlike the X chromosome, the Y chromosome is passed exclusively from father to son. This is the first study to examine a Neanderthal Y chromosome, Mendez said. Previous studies sequenced DNA from the fossils of Neanderthal women or from mitochondrial DNA, which is passed to children of either sex from their mother.

Other research has shown that the DNA of modern humans is from 2.5 to 4 percent Neanderthal DNA, a legacy of breeding between modern humans and Neanderthals 50,000 years ago. As a result, the team was excited to find that, unlike other kinds of DNA, the Neanderthal Y chromosome DNA was apparently not passed to modern humans during this time.

"We've never observed the Neanderthal Y chromosome DNA in any human sample ever tested," Bustamante said. "That doesn't prove it's totally extinct, but it likely is."

Why no Neanderthal DNA?

Why is not yet clear. The Neanderthal Y chromosome genes could have simply drifted out of the human gene pool by chance over the millennia. Another possibility, said Mendez, is that Neanderthal Y chromosomes include genes that are incompatible with other human genes, and he and his colleagues have found evidence supporting this idea. Indeed, one of the Y chromosome genes that differ in Neanderthals has previously been implicated in transplant rejection when males donate organs to women.

"The functional nature of the mutations we found," said Bustamante, "suggests to us that Neanderthal Y chromosome sequences may have played a role in barriers to gene flow, but we need to do experiments to demonstrate this and are working to plan these now."

Several Neanderthal Y chromosome genes that differ from those in humans function as part of the immune system. Three are "minor histocompatibility antigens," or H-Y genes, which resemble the HLA antigens that transplant surgeons check to make sure that organ donors and organ recipients have similar immune profiles. Because these Neanderthal antigen genes are on the Y chromosome, they are specific to males.

Theoretically, said Mendez, a woman's immune system might attack a male fetus carrying Neanderthal H-Y genes. If women consistently miscarried male babies carrying Neanderthal Y chromosomes, that would explain its absence in modern humans. So far this is just a hypothesis, but the immune systems of modern women are known to sometimes react to male offspring when there's genetic incompatibility.

When did we part ways?

The Y chromosome data also shed new light on the timeline for the divergence of humans and Neanderthals. The human lineage diverged from other apes over several million years, ending as late as 4 million years ago. After the final split from other apes, the human lineage branched into a series of different types of humans, including separate lineages for Neanderthals and what are now modern humans.

Previous estimates based on mitochondrial DNA put the divergence of the human and Neanderthal lineages at between 400,000 and 800,000 years ago. The last common ancestor of Neanderthals and humans -- based on the Y chromosome DNA sequenced in the study -- is about 550,000 years ago.

Sequencing the Neanderthal Y chromosome may shed further light on the relationship between humans and Neanderthals. One challenge for the research team is to find out whether the Y chromosome Neanderthal gene variants identified were indeed incompatible with human genes.

The data for the study came from public gene sequencing databases. "We did not collect any data for this work," said Mendez. "It was all public data."

Another Stanford-affiliated co-author is former graduate student David Poznik, PhD.

A researcher at the Max Planck Institute for Evolutionary Anthropology also co-authored the study.

The work was supported by the Stanford Center for Computational, Evolutionary and Human Genomics; the National Science Foundation; the National Library of Medicine; and the Max Planck Society.

Stanford's departments of Genetics and of Biomedical Data Science supported the work.

http://bit.ly/1NqzF78

HIV defies attempt to edit virus out of human cells with CRISPR

Vanquishing HIV just got that little bit harder. A promising technique to weaken the virus has in some cases made it stronger.

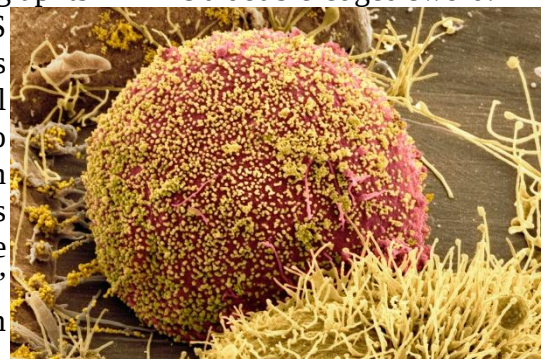
HIV's ability to evolve resistance to antiretroviral drugs has become legendary. It had been thought that a new precision gene-editing tool called CRISPR would have more success, enabling the viral genome to be "cut" from all infected cells. Now it seems that hope may be in vain – at least for now.

Curing people with HIV has proved impossible so far. Several prominent reports of cures three years ago turned out to provide false hope, after the virus bounced back.

The problem begins with the fact that HIV integrates its genome into the host cell's DNA. While antiretroviral drugs keep people free of active infection, this viral DNA hides out in parts of the body they can't reach, ready to revive active infection if the drug treatment is stopped.

CRISPR cuts

Using CRISPR to cut up the HIV genome in all cells – including those where it's hiding out – is one of several promising strategies to clear the infection. But it has been hit with a serious setback. Research shows that the use of CRISPR to destroy the virus in white blood cells by messing up its DNA is a double-edged sword.



Not defeated yet **Thomas Deerinck, NCMIR/SPL**

Chen Liang of McGill University AIDS Center in Montreal, Canada, and his team used CRISPR to cut up the viral DNA that had been incorporated into the host cell. The idea was that when the cell's natural repair mechanisms patched up the broken genetic sequence it would introduce genetic "scar tissue" that would prevent the viral DNA from functioning.

Sometimes this did, indeed, happen – the gene alterations "killed" the virus. But to the surprise of the researchers, in other cases the scar tissue made the virus stronger – sometimes it was able to replicate faster, for example.

What's more, because the patched up DNA looks different, the CRISPR cutting system couldn't recognise and attack it again. HIV had become resistant to the gene-editing technique.

Double-edged sword

"On the one hand, CRISPR inhibits HIV, but on the other, it helps the virus to escape and survive," says Liang. "The surprise is that the resistance mutations are not the products of error-prone viral DNA copying, but rather are created by the cell's own repair machinery."

But all is not yet lost.

"The bright side is that when you know what the problem is, you can come up with the means to overcome it," says Liang. "Just as HIV is able to escape all antiretroviral drugs, understanding how HIV escapes only helps you discover better drugs or treatments."

One possibility is to "carpet-bomb" HIV with CRISPR at many sites within its DNA instead of just the one targeted in the experiment. This, says, Liang, would make it much more difficult for the virus to evolve resistance.

HIV neutralised

Another potential ploy is to attack the virus with CRISPR-like techniques that rely on different DNA repair machinery, making it less likely that the repair process itself would help the virus become resistant to editing.

Another team reporting early success against HIV using CRISPR isn't discouraged by the setback, echoing the possibility that the "carpet-bombing" solution could be the answer. "The key could be using multiple viral sites for editing," says Kamel Khalili of Temple University in Philadelphia, Pennsylvania. "This would reduce any chance for virus escape or the emergence of virus resistant to the initial treatment," he says.

Earlier this year Khalili's team showed that CRISPR neutralises HIV in cells that are latently as well as actively infected, suggesting that a cure could one day be possible.

Journal reference: Cell Reports, *DOI: 10.1016/j.celrep.2016.03.042*

http://bit.ly/1VHlkHE

Missing building block of life could be made on ice in space

The search for life in space just got a little sweeter.

In the early solar system, ice grains hit by sunlight may have formed sugar molecules on their surfaces, according to a new experiment. Those sugars include ribose: the backbone of RNA, which is implicated in the origin of life.

All known life makes at least some use of RNA as a genetic material, and as the "R" in RNA, ribose holds up the compounds that encode genetic messages. But it's been hard to understand how ribose could be made in the absence of living organisms, to be part of a precursor for life.

Other components of living cells, such as amino acids, which are the building blocks of proteins, have shown up in experiments and samples from meteorites for years. So have molecules that resemble cell membranes. If they and ribose had all existed at the same time, it could have set the stage for life to evolve.

But sugars like ribose are hard to come by, since they often stick together in a way that makes them impossible to extract. "Sugars like to react with each other," says Cornelia Meinert at the University of Nice Sophia Antipolis in France. "In the end, everything is brown like caramel."

Now Meinert's team was able to produce ribose by shining ultraviolet light on a frozen blend of water, methanol and ammonia. This mixture represents our solar system in its infancy, before tiny grains of dust and ice collapsed into planets.

Lego castle of life

"It's another example of how the universe seems to be hardwired to produce a lot of the kinds of compounds you would like to be around if you want to get life going," says Scott Sandford of NASA Ames Research Center in California. Sandford's own team is reporting similar results in a paper now in press, he says.

Whether sugars are made on real interstellar ice grains is still an open question. Because these grains are preserved if they gently settle on small bodies far from the sun, checking the surfaces of comets or meteorites may help resolve the issue.

ESA's Rosetta mission and radio astronomers have picked up simple sugars on comets before, but they may struggle to find something complex like ribose, Meinert thinks.

Finding these sugars on comets would tell us that amino acids, molecules in cell membranes and ribose could all have been made in space, then dropped on Earth just in time for the genesis of life.

We're far from understanding what happened next, though. "Just because now you have all the molecules doesn't mean you have life," Meinert says.

Still, it doesn't hurt. "If you think of all these little molecules we're making as Lego blocks, and life as a kind of very complex, organised Lego castle, the fact that Lego blocks are falling out of the sky can't be a bad thing," Sandford says.

Journal reference: Science, DOI: 10.1126/science.aad8137

http://bit.ly/23rWJt0

Extreme morning sickness? You're less likely to have a boy

Women who suffer extreme morning sickness may be less likely to give birth to sons.

Hyperemesis gravidarum (HG) involves severe vomiting – sometimes up to 50 times a day – and its causes are unknown. Kate Middleton suffered from it during both of her pregnancies. Now a study of 1.65 million pregnancies in Sweden has found that less well-educated women are more likely to develop HG, and that women who develop HG are more likely to have daughters.

Using education level as an indicator of someone's social and financial status, Lena Edlund of Columbia University in New York and her team found that women who left school at 16 were 76 per cent more likely to develop HG than women who went on to attain masters or PhD degrees.

Their analysis also revealed that, regardless of socioeconomic status, women who have HG are less likely to give birth to sons. "Normally, slightly more boys than girls are born, we don't quite know why that is," says Edlund. But her team found that 56 per cent of the women in the study with extreme morning sickness who had successful pregnancies gave birth to daughters.

Women with HG have a higher chance of miscarriage, and it is possible that a male fetus is more likely to be lost than a female one. Out of the nearly 18,000 women in the study who had HG, 6000 pregnancies didn't reach full term. If these women had started out with fetuses matching the normal sex ratio, then we would expect around 4000 of these lost pregnancies to be boys.

Evolutionary strategy

"The team do not know the genders of these miscarried pregnancies. But if more were male, this could back up an old evolutionary idea. First proposed in 1973, the Trivers-Willard hypothesis suggests that when times are good, it is best to have a son; but in tough times, a daughter is the safest bet.

The reasoning behind this theory is that in many species, strong males try to monopolise females, while weaker males don't stand a chance of passing on their genes. If a mother is in poor health or food is scarce – or perhaps if her socioeconomic status is low – her newborn son might fail to find a partner and pass on her genes to the next generation.

Stress does seem to affect sex ratio in humans. A number of studies have shown that traumatic events, such as the murder of President John F. Kennedy, the 9/11 attacks, and the Troubles in Northern Ireland, are associated with a dip in the number of boys born locally in following months. But the mechanism for how stress affects sex ratios has remained elusive. Edlund thinks HG could be responsible. "Vomiting is like forced fasting, lowering the blood sugar levels. Fasting and dieting have been shown to influence the sex ratio, so it seems plausible that there is a link," she says.

Emergency signal

That is an interesting finding," says David Haig, an evolutionary biologist at Harvard University. But he says the study doesn't prove that HG is the factor skewing the sex ratio, and that female fetuses may be more likely to cause the condition in the first place. There is circumstantial evidence that the hormone human chorionic gonadotropin can cause nausea, and some studies have shown that women carrying female fetuses have higher levels of this hormone. It's therefore possible that female fetuses could be triggering HG in this way, although Haig says this evidence is from later in pregnancy than when the condition mostly occurs.

Scott Forbes, a biologist at the University of Winnipeg in Canada, thinks rather than acting as a sex-ratio skewing adaptation for stressful times, HG is more likely to be a sign that something is going wrong. "Given that HG is sometimes fatal, it seems unlikely to be adaptive," he says.

Journal reference: Economics and Human Biology, DOI: 10.1016/j.ehb.2016.02.001

http://www.bbc.com/news/health-35977200

Huge leap to mass produced platelets

Scientists have made a significant leap towards mass producing platelets - the part of the blood that forms clots.

By James Gallagher Health editor, BBC News website

The NHS and University of Cambridge team have discovered how to grow the body's platelet factories in the laboratory. It could provide a new source of platelets to stop heavy bleeding, for example after a car crash. But the researchers need to make the process more efficient before starting trials.

If you donate blood, then it is separated out into red blood cells, plasma and platelets so patients are given only the component they need. Platelets are needed after trauma, surgery, leukaemia therapy and in some blood disorders like haemophilia.

"We're totally dependent on blood donation to produce those platelets," said Dr Cedric Ghevaert, a consultant haematologist.

His team has been trying to grow megakaryocytes - the platelet mother cells that live in your bone marrow and manufacture the clotting platelets. Their breakthrough, reported in the journal Nature Communications, was the discovery of a set of chemical switches needed to create megakaryocytes in the lab.

Dr Ghevaert described their results as a "major step forward" and told the BBC News website that "the next big step is to get enough platelets out of each megakaryocyte". The lab-made cells produce around 10 platelets each. But each one functioning normally in the bone marrow would produce up to 2,000.

It is hoped that recreating the same conditions as in the bone marrow could make the cells more effective. If the researchers are successful, then lab-grown platelets could be more useful than ones collected in a blood donation.

Dr Ghevaert added: "We can modify the platelets so they can trigger the clotting even better which would have huge advantages indeed for patients who have had a crash or a bleed or even in soldiers who have been injured."

It could also allow doctors to have stockpiles customised to different patients. Platelets come in different forms just as red blood cells come in A, B, O and AB. And some platelet types, particularly those common in black and Asian ethnic groups, are relatively rare.

http://www.eurekalert.org/pub_releases/2016-04/jic-sdh040616.php

Scientists discover how Chinese medicinal plant makes anti-cancer compound

Plant used in traditional Chinese medicine produces compounds that may help to treat cancer and liver diseases

New research led by Professor Cathie Martin of the John Innes Centre has revealed how a plant used in traditional Chinese medicine produces compounds which may help to treat cancer and liver diseases. The Chinese skullcap, *Scutellaria baicalensis* - otherwise known in Chinese medicine as Huang-Qin - is traditionally used as a treatment for fever, liver and lung complaints.

Previous research on cells cultured in the lab has shown that certain compounds called flavones, found in the roots of this plant, not only have beneficial anti-viral and anti-oxidant effects, but they can also kill human cancers while leaving healthy cells untouched. In live animal models, these flavones have also halted tumour growth, offering hope that they may one day lead to effective cancer treatments, or even cures.

As a group of compounds, the flavones are relatively well understood. But the beneficial flavones found in Huang-Qin roots, such as wogonin and baicalin, are different: a missing - OH (hydroxyl) group in their chemical structure left scientists scratching their heads as to how they were made in the plant.

Professor Cathie Martin, lead author of the paper published in Science Advances, explains: "Many flavones are synthesised using a compound called naringenin as a building block. But naringenin has this -OH group attached to it, and there is no known enzyme that will remove it to produce the flavones we find in Huang-Qin roots."

New research from the John Innes Centre reveals how a plant used in traditional Chinese medicine produces compounds that may help to treat cancer and liver diseases.

Qing Zhao, Chinese Academy of Sciences

Working in collaboration with Chinese scientists, Cathie and her team explored the possibility that Huang-Qin's root-specific flavones (RSFs) were made via a different biochemical pathway. Step-by-step, the scientists unravelled the mechanism involving new enzymes that make RSFs using a different building block called chrysin.

"We believe that this biosynthetic pathway has evolved relatively recently in *Scutellaria* roots, diverging from the classical pathway that produces flavones in leaves and flowers, specifically to produce chrysin and its derived flavones," said Professor Martin.

"Understanding the pathway should help us to produce these special flavones in large quantities, which will enable further research into their potential medicinal uses. It is wonderful to have collaborated with Chinese scientists on these traditional medicinal plants. Interest in traditional remedies has increased dramatically in China since Tu Youyou was awarded the Nobel Prize for Medicine in 2015 for her work on artemisinin. It's exciting to consider that the plants which have been used as traditional Chinese remedies for thousands of years may lead to effective modern medicines."

This publication is the first high-profile output from the Centre of Excellence for Plant and Microbial Sciences, established between the John Innes Centre and the Chinese Academy of Sciences (CAS) in 2014. The research was funded by the BBSRC, CEPAMS and supported by the Chinese Scholarship Council (CSC).

http://www.eurekalert.org/pub_releases/2016-04/uot-iap040816.php

Is a popular painkiller hampering our ability to notice errors?

New U of T research shows acetaminophen could be hindering error-detection in the brain.

It's been known for more than a century that acetaminophen is an effective painkiller, but according to a new U of T study it could also be impeding error-detection in the brain.

The research, authored by a team including postdoctoral fellow Dan Randles and researchers from the University of British Columbia, is the first neurological study to look at how acetaminophen could be inhibiting the brain response associated with making errors.

"Past research tells us physical pain and social rejection share a neural process that we experience as distress, and both have been traced to same part of the brain," says Randles.

Recent research has begun to show how exactly acetaminophen inhibits pain, while behavioural studies suggest it may also inhibit evaluative responses more generally. Randles own past research has found that people are less reactive to uncertain situations when under the effect of acetaminophen.

"The core idea of our study is that we don't fully understand how acetaminophen affects the brain," says Randles. "While there's been recent behavioural research on the effects of acetaminophen, we wanted to have a sense of what's happening neurologically."

To test the idea two groups of 30 were given a target-detection task called the Go or No Go. Participants were asked to hit a Go button every time the letter F flashed on a screen but refrain from hitting the button if an E flashed on the screen.

"The trick is you're supposed to move very quickly capturing all the GOs, but hold back when you see a No Go," says Randles.

Each participant was hooked up to an electroencephalogram (EEG), which measures electrical activity in the brain. The researchers were looking for a particular wave called Error Related Negativity (ERN) and Error Related Positivity (Pe). Essentially what happens is that when people are hooked up to an EEG and make an error in the task there is a robust increase in ERN and Pe.

One group, which was given 1,000 mg of acetaminophen - the equivalent of a normal maximum dose - showed a smaller Pe when making mistakes than those who didn't receive a dose, suggesting that acetaminophen inhibits our conscious awareness of the error.

"It looks like acetaminophen makes it harder to recognize an error, which may have implications for cognitive control in daily life," says Randles.

Cognitive control is an important neurological function because people are constantly doing cognitive tasks that flow automatically like reading, walking or talking. These tasks require very little cognitive control because they are well mapped out neurological processes, notes Randles.

"Sometimes you need to interrupt your normal processes or they'll lead to a mistake, like when you're talking to a friend while crossing the street, you should still be ready to react to an erratic driver," explains Randles.

"The task we designed is meant to capture that since most of the stimuli were Go, so you end up getting into a routine of automatically hitting the Go button. When you see a No Go, that requires cognitive control because you need to interrupt the process."

The study was double blind, so neither the researcher running the study nor the participant knew whether they had been given a placebo or acetaminophen.

An unexpected and surprise finding that Randles plans to explore more closely is that those who received an acetaminophen dose appeared to miss more of the Go stimuli than they should have. He plans on expanding on the error detection aspect of the research to see whether acetaminophen is possibly causing people to "mind wander" and become distracted.

"An obvious question is if people aren't detecting these errors, are they also making errors more often when taking acetaminophen? This is the first study to address this question, so we need more work and ideally with tasks more closely related to normal daily behaviour."

The research is published in the current edition of the journal Social Cognitive and Affective Neuroscience.

http://www.eurekalert.org/pub_releases/2016-04/foas-rm040816.php

'Marijuana receptor' might hold the key to new fertility treatments for men

Research in The FASEB Journal suggests that cannabis exposure may affect DNA-bound proteins, sperm chromatin and have an impact on fertility, embryo development and offspring health

In a research report appearing in the April 2016 issue of The FASEB Journal, scientists show that a cannabinoid receptor, called "CB2," helps regulate the creation of sperm. Not only does this provide more evidence that marijuana can disrupt fertility in males, but it also suggests a therapeutic strategy for treating male infertility.

"The possibility to improve male fertility is one of the main focuses of this study, since infertility is a worldwide problem that affect up to 15% of couples in which male factors account for almost 20-70%," said Paola Grimaldi, Ph.D., a researcher

involved in the work from the Department of Biomedicine and Prevention, School of Medicine at the University of Rome Tor Vergata in Rome, Italy.

To make their discovery, Grimaldi and colleagues treated three groups of mice with different agents for 14 to 21 days. The first group was treated with a specific activator of the CB2 receptor. The second group was treated with a specific inhibitor of the CB2 receptor. The third group received only a saline solution and served as the control group. The group treated with the CB2 activator showed an acceleration of spermatogenesis, while the group treated with the inhibitor displayed a slower rate of the process. This suggests that a tight balance of CB2 activation is required for the proper progression of spermatogenesis.

"That the normal beneficial effects of endogenous cannabinoids on spermatogenesis can be stimulated further by a chemical mimic, an agonist, is a potentially promising new idea for treating male infertility," said Thoru Pederson, Ph.D., Editor-in-Chief of The FASEB Journal.

Details: Daniele Di Giacomo, Emanuela De Domenico, Claudio Sette, Raffaele Geremia, and Paola Grimaldi. Type 2 cannabinoid receptor contributes to the physiological regulation of spermatogenesis. FASEB J. April 2016 30:1453-1463; Final publication April 1, 2016. Early online publication December 15, 2015. doi:10.1096/fj.15-279034 ; http://www.fasebj.org/content/30/4/1453.abstract

http://www.bbc.com/news/science-environment-35996813

Planet Nine's profile fleshed out

Astrophysicists have outlined what Planet Nine might be like - if indeed it exists.

By Paul Rincon Science editor, BBC News website

In January, researchers at Caltech in the US suggested a large, additional planet might be lurking in the icy outer reaches of the Solar System. Now, a team at the University of Bern in Switzerland has worked out what they say are upper and lower limits on how big, bright and cold it might be.

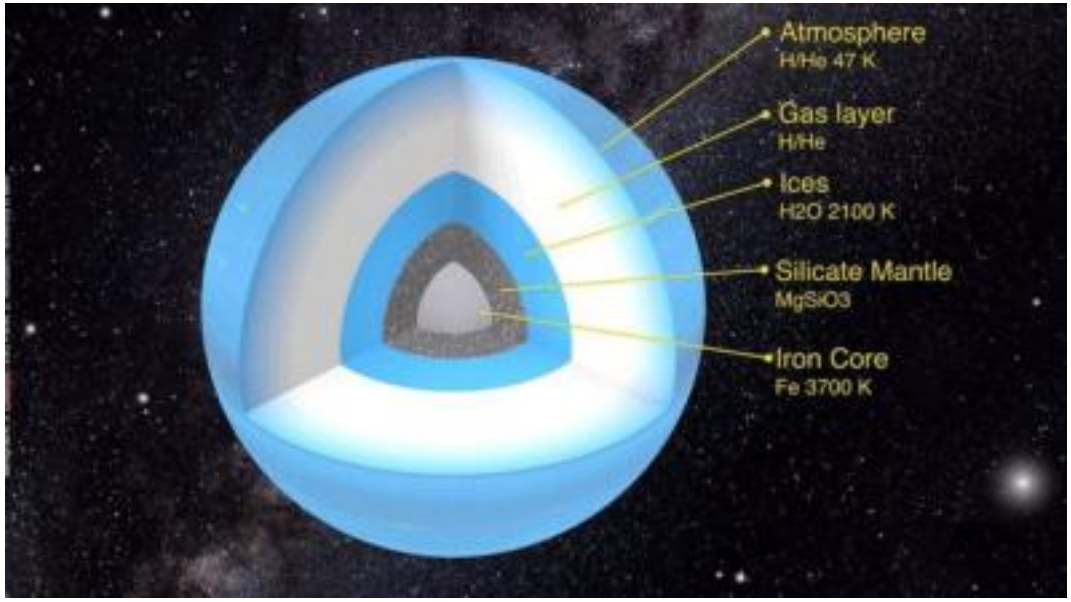
The study has been accepted by the journal Astronomy and Astrophysics.

Prof Mike Brown and Dr Konstantin Batygin made their case for the existence of a ninth planet in our Solar System orbiting far beyond even the dwarf world Pluto.

There are no direct observations of this much bigger object yet, but a search is now underway using the world's largest telescopes.

The California Institute of Technology (Caltech) scientists based their findings on the way other far-flung objects are seen to move. This prompted the Bern team, Prof Christoph Mordasini and Esther Linder, to use computer simulations to work out basic characteristics for the hypothetical ninth planet.

The Bern-based astrophysicists assumed that Planet Nine was a smaller version of Uranus and Neptune - a small ice giant with an envelope of hydrogen and helium.



The Swiss team have worked out possible physical properties for the proposed ninth planet **LINDER / MORDASINI / UNI BERN**

Using their planet evolution model, they calculated how parameters like the planetary radius or the brightness evolved over time since the Solar System formed 4.6 billion years ago. Their results suggest that for a planet 10 times more massive than Earth (the estimate obtained by Brown and Batygin), it would have a diameter 7.5 times bigger than our planet's. They also estimate that its temperature would be an icy -226C (-375F).

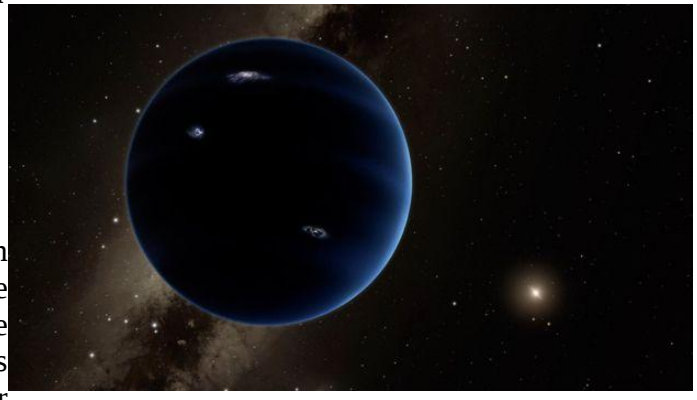
"With our study, candidate Planet Nine is now more than a simple point mass, it takes shape - having physical properties," said Prof Mordasini.

Astronomers expect to discover Planet Nine about 700 times further out than the distance between the Earth and the Sun (over 100 billion km away). Here in the cold outer reaches of the Solar System, this ninth world would reflect very little sunlight.

Instead, most of its emission would be internal heat from the core. This would make Planet Nine more easily detectable at infrared wavelengths than through optical telescopes.

And the work might explain why telescopes have failed to detect the object so far. Mordasini and and Linder calculated the brightness of smaller and bigger planets on various orbits. They concluded that Planet Nine was probably too faint for past astronomical surveys to detect - especially if the object was near the farthest point of its orbit around the Sun.

But Nasa's Wide-field Infrared Survey Explorer (Wise) space telescope might have spotted a planet with a mass equal to 50 Earth masses or more. "This puts forward an interesting upper mass limit for the planet," explained Ms Linder.



The Bern team's research assumes that Planet Nine formed from the same dense disk of dust and gas as the rest of our Solar System.

Artist's impression of a ninth planet: Telescopes are sure to try to track down the object... if it really exists **Caltech/R. Hurt (IPAC)**

But according to other researchers, Planet Nine could, in theory, have more exotic origins.

Alexander Mustill from the Lund Observatory in Sweden and colleagues have suggested that the distant world could be an exoplanet that formed around a nearby star and was later stolen by our Sun.

But other scientists - including Brown and Batygin - believe it's perfectly possible for Planet Nine to have emerged from the same maelstrom that produced the other worlds in our cosmic neighbourhood.

Brown and Batygin have stated that the ninth planet could have been the core of a gas giant that was ejected from the inner solar system early in its formation.

Brown and Batygin's initial evidence for Planet Nine was based on the alignments among the icy worlds that populate the Kuiper Belt region in the outer Solar System - and in particular two of its larger members, known as Sedna and 2012 VP113.

These alignments, they argued, were best explained by the existence of a hitherto unidentified large planet.

Then, last month, the Outer Solar System Origins Survey (Ossos) announced the discovery of a new Kuiper Belt Object (KBO) on a very eccentric orbit. This world - given the provisional name uo3L91 - was, according to Prof Brown, "exactly where Planet Nine says it should be".

In addition, Agnès Fienga at the Côte d'Azur Observatory in France and colleagues have presented evidence that a ninth planet could better explain the gravitational tug on Nasa's Cassini orbiter, which is exploring Saturn.

http://www.medscape.com/viewarticle/861483

CDC Opioid Prescribing Guidelines Misguided, Docs Say

How Did We Get in This Mess?

Brandon Cohen

Recent guidelines handed down from the Centers for Disease Control and Prevention (CDC) concerning the prescription of opioids have made waves among healthcare professionals. The CDC condemned the practice of prescribing these drugs in the vast majority of cases. Furthermore, these guidelines characterized the widespread abuse of opioids as a "doctor-driven epidemic." A Medscape news article on this topic prompted fierce opposition from many healthcare professionals against what they saw as the uninformed overreach of a government agency.

The pushback began immediately. One physician turned the blame away from doctors and back on regulatory agencies:

The opioid epidemic was created by the government and the media under the direction of their bosses in the pharmaceutical companies. Physicians were demonized if they did not compassionately prescribe potent, newly branded extended-release opioids for chronic pain. Pharmaceuticals' profits soared and Americans got hopelessly addicted. Now the government says we physicians were to blame and need to immediately stop prescribing opioids to these addicted patients.

An orthopedic surgeon carried on the impassioned defense:

There is little doubt that the designation of pain [as the] "fifth vital sign" has ignited the notion that all pain is unnecessary and must be fully eradicated if we are to do our job correctly. This, coupled with short patient interactions, has created a real misconception of pain and its consequences.

An emergency department (ED) physician agreed and added, "This is not a doctor-driven epidemic. It is driven by [government health agencies] and patient satisfaction surveys."

Another ED physician continued the thread, citing personal experience and blaming Press Ganey (a provider of patient satisfaction surveys and doctor rating systems) as one of the prime causes of the epidemic of addiction:

Every day [I hear from patients,] "All they gave me was Advil®" over and over. You want to fix this: get rid of pain scores, stop telling me I'm undertreating pain, stop the easy route for complaints against us, get rid of Press-Ganey ... The pendulum swings. Soon we will be told we aren't writing enough again.

Another ED physician employed stinging sarcasm:

Great! The patient with chronic shoulder or back pain will be so happy when I tell him or her to try naproxen, acetaminophen, or ibuprofen—bet they hadn't thought of that. And then I will refer them to a cognitive-behavioral therapist who specializes in pain, which will hardly take any time out of their lives, will be convenient to get to, and will

of course be covered so fully by their insurance. What's the [chance] they will be trying to get drugs on the street?

Concern for the Consequences

A pain management physician picked up on this idea and predicted dire consequences:

I see a huge chill on opiate prescribing followed by a massive increase in heroin deaths. Addiction care needs to be funded before the storm. Things are going to get way worse before they get better.

A colleague saw another potential danger:

[Have the government agencies] considered the number of patient suicides that have occurred as a result of unrelieved chronic pain? Get ready for a big increase, there cannot be a more tragic situation.

A registered nurse was clear and blunt:

Perhaps the government needs to look in the mirror before it blames providers for opioid addiction ... We all went to school for a long time and worked hard to get where we are. We should be allowed to make appropriate medical decisions without fear of administrative sanctions tied to satisfaction.

A retired orthopedic surgeon agreed, recalling years of practice:

It has been my clinical and personal experience that patients treated for true traumatic and post-surgical pain rarely, if ever, become dependent. I certainly saw my share of drug seekers, disability fraudsters, and street addicts who were not very difficult to recognize and were properly dealt with.

Another ED physician offered notes from the field:

Non-medical agencies have mandated pain scores from patients, and inevitably patients exaggerate their pain. Every shift, I have patients say their pain is a 10 while they are watching TV or texting on their phones .... Am I supposed to call them liars? .... What will their satisfaction scores then be with respect to how well their pain was managed?

A colleague recalled patients pointing to the pain scale sign in a treatment room and yelling, "This says I have a right to drugs!"

And a nurse offered powerful personal testimony suggesting that the CDC's recommendations were missing the real sources of addiction:

When my daughter became addicted to oxycontin at 16 years old, it was supplied by another 16-year-old who was stealing it from his grandmother with cancer. That was obviously not a doctor-driven issue. As an ED nurse, most of the overdoses that I see are not patients taking prescribed amounts, but diverted meds or [patients] taking way more than what was prescribed.

Is CDC on the Right Track?

A few voices supported the CDC's new guidelines. One physician proudly wrote:

Good to know I was right all along by denying patients opiates when other docs handed them out like candy—ridiculous! I've been cursed out by many opiate-addicted patients, but I stood my ground and I was right. I'm happy for this validation.

A pain management specialist saw much to criticize in the defensiveness of colleagues and implicitly buoyed the CDC's message:

The greatest disaster is that it seems too many primary care physicians (and nurse practitioners and physician assistants) really believe that they know more than they do about pain management ... I am plagued by referrals from individuals who send me their patients long after they have gone too far with opioid management.

The final word goes to a registered nurse who coupled work experience with personal anguish: "CDC, take my pain for a month; you would be on the streets trying to get your next fix. Let the doctors be doctors."

http://bit.ly/1RYTnq8

Mars moons may have formed after collision with Pluto-like World

Phobos and Deimos may be a chip off the old Martian block.

The Red Planet's tiny, misshapen moons are often thought to be captured asteroids, but an alternative theory suggests they are shrapnel left over from an ancient impact on Mars. Now we have a model showing how this could have happened.

The argument against the moons being asteroids rests on the fact that both have a roughly circular orbit around Mars. If they were asteroids snared by Mars's gravity, they would probably have much less regular orbits. One circular orbit could happen by chance, but two seems unlikely, says Julien Salmon of the Southwest Research Institute in Boulder, Colorado.

Phobos – just a bit of leftover rubble? **NASA**

In previous simulations of a moon-forming impact on Mars, the material that is thrown into an orbiting disc eventually comes back down, meaning nothing is left to form Phobos and Deimos. Now Salmon and his colleague Robin Canup have adapted models used to study the formation of Earth's moon, which is also thought to be the result of a large collision. They have found that an impacting object with around 3 per cent of the mass of Mars could create the right kind of disc.

The results show that such an object – with roughly the mass of Pluto – would throw around a thousandth of Mars's mass into orbit, and the edge of the disc would reach beyond the 24,000-kilometre orbit of Deimos, the outer moon.

Over time, the material nearer to Mars would coalesce into large bodies, but the planet's gravity would eventually drag them back down. But the outer part of the disk would spin fast enough to keep it out of gravity's clutches, and the material would form into the Phobos and Deimos we see today.

"The idea is that Phobos and Deimos are the only two survivors of a once much larger population of satellites," says Salmon, who presented the work at the Lunar and Planetary Science Conference in The Woodlands, Texas, last month.

Such a large object hitting Mars in its past could also explain some other features we see today, like the planet's relatively fast rotation and the large differences in average surface height between its northern and southern hemisphere, says Salmon. "It makes sense to think about a big impact for Mars."

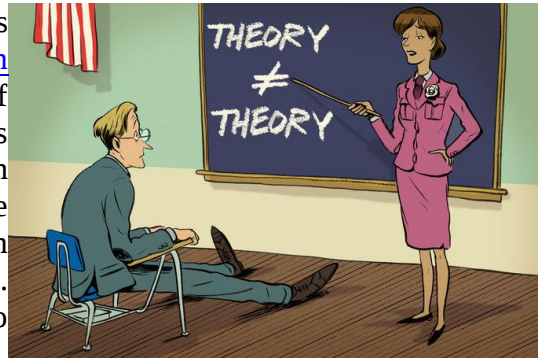
http://nyti.ms/1NiibY0

In Science, It's Never 'Just a Theory'

Misconception: It's just a theory.

By CARL ZIMMER APRIL 8, 2016

Actually: Theories are neither hunches nor guesses. They are the crown jewels of science. One day, it's Megyn Kelly who has a theory about why Donald J. Trump hates her. Another day, the newly released trailer for the next Star Wars movie inspires a million theories from fans about who Rey's parents are. And on Twitter, someone going by the name of Mothra P.I. has a theory about how cats can assume a new state of matter: In everyday conversation, we tend to use the word "theory" to mean a hunch, an idle speculation, or a crackpot notion. That's not what "theory" means to scientists.



Credit Zohar Lazar

"In science, the word *theory* isn't applied lightly," Kenneth R. Miller, a cell biologist at Brown University, said. "It doesn't mean a hunch or a guess. A theory is a system of explanations that ties together a whole bunch of facts. It not only explains those facts, but predicts what you ought to find from other observations and experiments."

Dr. Miller is one of the few scientists to have explained the nature of theories on a witness stand under oath. He is a co-author of a high school biology textbook that puts a strong emphasis on the theory of evolution. In 2002, the board of education in Cobb County, Ga., adopted the textbook but also required science teachers to put a warning sticker inside the cover of every copy. "Evolution is a theory, not a fact, regarding the origin of living things," the sticker read, in part.

In 2004, several Cobb County parents filed a lawsuit against the county board of education to have the stickers removed. They called Dr. Miller, who testified for about two hours, explaining, among other things, the strength of evidence for the theory of evolution. Once the lawyers had finished questioning Dr. Miller, he stepped down from the stand and made his way out of the courtroom. On the way, he noticed a woman looking him straight in the eye.

"She said, 'It's only a theory, and we're going to win this one,' " Dr. Miller recalled. They didn't. In 2005 the judge ruled against the board of education. The board appealed the decision but later agreed to remove the stickers.

Peter Godfrey-Smith, the author of "Theory and Reality: An Introduction to the Philosophy of Science," has been thinking about how people can avoid the misunderstanding embedded in the phrase, "It's only a theory."

It's helpful, he argues, to think about theories as being like maps.

"To say something is a map is not to say it's a hunch," said Dr. Godfrey-Smith, a professor at the City University of New York and the University of Sydney. "It's an attempt to represent some territory." A theory, likewise, represents a territory of science. Instead of rivers, hills, and towns, the pieces of the territory are facts.

"To call something a map is not to say anything about how good it is," Dr. Godfrey-Smith added. "There are fantastically good maps where there's not a shred of doubt about their accuracy. And there are maps that are speculative."

To judge a map's quality, we can see how well it guides us through its territory. In a similar way, scientists test out new theories against evidence. Just as many maps have proven to be unreliable, many theories have been cast aside.

But other theories have become the foundation of modern science, such as the theory of evolution, the general theory of relativity, the theory of plate tectonics, the theory that the sun is at the center of the solar system, and the germ theory of disease. "To the best of our ability, we've tested them, and they've held up," said Dr. Miller. "And that's why we've held on to these things."

http://bit.ly/23mnrH4

A Safe Drug to Boost Brainpower

Rigorous analysis shows the drug modafinil significantly enhances cognition

By Melinda Wenner Moyer on March 1, 2016

What if you could pop a pill that made you smarter? It sounds like a Hollywood movie plot, but a new systematic review suggests that the decades-long search for a safe and effective "smart drug" (*see below*) might have notched its first success. Researchers have found that modafinil boosts higher-order cognitive function without causing serious side effects.

Modafinil, which has been prescribed in the U.S. since 1998 to treat sleep-related conditions such as narcolepsy and sleep apnea, heightens alertness much as caffeine does. A number of studies have suggested that it could provide other cognitive benefits, but results were uneven. To clear up the confusion, researchers then at the University of Oxford analyzed 24 studies published between 1990 and 2014 that specifically looked at how modafinil affects cognition. In their review, which was published last year in *European Neuropsychopharmacology*, they found that the methods used to evaluate modafinil strongly affected the outcomes. Research that looked at the drug's effects on the performance of simple tasks—such as pressing a particular button after seeing a certain color—did not detect many benefits.

Yet studies that asked participants to do complex and difficult tasks after taking modafinil or a placebo found that those who took the drug were more accurate, which suggests that it may affect "higher cognitive functions—mainly executive functions but also attention and learning," explains study co-author Ruairidh Battleday, now a medical doctor and Ph.D. student at the University of California, Berkeley.

But don't run to the pharmacy just yet. Although many doctors very likely prescribe the drug off-label to help people concentrate—indeed, a 2008 survey by the journal *Nature* found that one in five of its readers had taken brain-boosting drugs, and half those people had used modafinil—trials have not yet been done on modafinil's long-term effectiveness or safety. Studies of the drug have been "carried out in a controlled scientific environment and usually only looked at the effects of a single dose," explains Oxford neuropsychologist and review co-author Anna-Katharine Brem—so no one yet knows whether it is safe for long-term use in healthy people. Nor is it known whether modafinil might lose its edge with repeated use, a phenomenon familiar to many coffee drinkers.

Side effects are another important consideration. Modafinil has been shown to cause insomnia, headache and stomachache in some users. Although these kinds of problems may be worth enduring for a drug that treats an illness, "if you don't have a medical condition, the risks versus benefits change dramatically," says Sharon Morein-Zamir, a psychologist at the University of Cambridge who studies ethical considerations associated with the use of cognition-enhancing drugs. "For some, the benefits will likely outweigh risks, at least some of the time," she says, whereas "for others this may not be the case." A pill you take to ace an exam, for instance, won't do you much good if it also causes a grueling stomachache.

The Search for an Intelligence Drug

People have been searching for ways to boost their brainpower perhaps for all of history. In the past century scientific efforts have revealed a few promising chemicals, but only modafinil has passed rigorous tests of cognitive enhancement.

Caffeine: One of the oldest and most popular stimulants. People recognized caffeine's stimulant properties hundreds (perhaps thousands) of years ago. It can enhance alertness and attention; however, effects are short-lived, and tolerance builds up quickly.

Nicotine: Also a stimulant, used for hundreds of years for a range of medicinal purposes. It is very addictive and has many dangerous side effects.

Amphetamine (Benzedrine, Adderall): First synthesized in 1887. Benzedrine was the first drug to treat hyperactivity in children. Amphetamine can enhance attention and memory by increasing levels of norepinephrine and dopamine in the brain, but the compound can be addictive and comes with a range of side effects, including hyperactivity, loss of appetite, disturbed sleep, even psychosis.

Methylphenidate (Ritalin): First marketed in 1954 and prescribed in the 1960s for treating hyperactivity. It became popular for ADHD in the 1990s. As with amphetamine, it can improve memory and focus for those with ADHD, but it is also used off-label as a study and work aid. Some individuals build up a tolerance to Ritalin over time.

Acetylcholinesterase inhibitor (Aricept): Approved to treat Alzheimer's disease in the 1990s. It has been shown in some studies to enhance memory and attention in healthy individuals.

Modafinil: Originally used to treat narcolepsy. It can also enhance cognitive function, especially when completing difficult tasks. Experts are not quite sure how it works or what long-term effects would look like.

Should Everyone Take Cognition-Enhancing Drugs?

As is the case with all medications, cognition-enhancing drugs affect different people in various ways. Setting aside the ethical questions about brain boosters, here is a look at groups who may deserve special consideration.

CHILDREN AND TEENS. Cognition-enhancing drugs could present unique risks to the developing brain. Several clinical trials found modafinil to be safe when given to children with attention-deficit/hyperactivity disorder (ADHD), but the trials lasted only a few months, making it difficult to ascertain the potential effects of long-term use. In a 2014 review article examining the biochemical effects of modafinil and other common "smart drugs," researchers at the University of Delaware and Drexel University raised concerns that the use of these drugs could affect the developing brain's ability to adapt to new situations and might increase the risk for addictive behaviors.

PEOPLE WITH LOWER IQs. Research suggests thatcognition-enhancing drugs offer the greatest performance boost among individuals with low-to-average

intelligence. These findings led University of Oxford researchers to propose in a 2014 paper that if such drugs were selectively given to people who need them most, many ethical concerns about the drugs' use would be alleviated, and they might even reduce opportunity inequality.

SENIORS. Some studies suggest that older adults may not derive much benefit from cognition-enhancing drugs. One study found that methylphenidate (Ritalin), which boosts working memory and attention in young adults, had no effect on performance among healthy elderly volunteers who were asked to perform various cognitive tasks.

http://www.eurekalert.org/pub_releases/2016-04/jhub-mom040716.php

Millions of maternal and child lives could be saved every year for less than $5 a person

Improving care at the time of birth gives a quadruple return on investment

By spending less than $5 per person on essential health care services such as contraception, medication for serious illnesses and nutritional supplements, millions of maternal and child lives could be saved every year, according to a new analysis led by the Johns Hopkins Bloomberg School of Public Health.

The findings, published April 9 in The Lancet, suggest it is possible to save many lives by broadly expanding basic services in the 74 low- and middle-income countries where more than 95 percent of the world's maternal and child deaths occur annually.

In 2015, nearly six million children under the age of five died as did more than 300,000 women from pregnancy-related causes across the globe. These numbers fall short of the Millennium Development Goals for reducing maternal and child mortality by 2015 that world leaders committed to back in September of 2000. The goals called for a two-thirds reduction in child mortality from 1990 levels and a three-quarters reduction in maternal mortality from 1990 levels.

"Many of these deaths could be prevented if high-impact and affordable solutions reached the populations that needed them most," says study leader Robert Black, PhD, a professor in the Department of International Health at the Bloomberg School. "Our analysis shows that expanding access to care to keep more mothers and children alive and healthy is feasible and a highly cost-effective investment."

Black will present the research April 9 at the Consortium of Universities for Global Health conference in San Francisco.

For the study, the researchers analyzed three essential packages of care presented in the Reproductive, Maternal, Newborn, Child Health volume of Disease Control Priorities, 3rd edition, published by the World Bank Group. The three packages (maternal and newborn health, child health and reproductive health) together comprise 66 proven health interventions that focus on a range of health problems.

The researchers found that four million lives could be saved every year by reaching 90 percent of the target populations with services included in the maternal and newborn health and child health packages. Interventions ranged from improving pregnancy and delivery care, to treating life-threatening infectious diseases like pneumonia, diarrhea, and malaria, and better childhood nutrition.

These services, they found, could prevent 1.5 million newborn deaths, 1.5 million child deaths, and 149,000 maternal deaths -- equivalent to half of all maternal, newborn and child deaths annually. They could also prevent 849,000 stillbirths, or more than a third of all annual stillbirths.

The authors looked separately at the reproductive health package. By meeting unmet demand for family planning, more than 1.5 million lives could be saved every year by preventing just under 28 million pregnancies. Increased access to contraception would reduce maternal deaths by 67,000, newborn deaths by 440,000, child deaths by 473,000 and stillbirths by 564,000, they found.

Health services from all three packages with the largest impact included management of acute malnutrition; pre-term birth care; provision of contraception; management of labor and delivery; and treatment of serious infections including pneumonia, diarrhea, malaria and neonatal sepsis.

Researchers also estimated the cost of expanding coverage for all three packages to reach 90 percent of the target populations. Estimates produced for this analysis show that all three packages could be immediately scaled up to nearly all people in need with an investment of $6.2 billion in low-income countries, $12.4 billion in lower middle-income countries, and $8 billion in upper middle-income countries. This is equivalent to an average investment per person in 2015 of just $6.70, $4.70, and $3.90, respectively -- or $4.70 overall.

"For less than $5 per person, essential health services could reach the people who are most in need of them," Black says. "Community health workers or primary health centers can deliver the majority of these services, which reduces the cost of expanding coverage.

"The benefits of scaling up these interventions extend well beyond health. For example, improving care at the time of birth gives a quadruple return on investment by saving mothers' and children's lives and preventing stillbirths and disability, while investing in nutrition can help children reach their potential in cognitive development." *"Reproductive, maternal, newborn, and child health: key messages from Disease Control Priorities, 3rd Edition" was written by Robert E Black, Carol Levin, Neff Walker, Doris Chou, Li Liu, Marleen Temmerman, for the DCP3 RMNCH Authors Group.*

The study was funded by the Bill & Melinda Gates Foundation.