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Why Alzheimer's Drugs Keep Failing

Drug candidates have a 99.6 percent failure rate, and poor early detection methods make clinical trials difficult and costly

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The world needs to tackle head-on the market failures undermining dementia research and drug development, UK Prime Minister David Cameron told a summit of world health and finance leaders in London in June. He announced an investigation into how to get medicines to patients earlier, extend patents and facilitate research collaborations, to report this autumn. But just how much difference will these sorts of measures make when scientists are still grappling with exactly what causes different types of dementia?

Added to these problems is that dementia has become a graveyard for a large number of promising drugs. A recent study looked at how 244 compounds in 413 clinical trials fared for Alzheimer's disease between 2002 and 2012. The researchers findings paint a gloomy picture. Of those 244 compounds, only one was approved. The researchers report that this gives Alzheimer's disease drug candidates one of the highest failures rates of any disease area – 99.6%, compared with 81% for cancer.

'Dementia is a ticking bomb costing the global economy £350 billion and yet progress with research is achingly slow,' warned the World Dementia Envoy, Dennis Gillings. Businesses need incentives to invest in research and bring in faster, cheaper clinical trials, or the world won't meet the ambition to find a cure or disease-modifying therapy by 2025, he added. 'We need to free up regulation so that we can test ground-breaking new drugs, and examine whether the period for market exclusivity could be extended.'

What's behind dementia

Dementia is an umbrella term used to describe a set of symptoms that can vary a great deal but include memory loss, confusion and mood changes. It can be caused by a number of different diseases, usually neurodegenerative diseases, such as Alzheimer's disease (about two-thirds of cases), frontotemporal dementia and dementia with Lewy bodies. With these diseases, the brain cells degenerate and die more quickly than is normal. Damage to brain cells is caused by a build up of abnormal proteins in the brain, which are different in each type of neurodegenerative dementia. However, vascular dementia is caused when the brain's blood supply is restricted or stopped, leading brain cells to die.

In Alzheimer's disease, the loss of brain cells leads to the brain shrinking, particularly the cerebral cortex. This is the layer of grey matter covering the brain that is responsible for processing thoughts and many of the higher functions, such as memory. Clumps of protein, known as plaques and tangles, progressively form in the brain; they are thought to result in the loss of brain cells. As connections between brain cells are lost there are fewer neurotransmitter chemicals, such as dopamine and acetylcholine, available to carry messages from one brain cell to another. Dopamine and acetylcholine are thought to play an important role in regulating brain functions, such as memory, learning, mood and attention.

Dementia with Lewy bodies is where small, circular lumps of protein develop inside brain cells. It is not known what causes them or how they damage the brain, leading to dementia. One theory is that these Lewy bodies interfere with the production of two neurotransmitters, dopamine and acetylcholine.

Frontotemporal dementia is caused by damage and shrinking in the temporal lobe and the frontal lobe. This type of dementia often occurs in those under 65, and an estimated 20% of patients have inherited a genetic mutation from their parents.

Other causes of dementia or dementia-like conditions may be treatable or non-progressive. These can include depression, infections and some brain tumours.

Treatment troubles

No treatment can currently halt the underlying disease processes in the brain. Presently, the UK has four licensed treatments that can help some people with their dementia symptoms, but the effects are temporary and don't work for everyone. In the UK, 820,000 people have dementia, and around 44.4 million people worldwide. The World Health Organization predicts that the number of people with dementia will almost double over the next 20 years.

Although companies have 198 compounds in various stages of development, dementia poses particular challenges because symptoms emerge a decade or more after the disease starts, says Bina Rawal of the Association of British Pharmaceutical Industry, making clinical trials expensive and lengthy. '[R&D] needs to be commercially viable for companies,' she says. 'In the UK, the government has a role to play in ensuring that companies are rewarded for their investment.'

Very few treatments are currently approved for Alzheimer's in the UK. Acetylcholinesterase inhibitors, such as donepezil and galantamine, are licensed to treat mild to moderate Alzheimer's disease. They can also be used to treat people with dementia with Lewy bodies, and can be particularly effective at treating hallucinations. They work by delaying the breakdown of the neurotransmitter acetylcholine by inhibiting the enzyme acetylcholinesterase.

Memantine hydrochloride is another Alzheimer's treatment and works by blocking the chemical messenger glutamate. Glutamate is released in excessive amounts when brain cells are damaged by Alzheimer's disease and this causes further damage. Memantine can protect brain cells by blocking the effects of excess

glutamate. It is licensed to treat severe Alzheimer's disease, but can also be used to treat moderate cases.

A slippery problem

The risks and barriers for companies working in dementia are huge, but so too, potentially, are the rewards, says Simon Ridley, head of research at Alzheimer's Research UK. He believes the first objective should be to recruit more researchers, but changes to the way drugs' intellectual property is controlled would help too. 'If the best chances of successful treatments are for early-stage disease patients, then these trials will be extremely long,' he explains. 'A patent would have expired before a trial had finished. That's why new models and approaches like adaptive licensing are needed. Currently, a trial has to show efficacy in cognition and daily living. These endpoints are not quick or easy to measure so perhaps a possibility is surrogate endpoints with conditional licences, almost like a Phase IV [post licensing] trial.'

Finding drugs to treat dementia is especially difficult because the brain is relatively inaccessible and harder to test and deliver compounds to, explains Simon Lovestone, a professor of translational neuroscience at the University of Oxford, UK. 'Less is known about the biology of the condition than, say, cancer.'

Until now, companies have mostly gone after the same target – amyloid-ß proteins that form aggregates or plaques in the brain of Alzheimer's disease patients. Evidence suggests that amyloid is deposited early during the course of the disease, even before clinical symptoms appear. So targeting amyloid in patients with mild to moderate Alzheimer's disease, as past failed clinical trials have done, may not be enough to stop the disease progressing.

Last July, Pfizer and Johnson & Johnson announced they would stop development of an Alzheimer's drug because it failed in two late-stage clinical trials. The monoclonal antibody bapineuzumab was designed to bind to, and trigger clearance of, amyloid proteins.

Dementia drugs are 'almost perfectly set up for expensive failures', comments Derek Lowe, medicinal chemist and blogger. 'Our level of ignorance is cripplingly high. This is coupled with the heterogeneous nature of the disease, the difficulty of diagnosing it in the first place – essential for selecting patients in a trial, and treating them later – and its very slow progression.' Researchers are 'still arguing, with great vigour, about the amyloid hypothesis. There's a lot of crucial information that we're missing.'

Taking a different tack

Companies are now diversifying their approaches and targeting the neuronal protein tau, for example, which, together with amyloid, defines Alzheimer's. Other disorders involve only tau such as frontotemporal dementia.

In Alzheimer's, tau is more highly phosphorylated than in a normal brain. Lovestone's group is working with the main enzyme responsible for this phosphorylation, glycogen synthase kinase-3 (GSK-3). They are one of many groups investigating lithium as a GSK-3 inhibitor and have been involved in Phase II trials with the company Noscira.

There is a growing focus on tau targets, but many of these are at an early stage, says Ridley. Some anti-tau therapies are reaching clinical trials, such as TauRx Therapeutics LMTX, which is entering Phase III trials for mild Alzheimer's and frontotemporal dementia. However, advances in biomarkers and tau imaging will undoubtedly be needed to ensure treatments are tested on the right patients at the right time, he adds.

Spotting dementia early

Research into biomarkers – tests to detect dementia early – has made great progress, says Lovestone. For biochemical markers, the best evidence is with spinal fluid assays for tau protein or amyloid. Some biomarkers are being used to help recruit and monitor people taking part in clinical trials. But, Lovestone adds, there are no fully confirmed biomarkers for Alzheimer's yet.

Researchers are also pursuing blood-based biomarkers. Lovestone's group has confirmed changes in the blood of large numbers of patients with dementia and will publish this work soon. It's likely that any blood test for dementia would involve a suite of biomarkers, Ridley says, and that future methods to detect Alzheimer's early will need to use a combination of tests.

While talk of a 'cure' is widely perceived to be a tall order, a disease-modifying treatment that prevents or slows down the disease is more likely, if challenging. Lovestone says: 'Some of the drugs that are already in Phase III trials might prove to work against the early-onset disease and slow its progression, and a large number of drugs that are failing clinical trials could be tried for earlier stage disease. In this case, it would be possible to have something in 10 years' time. But starting from scratch it is unlikely to have a new drug in less than 20 years.'

A flurry of funding announcements

The Medical Research Council (MRC) announced the world's biggest study group for dementia, with two million people participating. The public–private partnership involves six biopharma companies

Alzheimer's Research UK recently pledged £100 million for research. This includes a stem cell research centre, a network of drug discovery institutes and a £20 million global clinical development fund dedicated to supporting Phase I and II clinical trials; and a £2 million collaboration between University of Cambridge and University College London that will use donated cells from people with Alzheimer's to test potential new treatments

The Alzheimer's Society promised £100 million for dementia research over the next 10 years, including £15 million on studies to examine whether commonly available drugs could double as dementia treatments. Another £30 million will be spent training the next generation of dementia researchers

A new £3 million dementia consortium unites Alzheimer's Research UK, Eisai, Lilly and technology transfer organisation MRC Technology in the hunt for new drugs The Engineering and Physical Sciences Research Council has committed £5 million to improve tools for diagnosis and measuring disease progression

http://www.eurekalert.org/pub_releases/2014-07/cndi-msp071414.php

Manuel Serrano proposes a new vision of a process wrongly associated with ageing

Those who do research in ageing think senescence needs another name

For the Spanish Royal Academy, senescent is he who "begins to age". But laboratory biology results are contradicting the dictionary: not only is senescence not a synonym of ageing, it is also not intrinsically negative for the organism. Cellular senescence is such a badly named physiological process that those who do research in this area think it needs another name. That is the case of Manuel Serrano, from the Spanish National Cancer Research Centre (CNIO), one of the world's leading experts on senescence, who has just published a review on this topic.

Without actually renaming senescence, this edition of Nature Reviews promotes a paradigm shift: senescence is, above all, "a mechanism to eliminate unwanted cells", which ends with the remodelling of tissues. And it can be something of a double-edged sword for the body.

More than five decades ago, Leonard Hayflick and Paul Moorhead discovered that healthy human cells growing in culture stop proliferating after a certain number of divisions. They called the phenomenon cellular senescence and postulated that it could be the cause of ageing in the body. But more recent research, led largely by Serrano and his group - Daniel Muñoz-Espín is co-author of the current revision - has shown that this pioneering observation only told part of the story.

Today, we know that the relationship between senescence and ageing resembles that between firemen and fire: although there are many firemen at a fire, they are not the cause of the blaze but rather an attempt to put it out. In a similar way, Serrano and Muñoz-Espín propose that senescence activates when there is damage to a cell, to prevent it from spreading or even to repair the affected tissue. In ageing organisms, what happens is that the process stops halfway with a large number of senescent cells present in the tissues.

The authors talk of a sequence of events: "Senescence-clearance-regeneration". "Recent discoveries are redefining our vision of cellular senescence", they write. To achieve their goal: "senescent cells inhibit their own proliferation, induce their own elimination by attracting cells from the immune system and finally promote tissue regeneration". In aged tissues or with certain diseases, however: "this sequence is not completed, and the senescent cells accumulate".

That is why: "senescence can become part of the problem with ageing, instead of the solution", write the authors.

Today it is known that cells initiate their senescence programme in response to stimulants such as the activation of different oncogenes - cancer-causing genes; the absence or malfunction of anti-cancer genes; or the shortening of telomeres, the protein structures that protect the ends of chromosomes. All of these stimulants damage cells and senescence then works as a protective mechanism.

Furthermore, Serrano and Muñoz-Espín have recently discovered that senescence intervenes in another key process for the organism, in a stage very far removed from ageing: development. As the embryo grows, it needs to get rid of or redesign physiological structures, and the genetic orders it uses to that end are those related to senescence.

This discovery has allowed these researchers to complete their vision of senescence as a mechanism that is really there to: "eliminate unwanted cells" and end up regenerating tissue, even with a different than the one it had previously.

In this new vision, therefore, senescence is just a physiological mechanism. The question is: should we stimulate it, to fight cancer, for example, or should we prevent it, to stop ageing? Both, say the researchers.

The revision presents a list of pathologies in which senescence can have either a beneficial or harmful effect. In several types of cancer, for example, senescence stops the advance of the disease; in cardiovascular disease, it restricts atheroma formation; it is also beneficial against several types of fibrosis. With obesity and diabetes, however, it favours disease development, increasing resistance to insulin and inflammation.

Clinical research also reflects the two faces of senescence, given that both therapies based on promoting it - specifically against cancer and kidney and liver fibrosis - and on stopping it are being studied. The authors underline the success in breast cancer trials of a new drug that stimulates senescence: palbociclib.

But they leave one mystery unsolved: moles. Nowadays we know that moles are collections of senescent cells that have not been eliminated. Why? To be continued.

Cellular senescence: from physiology to pathology. Muñoz-Espín D, Serrano M. Nature Reviews Molecular Cell Biology (2014). doi: 10.1038/nrm3823

http://www.eurekalert.org/pub_releases/2014-07/aha-hbp070914.php

Home blood pressure-monitoring kits save insurance companies money

American Heart Association Rapid Access Journal Report

Home blood pressure-monitoring kits can save insurance companies money by improving healthcare quality and reducing healthcare costs, according to new research in the American Heart Association's journal Hypertension.

In the United States, more than 76 million adults have diagnosed high blood pressure, and many more are undiagnosed. Since high blood pressure typically has no symptoms, periodic testing is critical especially for people with the factors that put them at risk for the condition.

Home monitoring kits effectively test blood pressure at regular intervals over several days or weeks in a familiar environment. In the first analysis of its kind, researchers found that for each dollar invested in home monitoring kits, insurance companies could expect a return of $0.85 to $3.75 in the first year. Over 10 years, the return per dollar invested could increase to $7.50 to $19.34.

"Home blood pressure monitors should be reimbursed, widely adopted across America and integrated into current clinical practice for diagnosis and treatment of hypertension," said Alejandro Arrieta, Ph.D., the study's lead author and assistant professor in the Department of Health Policy and Management at Florida International University in Miami. "Our study provides evidence that reimbursement makes business sense for an insurance company."

Researchers analyzed 2008-11 data from two health insurance plans operated by a Midwestern health maintenance organization. One was a private employee plan with 25,478 members, and the other was a Medicare Advantage plan with 8,253 members. In both plans, most of the members were female.

High blood pressure affected 6 percent of the employee plan's members ages 20-44 and 34 percent of those 45-64. In the Medicare plan, in which members were 65 and older, 60 percent had high blood pressure.

Depending on the insurance plan and age-group, net savings associated with home blood pressure monitoring ranged from $33 to $166 per member in the first year, and $415 to $1,364 over 10 years.

Researchers found reasons for the savings differed by age groups and whether the monitors were used for treatment or diagnosis. In people 65 and older, home monitoring saved more when used to track high blood pressure treatment, by helping them avoid future adverse cardiovascular events. In people younger than 65, savings were higher in diagnostic use of the monitors with fewer false positive diagnoses and fewer people starting unnecessary treatment.

"By improving the accuracy of their blood pressure assessment and by monitoring their blood pressures outside the clinic setting, patients help themselves, help their physicians and save money for insurance companies," Arrieta said.

The American Heart Association recommends that people with high blood pressure monitor their levels at home, in addition to receiving regular monitoring by their health care provider. The association also recommends that patients be reimbursed for buying a home monitoring kit, and that healthcare providers receive reimbursement for associated costs.

Co-authors are John Woods, Ph.D.; Nan Qiao; and Stephen Jay, M.D. Author disclosures are on the manuscript.

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Domestication syndrome: White patches, baby faces and tameness

Neural crest hypothesis could explain why domestic mammals share characteristic traits

More than 140 years ago, Charles Darwin noticed something peculiar about domesticated mammals. Compared to their wild ancestors, domestic species are more tame, and they also tend to display a suite of other characteristic features, including floppier ears, patches of white fur, and more juvenile faces with smaller jaws. Since Darwin's observations, the explanation for this pattern has proved elusive, but now, in a Perspectives article published in the journal GENETICS, a new hypothesis has been proposed that could explain why breeding for tameness causes changes in such diverse traits.

The underlying link between these features could be the group of embryonic stem cells called the neural crest, suggest the authors. Although this proposal has not yet been tested, it is the first unified hypothesis that connects several components of the "domestication syndrome." It not only applies to mammals like dogs, foxes, pigs, horses, sheep and rabbits, but it may even explain similar changes in domesticated birds and fish.

"Because Darwin made his observations just as the science of genetics was beginning, the domestication syndrome is one of the oldest problems in the field. So it was tremendously exciting when we realized that the neural crest hypothesis neatly ties together this hodge-podge of traits," says Adam Wilkins, from the Humboldt University of Berlin. Wilkins is an editor at GENETICS and one of the paper's authors.

Neural crest cells are formed near the developing spinal cord of early vertebrate embryos. As the embryo matures, the cells migrate to different parts of the body

and give rise to many tissue types. These tissues include pigment cells and parts of the skull, jaws, teeth, and ears - as well as the adrenal glands, which are the center of the "fight-or-flight" response. Neural crest cells also indirectly affect brain development.

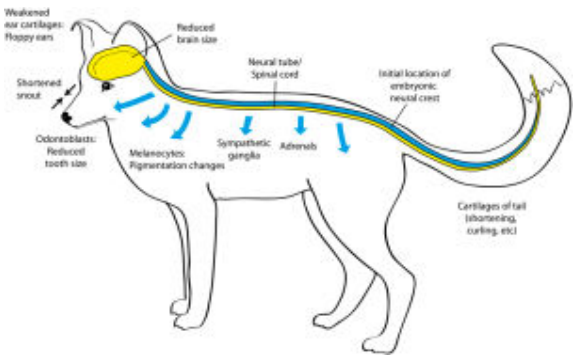
In the hypothesis proposed by Wilkins and co-authors Richard Wrangham of Harvard University and Tecumseh Fitch of the University of Vienna, domesticated mammals may show impaired development or migration of neural crest cells compared to their wild ancestors.

"When humans bred these animals for tameness, they may have inadvertently selected those with mild neural crest deficits, resulting in smaller or slow-maturing adrenal glands," Wilkins says. "So, these animals were less fearful."

But the neural crest influences more than adrenal glands. Among other effects, neural crest deficits can cause depigmentation in some areas of skin (e.g. white patches), malformed ear cartilage, tooth anomalies, and jaw development changes, all of which are seen in the domestication syndrome.

The authors also suggest that the reduced forebrain size of most domestic mammals could be an indirect effect of neural crest changes, because a chemical signal sent by these cells is critical for proper brain development.

"This interesting idea based in developmental biology brings us closer to solving a riddle that's been with us a long time. It provides a unifying hypothesis to test and brings valuable insight into the biology of domestication," says Mark Johnston, Editor-in-Chief of GENETICS.



Developmental schematic of the "domestication syndrome" in relation to the neural crest. The blue tube indicates the approximate position of the neural crest in the early embryo, and the blue arrows indicate pathways of neural crest cell migration.

Tests of the neural crest hypothesis may not be far off, as other scientists are rapidly mapping the genes that have been altered by domestication in the rat, fox, and dog. The hypothesis predicts that some of these genes will influence neural crest cell biology.

If so, we will have a much deeper understanding of the biology underlying a significant evolutionary event, Wilkins says. "Animal domestication was a crucial step in the development of human civilizations. Without these animals, it's hard to imagine that human societies would have thrived in the way they have."

Citation: The "Domestication Syndrome" in Mammals: A Unified Explanation Based on Neural Crest Cell Behavior and Genetics
Adam S. Wilkins, Richard W. Wrangham, and W. Tecumseh Fitch. GENETICS July 2014, 197:795-808, doi: 10.1534/genetics.114.165423
http://www.genetics.org/content/197/3/795.full

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Bothered by hot flashes? Acupuncture might be the answer

New meta-analysis shows benefits of ancient Chinese method on today's menopausal hot flashes

CLEVELAND, Ohio - In the 2,500+ years that have passed since acupuncture was first used by the ancient Chinese, it has been used to treat a number of physical, mental and emotional conditions including nausea and vomiting, stroke rehabilitation, headaches, menstrual cramps, asthma, carpal tunnel, fibromyalgia and osteoarthritis, to name just a few. Now, a meta-analysis of randomized controlled trials which is being published this month in Menopause, the journal of The North American Menopause Society (NAMS), indicates that acupuncture can affect the severity and frequency of hot flashes for women in natural menopause.

An extensive search of previous studies evaluating the effectiveness of acupuncture uncovered 104 relevant students, of which 12 studies with 869 participants met the specified inclusion criteria to be included in this current study. While the studies provided inconsistent findings on the effects of acupuncture on other menopause-related symptoms such as sleep problems, mood disturbances and sexual problems, they did conclude that acupuncture positively impacted both the frequency and severity of hot flashes.

Women experiencing natural menopause and aged between 40 and 60 years were included in the analysis, which evaluated the effects of various forms of acupuncture, including traditional Chinese medicine acupuncture (TCMA), acupressure, electroacupuncture, laser acupuncture and ear acupuncture.

Interestingly, neither the effect on hot flash frequency or severity appeared to be linked to the number of treatment doses, number of sessions or duration of treatment. However, the findings showed that sham acupuncture could induce a treatment effect comparable with that of true acupuncture for the reduction of hot flash frequency. The effects on hot flashes were shown to be maintained for as long as three months.

Although the study stopped short of explaining the exact mechanism underlying the effects of acupuncture on hot flashes, a theory was proposed to suggest that acupuncture caused a reduction in the concentration of β-endorphin in the hypothalamus, resulting from low concentrations of estrogen. These lower levels could trigger the release of CGRP, which affects thermoregulation.

"More than anything, this review indicates that there is still much to be learned relative to the causes and treatments of menopausal hot flashes," says NAMS executive director Margery Gass, MD. "The review suggests that acupuncture may be an effective alternative for reducing hot flashes, especially for those women seeking non- pharmacologic therapies."

A recent review indicated that approximately half of women experiencing menopause-associated symptoms use complementary and alternative medicine therapy, instead of pharmacologic therapies, for managing their menopausal symptoms.

The article, "Effects of acupuncture on menopause-related symptoms and quality of life in women on natural menopause: a meta-analysis of randomized controlled trials", will be published in the February 2015 print edition of Menopause. The meta-analysis was supported by grants from the Ministry of Science and Technology of Taiwan.

http://www.eurekalert.org/pub_releases/2014-07/uoea-urr071314.php

UEA research reveals how cannabis compound could slow tumour growth

Scientists at the University of East Anglia have shown how the main psychoactive ingredient in cannabis could reduce tumor growth in cancer patients.

Research published today reveals the existence of previously unknown signaling platforms which are responsible for the drug's success in shrinking tumours.

It is hoped that the findings could help develop a synthetic equivalent with anti-cancer properties. The research was co-led with the Universidad Complutense de Madridin, Spain. The team used samples of human breast cancer cells to induce tumours in mice. They then targeted the tumours with doses of the cannabis compound THC (Tetrahydrocannabinol). They found that two cell receptors in particular were responsible for the drug's anti-tumour effects.

Dr Peter McCormick, from UEA's school of Pharmacy, said: "THC, the major active component of marijuana, has anti-cancer properties. This compound is known to act through a specific family of cell receptors called cannabinoid receptors. However, it was unclear which of these receptors were responsible for the anti-tumour effects of THC. "We show that these effects are mediated via the joint interaction of CB2 and GPR55 - two members of the cannabinoid receptor family. Our findings help explain some of the well-known but still poorly understood effects of THC at low and high doses on tumour growth.

"There has been a great deal of interest in understanding the molecular mechanisms behind how marijuana, and specifically THC, influence cancer pathology. "There has also been a drive in the pharmaceutical industry to create synthetic equivalents that might have anti-cancer properties. "By identifying the receptors involved we have provided an important step towards the future development of therapeutics that can take advantage of the interactions we have discovered to reduce tumour growth." Dr McCormick added that cancer sufferers should not be tempted to self-medicate. "Our research uses an isolated chemical compound and using the correct concentration is vital. Cancer patients should not use cannabis to self-medicate, but I hope that our research will lead to a safe synthetic equivalent being available in the future."

'Targeting CB2 –GPR55 receptor heteromers modulates cancer cell signalling' is published in the Journal of Biological Chemistry.

http://www.eurekalert.org/pub_releases/2014-07/ucl-pl071414.php

Pre-diabetes label 'unhelpful and unnecessary'

Labelling people with moderately high blood sugar as pre-diabetic is a drastically premature measure with no medical value and huge financial and social costs

Labelling people with moderately high blood sugar as pre-diabetic is a drastically premature measure with no medical value and huge financial and social costs, say researchers from UCL and the Mayo Clinic, Minnesota.

The analysis, published in the BMJ, considered whether a diagnosis of pre-diabetes carried any health benefits such as improved diabetes prevention. The authors showed that treatments to reduce blood sugar only delayed the onset of type 2 diabetes by a few years, and found no evidence of long-term health benefits.

Type 2 diabetes is typically diagnosed with a blood test that measures levels of haemoglobin A1c, which indicates average blood sugar level over the last three months. People with an A1c over 6.5% can be diagnosed with diabetes but the latest guidelines from the American Diabetes Association (ADA) define anyone with an A1c between 5.7% and 6.4% as having pre-diabetes.

If the ADA guidelines were adopted worldwide, a third of the UK adult population and more than half of adults in China would be diagnosed with pre-diabetes. The latest study questions the logic of putting a label on such huge sections of the population, as it could create significant burdens on healthcare systems without conferring any health benefits. Previous research has shown that type 2 diabetes treatments can do more harm than good for people with A1c levels around 6.5%, let alone people below this level.

3.2 million people in the UK are currently diagnosed with type 2 diabetes, but approximately 16 million would fall into the ADA's pre-diabetes category. There is a condition known as impaired glucose tolerance (IGT) that affects around 3.7 million adults in the UK (8%). People with IGT are at high risk of diabetes, but the test is more time-consuming than a simple A1c blood test. There is evidence to suggest that interventions can delay the progression of IGT into diabetes, but the ADA category of pre-diabetes also includes another 12 million people who are at a

much lower risk of progressing to diabetes, for whom any benefit from treatment is unknown.

The World Health Organisation (WHO) has stated that "use of 'pre-diabetes' is discouraged to avoid any stigma associated with the word diabetes and the fact that many people do not progress to diabetes as the term implies." Guidance from the UK National Institute for Health and Care Excellence (NICE) broadly aligns with the WHO statement, looking to "move away from describing 'pre-diabetes' as a separate condition". So in the way of official authoritative organisations, ADA is pretty much on its own in using this term. Yet it has caught on heavily in the global scientific literature and because of ethnic differences in A1c levels, it may be an even less valid category in other countries and demographics.

"Pre-diabetes is an artificial category with virtually zero clinical relevance," says lead author John S Yudkin, Emeritus Professor of Medicine at UCL. "There is no proven benefit of giving diabetes treatment drugs to people in this category before they develop diabetes, particularly since many of them would not go on to develop diabetes anyway.

"Sensibly, the WHO and NICE and the International Diabetes Federation do not recognise pre-diabetes at present but I am concerned about the rising influence of the term. It has been used in many scientific papers across the world, and has been applied to a third of adults in the UK and half of those in China. We need to stop looking at this as a clinical problem with pharmaceutical solutions and focus on improving public health. The whole population would benefit from a more healthy diet and more physical activity, so it makes no sense to single out so many people and tell them that they have a disease."

Previous studies have tested the effectiveness of giving people with IGT a drug called metformin, which is used to lower blood sugar in people with diabetes. The drug reduced the risk of developing diabetes by 31% over 2.8 years, probably by delaying its onset rather than by completely halting its development. But people who go on to develop diabetes are often treated with metformin anyway and there is no evidence of long-term benefits to starting the treatment early.

"The ADA recommends treating pre-diabetes with metformin, but the majority of people would receive absolutely no benefit," explains Professor Yudkin. "There are significant financial, social and emotional costs involved with labelling and treating people in this way. And a range of newer and more expensive drugs are being explored as treatments for 'pre-diabetes.' The main beneficiaries of such recommendations would be the drug manufacturers, whose available market suddenly leaps to include significant swathes of the population. This is particularly true in emerging economies such as China and India, where regulating the healthcare market is a significant challenge."

"Healthy diet and physical activity remain the best ways to prevent and to tackle diabetes," says co-author Victor Montori, Professor of Medicine at the Mayo Clinic, Rochester, Minnesota, USA. "Unlike drugs they are associated with incredibly positive effects in other aspects of life. We need to keep making efforts to increase the overall health of the population, by measures involving public policy rather than by labelling large sub-sections of the population as having an illness. This is a not a problem to be solved at the bedside or in the doctor's surgery, but rather by communities committed to the health of their citizens."

http://www.eurekalert.org/pub_releases/2014-07/bmj-rro071014.php

Reduced range of facial expression indicates serious heart/lung disease

Inability to register surprise strongest indicator; can help prioritise care, say doctors

Patients with serious heart and lung conditions don't have the normal range of facial expressions, particularly the ability to register surprise in response to emotional cues, finds preliminary research published online in Emergency Medicine Journal. This finding could be used to help busy emergency care doctors decide whom to prioritise for treatment, and gauge who really needs often costly and invasive tests, suggest the researchers.

And it adds scientific credibility to the rapid visual assessment doctors make of how sick someone is, formally known as gestalt pretest probability, they say.

The researchers tested the diagnostic accuracy of reduced facial expression range in 50 adults with shortness of breath (dyspnoea) and chest pain in an emergency care department. The patients briefly viewed three visual cues, designed to evoke an emotional response, on a laptop. The computer webcam recorded their facial expressions in response to each of these cues, which included a humorous cartoon, a close-up of a surprised face, and a picture of someone in tears.

These recordings were analysed, using the Facial Action Coding System (FACS), which scores changes in facial muscle activity, reflecting the extent of smiling, frowning, and surprise. The patients were scanned to check for serious heart or lung disease, including acute coronary syndrome (heart attack, unstable angina); a blood clot in the lung (pulmonary embolism); pneumonia; problems in the major (aortic) artery or gut; and new cancers, and monitored for 14 days.

During the monitoring period, eight (16%) patients developed serious heart or lung disease. Among the 42 considered not to have any serious health problem, two developed worsening chronic obstructive pulmonary disease, two developed heart failure; and one an irregular heart rhythm (atrial fibrillation).

The analysis of the webcam recordings showed that patients with chest pain and shortness of breath who had a potentially serious heart or lung condition had a significantly narrower range of facial expression in response to visual cues than those who did not have these health problems. The difference in the ability to express surprise most strongly demarcated those with serious heart and lung problems from those without.

"We believe that due to the gravity of their illness, [these] patients may not have been able to process and respond to an emotional stimulus in the way that would be expected of most people under normal conditions," write the researchers.

They go on to say: "The ultimate goal of this work is to provide clinicians with a new physical finding that can be associated with a healthy state to avoid unnecessary [computed tomography] scanning," which could be added to the physical examination.

In an accompanying podcast, lead author Jeffrey Kline, says that there are several structured scoring systems to determine a patient's likelihood of developing a clot on the lungs, for example, but they are not always easy to remember or readily applicable to all patients. And looking at patients is a key part of a doctor's bedside manner, he says, adding that as consultations by Skype become more common, the ability to read a patient's face may become even more important.

[Decreased facial expression variability in patients with serious cardiopulmonary disease in the emergency care setting Online First doi 10.1136/emermed-2014-203602]

http://www.eurekalert.org/pub_releases/2014-07/afot-ppe071414.php

Proof: Parkinson's enhances creativity

New Tel Aviv University study confirms creative energy in Parkinson's sufferers is greater than in healthy individuals

Prof. Rivka Inzelberg of Tel Aviv University's Sackler Faculty of Medicine and the Sagol Neuroscience Center at Sheba Medical Center, Tel Hashomer, documented the exceptional creativity of Parkinson's patients two years ago in a review for Behavioral Neuroscience. Since then, she has conducted the first empirical study to verify a link between Parkinson's disease and artistic inclination.

That empirical study, now published in the Annals of Neurology, definitively demonstrates that Parkinson's patients are more creative than their healthy peers, and that those patients taking higher doses of medication are more artistic than their less-medicated counterparts.

"It began with my observation that Parkinson's patients have a special interest in art and have creative hobbies incompatible with their physical limitations," said Prof. Inzelberg. "In my last paper, I reviewed case studies from around the world and found them to be consistent. In my present research, we conducted the first comprehensive study to measure the creative thinking of Parkinson's patients. This was not a simple task, because how does one measure, or quantify, creativity? We had to think creatively ourselves."

Measuring artistic creativity

Prof. Inzelberg and a team of researchers from TAU, the Sheba Medical Center, and Bar-Ilan University conducted a full battery of tests on 27 Parkinson's patients treated with anti-Parkinson's drugs and 27 age- and education-matched healthy controls. Some of the tests were well-known and others newly adapted for the purpose of the study. The tests included the Verbal Fluency exam, in which a person is asked to mention as many different words beginning with a certain letter and in a certain category (fruit, for example) as possible.

The participants were then asked to undergo a more challenging Remote Association Test, in which they had to name a fourth word (following three given words) within a fixed context. The groups also took the Tel Aviv University Creativity Test, which tested their interpretation of abstract images and assessed the imagination inherent in answers to questions like "What can you do with sandals?" The final exam was a version of the Test for a Novel Metaphor, adapted specifically for the study.

Throughout the testing, Parkinson's patients offered more original answers and more thoughtful interpretations than their healthy counterparts.

In order to rule out the possibility that the creative process evident in the hobbies of patients was linked to obsessive compulsions like gambling and hoarding, to which many Parkinson's patients fall prey, participants were also asked to fill out an extensive questionnaire. An analysis indicated no correlation between compulsive behavior and elevated creativity.

Express yourself

The conclusions from the second round of testing - in which the Parkinson's participants were split into higher- and lower-medicated groups - also demonstrated a clear link between medication and creativity. Parkinson's patients suffer from a lack of dopamine, which is associated with tremors and poor coordination. As such, they are usually treated with either synthetic precursors of dopamine or dopamine receptor agonists

According to Prof. Inzelberg, the results are hardly surprising, because dopamine and artistry have long been connected. "We know that Van Gogh had psychotic spells, in which high levels of dopamine are secreted in the brain, and he was able to paint masterpieces during these spells – so we know there is a strong relationship between creativity and dopamine," said Prof. Inzelberg.

Prof. Inzelberg hopes her research will be instrumental in spreading awareness. Parkinson's patients often feel isolated by their physical limitations, so artistic work could provide a welcome outlet of expression. "After my first paper, I helped

organize exhibits of patients' paintings in Herzliya and Raanana and received feedback about similar exhibits in Canada and France," said Prof. Inzelberg. "These exhibits were useful in raising funds for Parkinson's research, providing occupational therapy for patients – and, most importantly, offering an opportunity for patients to fully express themselves." Prof. Inzelberg is currently researching additional forms of creativity in Parkinson's patients.

http://www.eurekalert.org/pub_releases/2014-07/tju-sif071014.php

Saltier intravenous fluids reduce complications from surgery

Infusing a saltier saline solution during and after surgery decreases overall complication rate for a complex procedure

PHILADELPHIA - Adequate hydration via a saline drip is essential during surgery, but recent reports suggest that getting the balance of salt and water just right could have an important impact on patient recovery. In the largest study of its kind researchers at Thomas Jefferson University found that a slightly saltier intravenous drip (hypertonic saline), and lower total volume of fluid received, reduced the overall rate of complications by 25 percent after the complex Whipple surgery for pancreatic cancer.

"This relatively minor change in intravenous fluids has had a tremendous effect on the overall complication rate for our patients," says first author Harish Lavu, M.D., Associate Professor of Surgery at Thomas Jefferson University. "Based on these findings we have already changed our practice in the operating room to use hypertonic saline," he added.

Saline delivered intravenously during and after surgery helps to maintain a patient's fluid balance and blood pressure within the appropriate range. The increased salt concentration in the hypertonic saline is designed to keep the body in equilibrium by helping to reduce fluid buildup in the lungs, interstitial spaces and swelling in the extremities.

The hypertonic saline draws out the excess fluid that builds up in these tissues. "Too much swelling can compromise the delivery of blood and oxygen to the organs. That reduction can slow the healing process," says Dr. Lavu.

The current study is the largest of its kind and shows a benefit when hypertonic saline is used for the Whipple operation, which can take from to 5-9 hours to perform. Patients undergoing this operation for pancreatic cancer can have complications such as blood clots, pneumonia, wound infection, urinary tract infections, and others.

A total of 264 patients were enrolled in the study, with 128 receiving standard fluid and 131 receiving a hypertonic saline solution. By examining all of the complications together, the researchers found a 25 percent reduction in overall complications in the group that received hypertonic saline. In absolute numbers, 93 patients in the hypertonic group had complications, compared with 123 patients in the standard fluid group.

"We are confident that this change in our surgical process will help our patients recover faster with fewer complications," says senior author Charles J. Yeo, M.D., The Samuel D. Gross Professor and Chair of the Department of Surgery at Thomas Jefferson University.

Article reference: H. Lavu et al., "The HYSLAR trial: A prospective randomized controlled trial of the use of a restrictive fluid regimen with 3% hypertonic saline (HYS) versus lactated ringers (LAR) in patients undergoing pancreaticoduodenectomy," Annals of Surgery, 2014.

http://www.medscape.com/viewarticle/828251

Moxibustion May Alleviate Arthritis Knee Pain

Moxibustion may safely relieve pain and improve function among patients with osteoarthritis of the knee

Jennifer Garcia

The practice of moxibustion, a therapy used in traditional Chinese medicine, may safely relieve pain and improve function for up to 18 weeks among patients with osteoarthritis of the knee, according to a new study published online June 24 in *Arthritis Research and Therapy*.

The randomized, double-blinded, placebo-controlled study enrolled 110 patients who had knee osteoarthritis diagnosed according to American College of Rheumatology criteria and who had a pain score of at least 3 out of 10 during the majority of the previous month, based on a 10-point visual analog scale.

Patients with previous experience with moxibustion or those who had used intra-articular or topical arthritis therapy in the preceding 6 months were excluded.

Patients were randomly assigned to receive either active moxibustion therapy (n = 55) or a sham moxibustion treatment (n = 55) 3 times a week for 6 weeks. Therapy was performed at acupoint Dubi (ST 35), estra-point Neixiyan (EX-LE 4), and an Ashi (tender) point.

Practitioners were acupuncturists with at least 5 years of acupuncture and moxibustion training. Response to therapy was assessed using the Western Ontario and McMaster University Osteoarthritis Scale (WOMAC VA 3.1). Patients were evaluated at the end of therapy and at 3, 12, and 24 weeks after therapy.

The researchers, led by Ling Zhao, MD, from Shanghai University of Traditional Chinese Medicine, China, noted greater improvements in WOMAC pain score among patients in the active treatment group at weeks 3 ($P = .012$), 6 ($P < .001$), 12 ($P = .002$), and 24 ($P = .002$) when compared with the scores for the control group. Physical function scores were also improved among the active treatment group at weeks 3 ($P = .002$), 6 ($P = .015$), and 12 ($P < .001$). The effect of therapy on

physical function, however, appeared to have waned by week 24 compared with in the placebo group (P = .058). No adverse effects were reported in either group.

The authors note that the mechanism of action of moxibustion therapy is still not well understood but is thought to be similar to that of acupuncture therapy.

"The findings of the present trial show that moxibustion, like acupuncture, can be a useful adjunctive treatment for patients with [knee osteoarthritis]," the authors write.

In an interview with *Medscape Medical News*, independent commentator Jamie Starkey, LAc, lead acupuncturist at the Tanya I. Edwards Center for Integrative Medicine Wellness Institute at the Cleveland Clinic in Ohio, said: "This study showed clinical significance of the reduction in pain scores, as well as statistical significance with a moderate effect size."

Given the potential subjective nature of endpoint assessments, however, Starkey pointed out that "it would be beneficial to know if there were any objective measurements of change pre- and posttreatment, such as changes in inflammation. Also, moxibustion was used as an adjunct treatment, and it was unclear what conventional medications, if any, were being used by the subjects."

"It will take data from many more well-designed, randomized, controlled studies" before moxibustion becomes part of the routine management of patients with knee osteoarthritis, Starkey noted. "With that being said, however," she concluded, "I do feel this study is another step in the forward direction, providing supportive data of this noninvasive therapy's effectiveness in providing subjective pain relief and improved physical function."

Funding for this study was provided by the National Basic Research Program of China, the Key Program of the State Administration of TCM of China, the Shanghai Municipal Science Foundation, and the 2014 Innovation Program of the Shanghai Municipal First-Class Field of Traditional Chinese Medicine of Shanghai. The authors and independent commentator have disclosed no relevant financial relationships.

Arthritis Res Ther. Published online June 24 2014. Full text

http://www.eurekalert.org/pub_releases/2014-07/l-fos071514.php

Fish oil supplements reduce incidence of cognitive decline, may improve memory function

Alzheimer's disease affects more than 5 million each year in the US

PROVIDENCE, R.I. –Rhode Island Hospital researchers have completed a study that found regular use of fish oil supplements (FOS) was associated with a significant reduction in cognitive decline and brain atrophy in older adults.

The study examined the relationship between FOS use during the Alzheimer's Disease Neuroimaging Initiative (ADNI) and indicators of cognitive decline. The findings are published online in advance of print in the journal Alzheimer's & Dementia.

"At least one person is diagnosed every minute with Alzheimer's disease (AD) and despite best efforts, we have not yet found a cure for this pervasive and debilitating disease," said principal investigator Lori Daiello, PharmD, of the Alzheimer's Disease and Memory Disorders Center at Rhode Island Hospital."The field is currently engaged in numerous studies to find better treatments for people suffering with AD; however, researching ways to prevent AD or slow cognitive decline in normal aging is of utmost importance."

In this retrospective study, older adults involved in the ADNI study were assessed with neuropsychological tests and brain magnetic resonance imaging (MRI) every six months. The group included 229 older adults who were cognitively normal; 397 who were diagnosed with mild cognitive impairment; and 193 with AD.

The study found that fish oil supplement use during the study was associated with significantly lower rates of cognitive decline as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog), and the Mini Mental State Exam (MMSE), but this benefit was observed only for the group of participants without dementia at the time of enrollment.

"Additionally, serial brain imaging conducted during this study showed that the participants with normal cognition who reported taking fish oil supplements demonstrated less brain shrinkage in key neurological areas, compared to those who did not use the supplements," Daiello said.

"Also, the positive findings on cognitive testing and brain MRI were only observed in persons who did not carry the best-studied genetic risk factor for AD, APOE-4. More research is needed, but these findings are promising and highlight the need for future studies to expand the current knowledge of the effects of FOS use on cognitive aging and AD." It is estimated that more than 5 million people in the U.S. have Alzheimer's disease. It is the most common form of dementia and is the sixth leading cause of death in the U.S.

This research was funded by from the Agency for HealthCare Research and Quality (AHRQ) (K08 HS017735); National Institute on Alcohol Abuse and Alcoholism (NIAAA) (R00AA020235, P01AA019072, and R01NS080655); National Cancer Institute (R03 CA153942, R01 CA155381); National Institute of Nursing Research (R01 NR011295); National Heart, Lung and Blood Institute (R01HL109116, R01 CA159954, 5T32HL076134, R01 HL064342); National Center for Complementary and Alternative Medicine (R01AT006948); National Institute on Drug Abuse (R01 DA021729, R34 DA031057); National Institute of Diabetes and Digestive Kidney Disorders (R18 DK075371); National Institutes of Health (R01 HL089311, U01 CA1503878; R34 DA031057-02, P01 AA019072, R01 NS036524, R01 HL084178, R01 DA020725, R56 DK075119, and R01 MH074368); and support from Pfizer; Janssen; Baxter, Eli Lilly and Avid pharmaceutical companies. Daiello's principal affiliation is Rhode Island

Hospital, and she also holds academic appointments in the department of neurology (research) at The Warren Alpert Medical School of Brown University and Health Services, Policy & Practice in the Brown University School of Public Health. Other current and former Lifespan researchers involved in the study are Brian Ott, M.D (Rhode Island Hospital; Shira Dunsiger, Ph.D, of The Miriam Hospital, Assawin Gongvatana, Ph.D (University of California San Diego), and Ronald A. Cohen, Ph.D., (University of Florida).

http://www.bbc.com/news/health-28293678

Cancer sufferer fears future without 'life-saver' drug

When a pharmaceutical company stops making a drug, what happens to the patients who think it saved their life?

By Nicola Dowling File on 4

Peter Franklin, from Plymouth, in south-west England, has been told a cancer drug - which he says has kept him alive and healthy for the past five years - is to run out. He was given the drug as part of a trial. But Pfizer, the company which makes the drug, says it has not proved successful enough to continue developing, so no more is being made. Mr Franklin is now desperately hunting an alternative.

Doctors at the Royal Marsden Hospital in London told the 30-year-old that supplies of the drug figitumumab will run out in October. It was being trialled in lung, breast, prostate and colorectal cancers but was also offered to patients such as Mr Franklin, who suffers from Ewing's sarcoma, a rare and very aggressive bone cancer that affects young people and teenagers.

'Very frustrating'

He said: "It is not good news. It is very frustrating from a personal point of view and very sad that a drug that can effectively control my disease in a number of people, be it a very small number of people, can be withdrawn when there are very few conventional drugs which will cause a good response.

"I was expecting it to happen as it's been mooted a couple of times in the past that the drug has not been successful in the majority of patients and would therefore be discontinued - but it adds a huge amount of uncertainty to our future plans."

Last year Mr Franklin married his long-term girlfriend and the couple were looking to the future. But their plans are now on hold as Mr Franklin tries to find out what his options are once the drug runs out.

The chartered accountant was diagnosed with cancer when he was 23 and was treated with chemotherapy. But the cancer returned. So in the summer of 2009 he started having monthly infusions of the Pfizer drug as part of a clinical trial. After just a few months the cancer and a tumour in his back disappeared and he has been able to live a normal life ever since.

Mr Franklin hopes the cancer has gone for good but believes the drug has been holding it at bay and is concerned it will return if he stops taking it.

'Compassionate-use process'

Doctors at the Royal Marsden Hospital have suggested that if the cancer does come back he could try to find another trial of a drug that works in a similar way, but there are no guarantees any will be open, or that he will qualify to take part.

A spokeswoman for Pfizer said: "Pfizer discontinued development of figitumumab in January 2011, based on the negative outcome of a number of randomised clinical trials. "However, for a small number of patients globally, who in the medical judgement of their individual physicians benefited and tolerated it well, Pfizer continued supply through a compassionate-use process."

She said the company could not comment on Mr Franklin's individual case, but said the company had "clearly communicated" with doctors in 2012 and again recently that it no longer produced the drug and could only supply it until the shelf life of the research supplies expired. Pfizer advised doctors to look at other research into similar drugs. A spokeswoman for the Royal Marsden Hospital said it could not comment on individual cases.

http://www.eurekalert.org/pub_releases/2014-07/uomh-pci071514.php

Prostate cancer in young men - More frequent and more aggressive?

Early onset prostate cancer a newly identified, more aggressive subtype often linked to genetic mutations

ANN ARBOR, Mich. -- The number of younger men diagnosed with prostate cancer has increased nearly 6-fold in the last 20 years, and the disease is more likely to be aggressive in these younger men, according to a new analysis from researchers at the University of Michigan Comprehensive Cancer Center.

Typically, prostate cancer occurs more frequently as men age into their 70s or 80s. Many prostate cancers are slow-growing and many older men diagnosed with early stage prostate cancer will end up dying from causes other than prostate cancer.

But, the researchers found, when prostate cancer strikes at a younger age, it's likely because the tumor is growing quickly.

"Early onset prostate cancer tends to be aggressive, striking down men in the prime of their life. These fast-growing tumors in young men might be entirely missed by screening because the timeframe is short before they start to show clinical symptoms," says Kathleen A. Cooney, M.D., professor of internal medicine and urology at the University of Michigan.

Peter Rich was 59 when he was diagnosed with stage 4 prostate cancer. His PSA was only 9, but the disease had already spread to his ribs, spine and lymph nodes.

"To think of mortality was devastating. It was like any major loss – shock and numbness," says Rich, who had to retire from his job as a school social worker because of his cancer treatment.

Rich was diagnosed six years ago. Average survival for stage 4 disease is generally less than three years. "What we both said when we got the diagnosis was, well, that's not acceptable," Rich says of himself and his wife, Carol. "I'm a fighter."

Cooney and Scott Tomlins, M.D., Ph.D., assistant professor of pathology at U-M, are leading a new study supported by the U.S. Department of Defense to look at DNA of both normal and cancerous prostate tissue of men diagnosed with advanced prostate cancer before age 61.

They will be looking at whether these younger men are more likely to have inherited genetic mutations. For more information on this study, contact the U-M Cancer AnswerLine at 800-865-1125.

Men with a family history of prostate cancer have a two- to three-times greater chance of being diagnosed with prostate cancer. That risk increases for young men with multiple affected relatives. Prostate cancer runs in Rich's family. Like Rich, his brother was diagnosed in his 50s, and a cousin and uncle had prostate cancer as well.

The new analysis, which appears in Nature Reviews: Urology, found that men with early onset prostate cancer had more genetic variants than men diagnosed with prostate cancer at a later age. The researchers suggest that genetic counseling or increased surveillance in younger men with a family history of prostate cancer may be warranted.

American men have a 16 percent risk of developing prostate cancer in their lifetime, but only a 3 percent lifetime risk of dying from it. The challenge, Cooney says, is understanding which subset of prostate cancers are most likely to be aggressive and deadly.

"The unexpectedly poor prognosis of advanced stage early onset prostate cancer supports the idea that a new clinical subtype might exist in the subset of men with early onset prostate cancer. This subtype is more aggressive and requires more specialty expertise, including genetic sequencing," Cooney says.

Early Onset Prostate Cancer Statistics

The American Cancer Society estimates 241,740 Americans will be diagnosed with prostate cancer this year; about 10 percent will be early onset disease

Additional Authors

Claudia A. Salinas, Alex Tsodikov, Miriam Ishak-Howard, from the University of Michigan Medical School and School of Public Health

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http://www.eurekalert.org/pub_releases/2014-07/gi-ton071514.php

Transplantation of new brain cells reverses memory loss in Alzheimer's disease model

SAN FRANCISCO, CA - A new study from the Gladstone Institutes has revealed a way to alleviate the learning and memory deficits caused by apoE4, the most important genetic risk factor for Alzheimer's disease, improving cognition to normal levels in aged mice.

In the study, which was conducted in collaboration with researchers at UC San Francisco and published today in the Journal of Neuroscience, scientists transplanted inhibitory neuron progenitors - early-stage brain cells that have the capacity to develop into mature inhibitory neurons - into two mouse models of Alzheimer's disease, apoE4 or apoE4 with accumulation of amyloid beta, another major contributor to Alzheimer's. The transplants helped to replenish the brain by replacing cells lost due to apoE4, regulating brain activity and improving learning and memory abilities.

"This is the first time transplantation of inhibitory neuron progenitors has been used in aged Alzheimer's disease models," said first author Leslie Tong, a graduate student at the Gladstone Institutes and UCSF. "Working with older animals can be challenging from a technical standpoint, and it was amazing to see that the cells not only survived but affected activity and behavior."

The success of the treatment in older mice, which corresponded to late adulthood in humans, is particularly important, as this would be the age that would be targeted were this method ever to be used therapeutically in people.

"This is a very important proof of concept study," said senior author Yadong Huang, MD, PhD, an associate investigator at Gladstone Institutes and associate professor of neurology and pathology at UCSF. "The fact that we see a functional integration of these cells into the hippocampal circuitry and a complete rescue of learning and memory deficits in an aged model of Alzheimer's disease is very exciting."

A balance of excitatory and inhibitory activity in the brain is essential for normal function. However, in the apoE4 model of Alzheimer's disease - a genetic risk factor that is carried by approximately 25% of the population and is involved in 60-75% of all Alzheimer's cases - this balance gets disrupted due to a decline in inhibitory regulator cells that are essential in maintaining normal brain activity. The hippocampus, an important memory center in the brain, is particularly affected by this loss of inhibitory neurons, resulting in an increase in network activation that is thought to contribute to the learning and memory deficits characteristic of Alzheimer's disease. The accumulation of amyloid beta in the brain has also been linked to this imbalance between excitatory and inhibitory activity in the brain.

In the current study, the researchers hoped that by grafting inhibitory neuron progenitors into the hippocampus of aged apoE4 mice, they would be able to combat these effects, replacing the lost cells and restoring normal function to the area.

Remarkably, these new inhibitory neurons survived in the hippocampus, enhancing inhibitory signaling and rescuing impairments in learning and memory.

In addition, when these inhibitory progenitor cells were transplanted into apoE4 mice with an accumulation of amyloid beta, prior deficits were alleviated. However, the new inhibitory neurons did not affect amyloid beta levels, suggesting that the cognitive enhancement did not occur as a result of amyloid clearance, and amyloid did not impair the integration of the transplant.

According to Dr. Huang, the potential implications for these findings extend beyond the current methods used. "Stem cell therapy in humans is still a long way off. However, this study tells us that if there is any way we can enhance inhibitory neuron function in the hippocampus, like through the development of small molecule compounds, it may be beneficial for Alzheimer disease patients."

Other scientists who participated in this research include Biljana Djukic, Anna Gillespie, Seo Yeon Yoon, Max Wang, Olivia Zhang, and Johanna Knoferle from Gladstone Institutes, and Christine Arnold, John Rubenstein, and Arturo Alvarez-Buylla from UCSF. Funding was provided by the California Institute for Regenerative Medicine, National Institutes of Health, S.D. Bechtel, Jr. Foundation, Roddenberry Foundation, and Hellman Foundation.

http://www.eurekalert.org/pub_releases/2014-07/acs-bws071614.php

Bubble wrap serves as sheet of tiny test tubes in resource-limited regions

Scientists propose reusing bubble wrap as a sheet of small, test tube-like containers

Popping the blisters on the bubble wrap might be the most enjoyable thing about moving. But now, scientists propose a more productive way to reuse the popular packing material - as a sheet of small, test tube-like containers for medical and environmental samples. Their report, which shows that analyses can take place right in the bubbles, appears in the ACS journal Analytical Chemistry.

George Whitesides and colleagues explain that although bubble wrap filled with biological samples, like blood or urine, or chemicals would have to be handled carefully, the material offers numerous advantages for those living in resource-limited areas. The material is available almost everywhere around the world, is inexpensive, doesn't generate sharp edges when broken (like glass containers), is easily disposed of by burning and is flexible. The interiors of the bubbles also are sterile, so there's no need for costly autoclaves that have to be plugged in - a huge plus for the nearly 2 billion people around the world who do not have regular access to electricity.

To show that their idea could work, the team injected liquids into the air-filled pockets of bubble wrap with syringes and sealed the holes with nail hardener. They successfully ran anemia and diabetes tests on the liquids. They also could grow microbes such as E. coli in the blisters, which is important for detecting contamination in water samples. "The bubbles of bubble wrap, therefore, can be used for storing samples and performing analytical assays, a function that has the potential to be especially beneficial in resource-limited regions, and in very cost-sensitive applications," they conclude.

The authors acknowledge funding from the Bill and Melinda Gates Foundation.

http://www.eurekalert.org/pub_releases/2014-07/w-dak071114.php

Donating a kidney may make it difficult to change or initiate life and health insurance

People who selflessly step up and donate a kidney can face insurance challenges afterwards, despite the lack of evidence that they have increased health risks.

The finding, which comes from a new study published in the American Journal of Transplantation, suggests that actions by insurers may create unnecessary burden and stress for those choosing to donate and could negatively impact the likelihood of live kidney donation.

The impact of kidney donation on the ability to change or initiate health or life insurance following donation is unknown. To investigate, Dorry Segev, MD, PhD, of the Johns Hopkins University School of Public Health, and his colleagues surveyed 1046 individuals who donated a kidney at their center between 1970 and 2011. Participants were asked whether they changed or initiated health or life insurance after donation, and if they had any difficulty doing so.

Among 395 donors who changed or initiated health insurance after donation, 27 (7 percent) reported difficulty. Among those who reported difficulty, 15 were denied altogether, 12 were charged a higher premium, and eight were told they had a pre-existing condition because they were kidney donors.

Among 186 donors who changed or initiated life insurance after donation, 46 (25 percent) reported difficulty. Among those who reported difficulty, 23 were denied altogether, 27 were charged a higher premium, and 17 were told they had a preexisting condition because they were kidney donors.

The results suggest that a high proportion of kidney donors may have difficulty changing or initiating insurance, particularly life insurance. The findings also highlight the serious problems related to coverage in the nation's fragmented health insurance system even though, as stated in the Patient Protection and Affordable

Care Act, insurance companies can no longer refuse health insurance to live kidney donors or charge them a higher insurance rate.

"Kidney donors are among the healthiest individuals in the population. It's such a shame that some insurance companies are giving donors a hard time, often because of a misinterpretation that the normal biological changes that occur after donation are an indication of kidney disease," said Dr. Segev. "This is a reminder that we need to remain strong advocates for our donors, and they need to remain strong advocates for themselves, educating insurance companies when these situations arise."

http://nyti.ms/1mqDXKs

Death Toll From Ebola Surges in West Africa, Prompting Alarm

Ministries of health and W.H.O. step up outbreak containment measures

By RICK GLADSTONE JULY 15, 2014

New cases and deaths from the Ebola virus outbreak in the West African countries of Guinea, Liberia and Sierra Leone, already the worst ever recorded for the disease, have surged by double-digit percentages in the past week, the World Health Organization reported Tuesday, with no sign of a slowdown. Alarmed Ivory Coast border authorities blocked hundreds of Ivorian refugees in Liberia from returning, news agencies reported.

In its latest update, the W.H.O. said the number of suspect, probable and confirmed cases as of Saturday totaled 964, up about 14 percent from a week earlier. Deaths totaled 603, up about 16 percent from a week earlier. Half the deaths have been in Guinea. “This trend indicates that a high level of transmission of the Ebola virus continues to take place in the community,” the W.H.O. said in the update. “The respective ministries of health are working with W.H.O. and partners to step up outbreak containment measures.”

The latest figures were reported as the W.H.O. helped complete a coordination center in Conakry, Guinea’s capital, in an attempt to slow the spread of Ebola, a hemorrhagic fever with no known cure and a death rate that can reach 90 percent. The virus first appeared in 1976 near the Ebola River in the Democratic Republic of Congo and is believed to have been spread originally by fruit bats. Gorillas, chimpanzees, forest antelopes and porcupines can also spread the virus.

Despite the latest outbreak, the W.H.O. said it was not recommending any travel or trade restrictions in the three affected countries. Nonetheless, news agencies reported Tuesday that Ivory Coast had prevented 400 refugees who had fled to neighboring Liberia during the violent 2010-11 Ivorian political upheaval from re-entering the country. Agence France-Presse said Bruno Kone, an Ivorian government spokesman, had justified the move, quoting him as saying, “We cannot be lax in this area.”

http://www.bbc.com/news/health-28325761

Aids epidemic under control by 2030 'is possible'

There is a chance the Aids epidemic can be brought under control by 2030, according to a report by the United Nations Aids agency.

By James Gallagher Health editor, BBC News website

It said the number of new HIV infections and deaths from Aids were both falling. However, it called for far more international effort as the "current pace cannot end the epidemic". And charity Medecins Sans Frontieres warned most of those in need of HIV drugs still had no access to them. The report showed that 35 million people around the world were living with HIV.

There were 2.1 million new cases in 2013 - 38% less than the 3.4 million figure in 2001. Aids-related deaths have fallen by a fifth in the past three years, standing at 1.5 million a year. South Africa and Ethiopia have particularly improved.

Many factors contribute to the improving picture, including increased access to drugs. There has even been a doubling in the number of men opting for circumcision to reduce the risk of spreading or contracting HIV.

Warning

While some things are improving, the picture is far from rosy. Fewer than four in 10 people with HIV are getting life-saving antiretroviral therapy. And just 15 countries account for three-quarters of all new HIV infections. The report said: "There have been more achievements in the past five years than in the preceding 23 years.

"There is evidence about what works and where the obstacles remain, more than ever before, there is hope that ending Aids is possible. "However, a business-as-usual approach or simply sustaining the Aids response at its current pace cannot end the epidemic."

Michel Sidibe, the executive director of UNAids, added: "If we accelerate all HIV scale-up by 2020, we will be on track to end the epidemic by 2030, if not, we risk significantly increasing the time it would take - adding a decade, if not more."

Analysis

Drugs have been a miracle in reducing deaths from Aids. Normally it takes about 10 years for Aids - acquired immune deficiency syndrome - to develop. "Opportunistic infections" that a healthy immune system could fight off then become deadly. But patients taking antiretroviral drugs can keep their HIV infection under control and have a near-normal life expectancy.

The tools are there, but too often they are beyond the reach of people who need them. Some 54% of people living with HIV do not know they are infected and 63% are not getting antiretroviral therapy. Diagnosing and treating the missing millions -

often in sub-Saharan Africa - would significantly reduce the 1.5 million Aids-related deaths each year.

Dr Jennifer Cohn, the medical director for Medecins Sans Frontieres' access campaign, said: "Providing life-saving HIV treatment to nearly 12 million people in the developing world is a significant achievement, but more than half of people in need still do not have access." In Nigeria, 80% of people do not have access to treatment.

Dr Cohn added: "We need to make sure no-one is left behind - and yet, in many of the countries where MSF works we're seeing low rates of treatment coverage, especially in areas of low HIV prevalence and areas of conflict. "In some countries, people are being started on treatment too late to save their lives, and pregnant women aren't getting the early support they need."

Marcus Low from South African campaign group Treatment Action Campaign told the BBC's Focus on Africa programme: "It is still a crisis in South Africa - we still have about 1,000 new infections every day. "On the treatment side, we have done well and people are living longer. "But we must do more to prevent new infections."

http://www.eurekalert.org/pub_releases/2014-07/ehs-tp070914.php

The 'obesity paradox': Cardiovascular mortality lowest among overweight patients

Is being overweight sometimes a good thing? Data suggest higher BMI protects against adverse cardiovascular outcomes, reports Mayo Clinic Proceedings

Rochester, MN - High body mass index (BMI) is associated with multiple cardiovascular diseases. However, emerging data suggest that there is an "obesity paradox," that being overweight may actually protect patients from cardiovascular mortality. Investigators have now confirmed that the risk of total mortality, cardiovascular mortality, and myocardial infarction is highest among underweight patients, while cardiovascular mortality is lowest among overweight patients, according to two reports published today in Mayo Clinic Proceedings.

Currently more than two-thirds of adult Americans are classified as overweight or obese. Because of the high prevalence of coronary heart disease (CAD), overweight and obese patients more frequently undergo revascularization procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG). Obesity has been considered a risk factor for worst clinical outcomes following cardiovascular procedures like these, however, emerging data suggest that higher BMI protects against adverse outcomes in many acute and chronic disease states. This prompted experts to reexamine assumptions about body fat and explore the counterintuitive phenomenon known as the "obesity paradox."

In a landmark meta-analysis of 36 studies, Abhishek Sharma, MD, Cardiology Fellow at the State University of New York Downstate Medical Center in Brooklyn, New York, and colleagues determined that low BMI (less than 20 kg/m2) in tens of thousands of patients with coronary artery disease who underwent coronary revascularization procedures was associated with a 1.8- to 2.7-fold higher risk of myocardial infarction and all-cause and cardiovascular mortality over a mean follow up period of 1.7 years. Conversely overweight and obese patients had more favorable outcomes. Cardiovascular mortality risk was lowest among overweight patients with a high BMI (25-30 kg/m2) compared to people with a normal BMI (20-25 kg/m2). Indeed, in obese and severely obese patients with a BMI in the 30-35 and over 35 kg/m2 range, all-cause mortality was 27% and 22% lower than people with normal BMI.

Dr. Sharma observes, "At this stage we can only speculate on the reasons for this paradox. One explanation may be that overweight patients are more likely to be prescribed cardioprotective medications such as beta blockers and statins and in higher doses than the normal weight population. Further, obese and overweight patients have been found to have large coronary vessel damage, which might contribute to more favorable outcomes. This population may have a higher metabolic reserve, which might act protectively in chronic conditions like CAD. Also, there could be a difference in the pathophysiology of cardiovascular disease in over- and underweight patients. A non-modifiable genetic predisposition may also play a role in underweight patients." He concludes, "However, this is still speculation. Further prospective studies are needed to investigate this association and explore potential underlying mechanisms."

In a second study published in the same issue, investigators examined the "obesity paradox" from another perspective by evaluating the effects of body composition as a function of lean mass index (LMI) and body fat (BF) on the correlation between increasing BMI and decreasing mortality. They estimated BF and LMI in nearly 48,000 people with a preserved left ventricular ejection fraction of more than 50% and examined the survival advantages of obesity across strata of these body compositions.

This large observational study showed that higher lean body mass was associated with 29% lower mortality, and while higher fat mass also exhibited survival benefits, this advantage disappeared after adjustment for lean body mass, suggesting that non-fat tissue bears the primary role in conferring greater survival. "Body composition plays a critical role in the obesity paradox," says senior investigator Carl Lavie, MD, FACC, FACP, FCCP, Medical Director of Cardiac Rehabilitation and Preventative Cardiology at the John Ochsner Heart & Vascular Institute, Ochsner Clinical School, the University of Queensland School of

Medicine, New Orleans. "Whenever examining a potential protective effect of body fat, lean mass index – which likely represents larger skeletal muscle mass – should be considered. At higher BMI, body fat is associated with an increase in mortality."
Noted expert Kamyar Kalantar-Zadeh, MD, MPH, PhD, of the Department of Medicine, University of California Irvine Medical Center, Orange, CA, observes that "although the underlying mechanisms of the obesity paradox and reverse epidemiology remain unclear, the consistency of the data is remarkable, leaving little doubt that these observational data are beyond statistical constellations and bear biologic plausibility.
"The findings in these studies should not be considered as an attempt to undermine the legitimacy of the anti-obesity campaign in the best interest of public health. Nonetheless, given the preponderance and consistency of epidemiologic data, there should be little doubt that in certain populations higher BMI, which is associated with higher risk of metabolic syndrome and poor cardiovascular outcomes in the long-term, confers short-term survival and cardiovascular advantages.
Metaphorically we can liken cardiovascular risk factors to a friend who is a negative influence, causing you to misbehave and be sentenced to jail, but once imprisoned the friend remains loyal and protects you against poor prison conditions and other inmates."

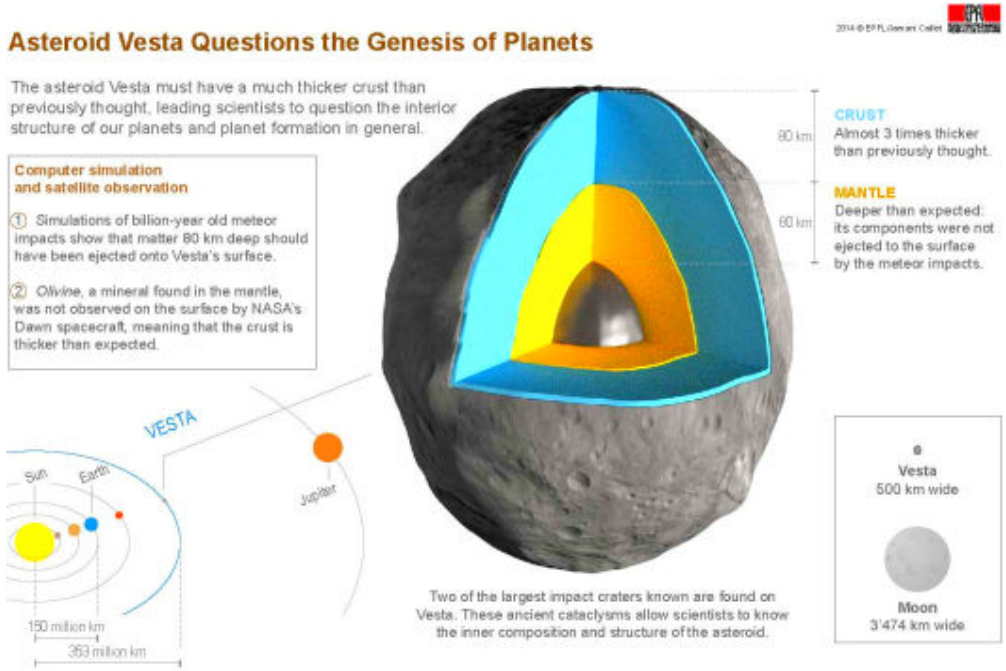
http://www.eurekalert.org/pub_releases/2014-07/epfd-avt071514.php

Asteroid Vesta to reshape theories of planet formation

New findings about the asteroid Vesta question contemporary models of rocky planet formation, including that of Earth

EPFL researchers have a better understanding of the asteroid Vesta and its internal structure, thanks to numerical simulations and data from the space mission Dawn. Their findings, published today in Nature, question contemporary models of rocky planet formation, including that of Earth.
With its 500 km diameter, the asteroid Vesta is one of the largest known planet embryos. It came into existence at the same time as the Solar System. Spurring scientific interest, NASA sent the Dawn spacecraft into Vesta's orbit for one year between July 2011 and July 2012.
Data gathered by Dawn were analyzed by a team of researchers from EPFL as well as the Universities of Bern, Brittany (France) and Arizona (USA). Conclusion: the asteroid's crust is almost three times thicker than expected. The study does not only have implications for the structure of this celestial object, located between Mars and Jupiter. Their results also challenge a fundamental component in planet formation models, namely the composition of the original cloud of matter that aggregated together, heated, melted and then crystallized to form planets.

At EPFL's Earth and Planetary Science Laboratory (EPSL), led by Philippe Gillet, Harold Clenet had a look at the composition of the rocks scattered across Vesta's ground. "What is striking is the absence of a particular mineral, olivine, on the asteroid's surface," said the researcher.
Olivine is a main component of planetary mantles and should have been found in large quantities on the surface of Vesta, due to a double meteorite impact that, according to computer simulations, "dug" the celestial body's southern pole to a depth of 80 km, catapulting large amounts of materials to the surface.
The two impacts were so powerful that more than 5% of Earth's meteorites come from Vesta. "But these cataclysms were not strong enough to pierce through the crust and reach the asteroid's mantle," Clenet continued.
The meteorites originating from Vesta and found on Earth confirm this since they generally lack Olivine, or contain only minute amounts compared to the amount observed in planetary mantles. Also, the spacecraft Dawn did not find olivine in the vicinity of the two impact craters.



"This means that the crust of the asteroid is not 30 km thick, as suggested by the models, but more than 80 km," said Clenet.

Composition of planets

These discoveries challenge models that describe the formation of Vesta, and consequently the formation of rocky planets in the Solar System, including planet Earth. Cooling theory and "re-melting" phenomena in the depths of previously solidified elements would also need to be reviewed. As the scientist explained, "The crust might have been thickened by the formation of 'plutons,' that is: igneous rock intrusions, hundreds of meters large, some of which emerged to the surface."

If Vesta has less of a (olivine-rich) mantle and more of a (pyroxene-rich) crust, then the proportion of materials making up Vesta, and probably the Earth and other telluric planets as well (Mars, Venus, Mercury), is different from what was previously expected.

A more complex model of planet formation therefore has to be considered, one that takes into account not only the original composition of planets, but also their orbits, sizes and related cooling times. Vesta is the only known asteroid that has an earth-like structure--with a core, mantle and crust--making it an incredible laboratory for testing hypotheses and theories.

Video on YouTube, EPFLnews: http://bit.ly/2014VestaYoutube

Nature Online PDF (after Embargo): http://dx.doi.org/10.1038/nature13499

http://www.eurekalert.org/pub_releases/2014-07/uota-woa071514.php

Walking on all fours is not backward evolution, study shows

Anthropology study shows quadrupedal humans are not products of 'devolution'

AUSTIN, Texas -- Contradicting earlier claims, "The Family That Walks on All Fours," a group of quadrupedal humans made famous by a 2006 BBC documentary, have simply adapted to their inability to walk upright and do not represent an example of backward evolution, according to new research by Liza Shapiro, an anthropologist at The University of Texas at Austin.

Five siblings in the family, who live in a remote corner of Turkey, walk exclusively on their hands and feet. Since they were discovered in 2005, scientists have debated the nature of their disability, with speculation they represent a backward stage of evolution.

Shapiro's study, published online this month in PLOS One, shows that contrary to previous claims, people with the family members' condition, called Uner Tan Syndrome (UTS), do not walk in the diagonal pattern characteristic of nonhuman primates such as apes and monkeys.

According to a theory developed by Uner Tan of Cukurova University in Turkey, people with UTS are a human model for reverse evolution, or "devolution," offering new insights into the human transition from four-legged to two-legged walking.

Previous research countering this view has proposed that the quadrupedalism associated with UTS is simply an adaptive response to the impaired ability to walk bipedally in individuals with a genetic mutation, but this is the first study that disproves claims that this form of walking resembles that of nonhuman primates.

The study's co-authors are Jesse Young of Northeast Ohio Medical University; David Raichlen of the University of Arizona; and Whitney Cole, Scott Robinson and Karen Adolph of New York University.

As part of the study, the researchers analyzed 518 quadrupedal walking strides from several videos of people with various forms of UTS, including footage from the BBC2 documentary of the five Turkish siblings, "The Family That Walks on All Fours." They compared these walking strides to previous studies of the walking patterns of healthy adults who were asked to move around a laboratory on all fours.

According to the findings, nearly all human subjects (in 98 percent of the total strides) walked in lateral sequences, meaning they placed a foot down and then a hand on the same side and then moved in the same sequence on the other side. Apes and other nonhuman primates, however, walk in a diagonal sequence, in which they put down a foot on one side and then a hand on the other side, continuing that pattern as they move along.

"Although it's unusual that humans with UTS habitually walk on four limbs, this form of quadrupedalism resembles that of healthy adults and is thus not at all unexpected," Shapiro says. "As we have shown, quadrupedalism in healthy adults or those with a physical disability can be explained using biomechanical principles rather than evolutionary assumptions."

The study also shows that Tan and his colleagues appeared to have misidentified the walking patterns among people with UTS as primate-like by confusing diagonal sequence with diagonal couplets. Sequence refers to the order in which the limbs touch the ground, while couplets (independent of sequence) indicate the timing of movement between pairs of limbs.

People with UTS more frequently use diagonal couplets than lateral couplets, but the sequence associated with the couplets is almost exclusively lateral.

"Each type of couplet has biomechanical advantages, with lateral couplets serving to avoid limb interference, and diagonal couplets providing stability," Shapiro says. "The use of diagonal couplets in adult humans walking quadrupedally can thus be explained on the basis of biomechanical considerations, not reverse evolution."

http://www.eurekalert.org/pub_releases/2014-07/nu-ntd071514.php

Niacin too dangerous for routine cholesterol therapy

Mainstay drug now linked to death risk, dangerous side effects and no benefits

CHICAGO - After 50 years of being a mainstay cholesterol therapy, niacin should no longer be prescribed for most patients due to potential increased risk of death, dangerous side effects and no benefit in reducing heart attacks and strokes, writes

Northwestern Medicine® preventive cardiologist Donald Lloyd-Jones, M.D., in a New England Journal of Medicine editorial.

Lloyd-Jones's editorial is based on a large new study published in the journal that looked at adults, ages 50 to 80, with cardiovascular disease who took extended-release niacin (vitamin B3) and laropiprant (a drug that reduces face flushing caused by high doses of niacin) to see if it reduced heart attack and stroke compared to a placebo over four years. All patients in the trial were already being treated with a statin medication.

Niacin did not reduce heart attacks and stroke rates compared with a placebo. More concerning, niacin was associated with an increased trend toward death from all causes as well as significant increases in serious side effects: liver problems, excess infections, excess bleeding, gout, loss of control of blood sugar for diabetics and the development of diabetes in people who didn't have it when the study began.

"There might be one excess death for every 200 people we put on niacin," said Lloyd-Jones, chair of preventive medicine at Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital. "With that kind of signal, this is an unacceptable therapy for the vast majority of patients."

"For the reduction of heart disease and stroke risk, statins remain the most important drug-based strategy by far because of their demonstrated benefit and their good safety profile," said Lloyd-Jones, who was a member of the task force that rewrote cholesterol treatment guidelines in 2013 for the American College of Cardiology and the American Heart Association.

Niacin should be reserved only for patients at very high risk for a heart attack and stroke who can't take statins and for whom there are no other evidence-based options, Lloyd-Jones said.

Niacin raises "good" HDL (high density lipoprotein) cholesterol levels, and having high HDL levels means a lowered risk for cardiovascular events. But clinical trials have not shown that niacin reduced the risk of coronary heart disease or the broader cardiovascular disease specifically by raising HDL. Niacin also produces a modest reduction in low-density lipoprotein (LDL cholesterol) and a more substantial reduction in triglyceride levels, which might be expected to lower the risk of coronary heart disease, Lloyd-Jones notes in the article.

But the new study suggests that higher HDL levels only are a sign of lowered risk for heart attacks and stroke. Raising HDL levels with niacin does not appear to impact cardiovascular outcomes nor does lowering triglyceride levels, Lloyd-Jones points out.

"The recent niacin clinical trials offer important new evidence that raising 'good' cholesterol (HDL) levels on top of statin therapy does not have the positive outcome that had been hoped for," said Neil Stone, M.D., the Robert Bonow MD Professor in Cardiology at Feinberg and a cardiologist at Northwestern Memorial Hospital. "Lowering 'bad' cholesterol (LDL) with an optimal intensity of tolerated statins and adherence to healthy lifestyle changes remains the most effective approach to prevent strokes and heart attacks for patients at risk of cardiovascular disease."

Stone was chair of the expert panel that wrote rewrote cholesterol treatment guidelines in 2013 for the American College of Cardiology and the American Heart Association.

http://bit.ly/1qo3T1z

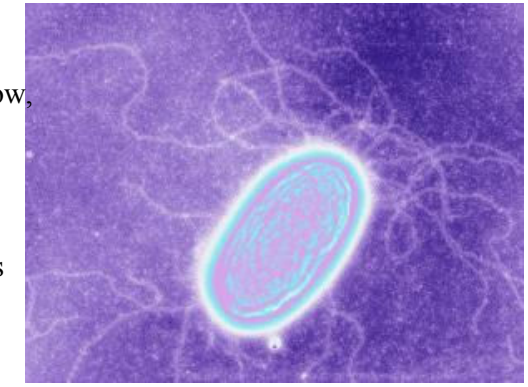
Meet the electric life forms that live on pure energy

Unlike any other life on Earth, these extraordinary bacteria use energy in its purest form – they eat and breathe electrons – and they are everywhere

17:08 16 July 2014 by Catherine Brahic

STICK an electrode in the ground, pump electrons down it, and they will come: living cells that eat electricity. We have known bacteria to survive on a variety of energy sources, but none as weird as this. Think of Frankenstein's monster, brought to life by galvanic energy, except these "electric bacteria" are very real and are popping up all over the place.

Unlike any other living thing on Earth, electric bacteria use energy in its purest form – naked electricity in the shape of electrons harvested from rocks and metals. We already knew about two types, *Shewanella* and *Geobacter*. Now, biologists are showing that they can entice many more out of rocks and marine mud by tempting them with a bit of electrical juice. Experiments growing bacteria on battery electrodes demonstrate that these novel, mind-boggling forms of life are essentially eating and excreting electricity.



Geobacter – a current favourite **Derek Lovley/SPL**

That should not come as a complete surprise, says Kenneth Nealson at the University of Southern California, Los Angeles. We know that life, when you boil it right down, is a flow of electrons: "You eat sugars that have excess electrons, and you breathe in oxygen that willingly takes them." Our cells break down the sugars, and the electrons flow through them in a complex set of chemical reactions until they are passed on to electron-hungry oxygen.

In the process, cells make ATP, a molecule that acts as an energy storage unit for almost all living things. Moving electrons around is a key part of making ATP.

"Life's very clever," says Nealson. "It figures out how to suck electrons out of everything we eat and keep them under control." In most living things, the body packages the electrons up into molecules that can safely carry them through the cells until they are dumped on to oxygen.

"That's the way we make all our energy and it's the same for every organism on this planet," says Nealson. "Electrons must flow in order for energy to be gained. This is why when someone suffocates another person they are dead within minutes. You have stopped the supply of oxygen, so the electrons can no longer flow."

The discovery of electric bacteria shows that some very basic forms of life can do away with sugary middlemen and handle the energy in its purest form – electrons, harvested from the surface of minerals. "It is truly foreign, you know," says Nealson. "In a sense, alien."

Nealson's team is one of a handful that is now growing these bacteria directly on electrodes, keeping them alive with electricity and nothing else – neither sugars nor any other kind of nutrient. The highly dangerous equivalent in humans, he says, would be for us to power up by shoving our fingers in a DC electrical socket.

To grow these bacteria, the team collects sediment from the seabed, brings it back to the lab, and inserts electrodes into it.

First they measure the natural voltage across the sediment, before applying a slightly different one. A slightly higher voltage offers an excess of electrons; a slightly lower voltage means the electrode will readily accept electrons from anything willing to pass them off. Bugs in the sediments can either "eat" electrons from the higher voltage, or "breathe" electrons on to the lower-voltage electrode, generating a current. That current is picked up by the researchers as a signal of the type of life they have captured.

"Basically, the idea is to take sediment, stick electrodes inside and then ask 'OK, who likes this?'," says Nealson.

Shocking breath

At the Goldschmidt geoscience conference in Sacramento, California, last month, Shiue-lin Li of Nealson's lab presented results of experiments growing electricity breathers in sediment collected from Santa Catalina harbour in California. Yamini Jangir, also from the University of Southern California, presented separate experiments which grew electricity breathers collected from a well in Death Valley in the Mojave Desert in California.

Over at the University of Minnesota in St Paul, Daniel Bond and his colleagues have published experiments showing that they could grow a type of bacteria that harvested electrons from an iron electrode. That research, says Jangir's supervisor Moh El-Naggar, may be the most convincing example we have so far of electricity eaters grown on a supply of electrons with no added food.

But Nealson says there is much more to come. His PhD student Annette Rowe has identified up to eight different kinds of bacteria that consume electricity. Those results are being submitted for publication.

Nealson is particularly excited that Rowe has found so many types of electric bacteria, all very different to one another, and none of them anything like *Shewanella* or *Geobacter*. "This is huge. What it means is that there's a whole part of the microbial world that we don't know about."

Discovering this hidden biosphere is precisely why Jangir and El-Naggar want to cultivate electric bacteria. "We're using electrodes to mimic their interactions," says El-Naggar. "Culturing the 'unculturables', if you will." The researchers plan to install a battery inside a gold mine in South Dakota to see what they can find living down there.

NASA is also interested in things that live deep underground because such organisms often survive on very little energy and they may suggest modes of life in other parts of the solar system.

Electric bacteria could have practical uses here on Earth, however, such as creating biomachines that do useful things like clean up sewage or contaminated groundwater while drawing their own power from their surroundings. Nealson calls them self-powered useful devices, or SPUDs.

Practicality aside, another exciting prospect is to use electric bacteria to probe fundamental questions about life, such as what is the bare minimum of energy needed to maintain life.

For that we need the next stage of experiments, says Yuri Gorby, a microbiologist at the Rensselaer Polytechnic Institute in Troy, New York: bacteria should be grown not on a single electrode but between two. These bacteria would effectively eat electrons from one electrode, use them as a source of energy, and discard them on to the other electrode.

Gorby believes bacterial cells that both eat and breathe electrons will soon be discovered. "An electric bacterium grown between two electrodes could maintain itself virtually forever," says Gorby. "If nothing is going to eat it or destroy it then, theoretically, we should be able to maintain that organism indefinitely."

It may also be possible to vary the voltage applied to the electrodes, putting the energetic squeeze on cells to the point at which they are just doing the absolute minimum to stay alive. In this state, the cells may not be able to reproduce or grow, but they would still be able to run repairs on cell machinery. "For them, the work that energy does would be maintaining life – maintaining viability," says Gorby.

How much juice do you need to keep a living electric bacterium going? Answer that question, and you've answered one of the most fundamental existential questions there is.

Wire in the mud

Electric bacteria come in all shapes and sizes. A few years ago, biologists discovered that some produce hair-like filaments that act as wires, ferrying electrons back and forth between the cells and their wider environment. They dubbed them microbial nanowires.

Lars Peter Nielsen and his colleagues at Aarhus University in Denmark have found that tens of thousands of electric bacteria can join together to form daisy chains that carry electrons over several centimetres – a huge distance for a bacterium only 3 or 4 micrometres long. It means that bacteria living in, say, seabed mud where no oxygen penetrates, can access oxygen dissolved in the seawater simply by holding hands with their friends.

Such bacteria are showing up everywhere we look, says Nielsen. One way to find out if you're in the presence of these electron munchers is to put clumps of dirt in a shallow dish full of water, and gently swirl it. The dirt should fall apart. If it doesn't, it's likely that cables made of bacteria are holding it together.

Nielsen can spot the glimmer of the cables when he pulls soil apart and holds it up to sunlight (see video).

Flexible biocables

It's more than just a bit of fun. Early work shows that such cables conduct electricity about as well as the wires that connect your toaster to the mains. That could open up interesting research avenues involving flexible, lab-grown biocables.

http://bit.ly/1zTi40x

'Burrito' Screen Rolls Up Like It's Your Lunch

Electronics continue to get more and more pliable and a new prototype from LG Display looks to be about the most flexible yet.

Jul 16, 2014 04:00 PM ET // by Tracy Staedter

The company unveiled two 18-inch OLED (organic light-emitting-diode) panels, one so bendable that it can be rolled up to a diameter of 6 centimeters without adversely affecting the screen's function. Another display of the same size was also demonstrated; that one stiffer and completely transparent.

According to LG, the paper-thin flexible screen has a resolution of 1,200 x 810 with almost 1 million megapixels. And that's just for starters. You can just imagine the myriad uses for flexible screens. For starters, all of those fitness monitoring bands and smart watches will get some of the same old-fashioned wearability as leather watchbands.

Displays could wrap around round surfaces, such as car bodies. The flexibility also reduces breakage. Where will the whole smartphone case market go?

LG Display is at the forefront of bendy displays. The company launched the flexible smartphone, the G Flex, and says a 60-inch flexible OLED TV will be for sale by 2017.

http://nyti.ms/1thSptZ

Scientists Begin to Demystify Hole Found in Siberian Permafrost

Scientists are starting to offer more informed views of a gaping crater in the permafrost in Siberia

By ANDREW C. REVKIN

After a flood of speculation - meteorite collision, methane explosion related to gas drilling, UFO - following the discovery of a gaping crater in the permafrost near big gas fields on the Yamal peninsula in Siberia, scientists are starting to offer more informed views.

The Siberian Times, the source of initial aerial images and video, has posted the first article citing scientists at the scene.

A view from the edge of a crater – about 100 feet across – that has opened in Siberian permafrost.Credit Marya Zulinova, press service of the Governor YaNAO

Here are some excerpts. The crater is smaller than initial reports:

Andrey Plekhanov, Senior Researcher at the State Scientific Centre of Arctic Research, said: "The crater has more of an oval than a circular shape, it makes it harder to calculate the exact diameter. As of now our estimates is about thirty metres."

Here's more from Plekharov, on a possible connection to the warming climate:

"Could it be linked to the global warming? We have to continue our research to answer this question. Two previous summers – years 2012 and 2013 were relatively hot for Yamal, perhaps this has somehow influenced the formation of the crater. But we have to do our tests and research first and then say it more definitively."

He also rebutted speculation that the black marks around the perimeter indicated a fiery explosion had taken place (one example):

"For now we can say for sure that under the influence of internal processes there was an ejection in the permafrost. I want to stress that it was not an explosion, but an ejection, so there was no heat released as it happened."

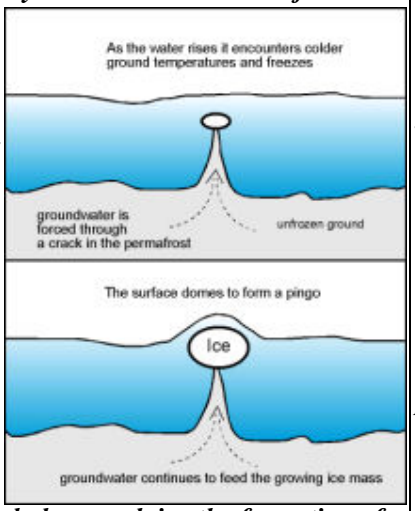
Earlier scientists were sure there was burning visible on the sides of the crater.

"I also want to recall a theory that our scientists worked on in the 1980s - it has been left and then forgotten for a number of years. The theory was that the number of Yamal lakes formed because of exactly such natural process happening in the permafrost.

Such kind of processes were taking place about 8,000 years ago. Perhaps they are repeating nowadays. If this theory is confirmed, we can say that we have witnessed a unique natural process that formed the unusual landscape of Yamal peninsula."

Chris Fogwill, an Australian paleoclimatologist and geologist, offers some helpful context in the Sydney Morning Herald on the process by which "pingos," ice formations in permafrost landscapes, transform into lakes.

The British Society for Geomorphology has produced a helpful diagram (at right) showing how this works. Click here for a larger version.



A diagram from the British Society for Geomorphology explains the formation of a pingo, a hill formed around a buried lump of ice in regions with frozen ground, or permafrost. **Credit British Society for Geomorphology**

http://www.wired.com/2014/07/pox-four/

Update on the Found Vials: There Weren't 6; There Were 327.

(Not All of Them Were Smallpox)

By Maryn McKenna

I was away reporting most of today, and while I was out, a few federal emails landed in my mail with what probably sounded like a thud. One was an official announcement from the Food and Drug Administration; the others were copies of FDA and NIH emails that people there thought I should see.

They all said the same thing: The six vials of smallpox virus found in an FDA cold-storage room on the National Institutes of Health campus July 1 and announced by the CDC last week had company. A lot of company: 321 other vials. Some of them contained other "select agents," infectious pathogens considered serious enough - for the illness they create, or the lack of a vaccine to prevent or drugs to treat them - to be considered potential bioterror agents.

(If you've missed this story so far, catch up here, here, here and here.)Here's the gist of the FDA's external announcement:

The investigation found 12 boxes containing a total of 327 carefully packaged vials labeled with names of various biological agents such as dengue, influenza, Q fever, and rickettsia. Upon the discovery of these vials on July 1, 2014, FDA employees followed standard protocol and turned them all over to the appropriate NIH safety program officials, who in turn transferred them to the appropriate investigative agencies, as per standard protocols.

As announced on July 8, 2014, six vials labeled "variola" (the causative agent of smallpox) along with ten other samples with unclear labeling were transported safely and securely with the assistance of federal and local law enforcement agencies in a government aircraft to CDC's high-containment facility in Atlanta. In addition, 32 samples were destroyed following inventory at the NIH facility, including 28 labeled as normal tissue and four labeled as "vaccinia," the virus used to make the smallpox vaccine. To be clear, vaccinia does not cause smallpox. These vials represented no value to forensic sciences and were destroyed according to standard protocols.

The remaining 279 biological samples were then transferred by the investigating agencies to the U.S. Department of Homeland Security's National Bioforensic Analysis Center for safeguarding. There were no smallpox samples included in this transfer. The FDA received confirmatory information about the samples yesterday, thus permitting public disclosure of this additional information.

The rest of the announcement confirms what my reporting uncovered last week: The room where the vials were found, though now belonging to the FDA, was once the property of NIH's Division of Biological Standards, which worked on the reliability of vaccines:

…this collection was most likely assembled between 1946 and 1964 when standards for work with and storage of biological specimens were very different from those used today. All of the items labeled as infectious agents found in the collection of samples were stored in glass, heat-sealed vials that were well-packed, intact, and free of any leakage, and there is no evidence that anyone was exposed to these agents.

The internal NIH announcement, signed by director Dr. Francis Collins, goes into detail about what comes next:

…the safety of NIH employees and the public is of utmost importance and overlooking such a sample collection for years is clearly unacceptable. We take very seriously this incident and our need to apply a number of responsive new precautionary measures. As you know, we are instituting a comprehensive search of our facilities to identify any other select agents, toxins, or hazardous biological materials improperly stored in any of our facilities, owned, leased, or through contract arrangements. We have developed a plan of action for the conduct of this search: it requires investigators to examine all freezers, refrigerators, cold rooms, storage shelves, and cabinets, as well as all other areas of storage such as offices associated with laboratories, to be sure that there are no further examples of potentially harmful materials that are being improperly stored.

Much more to come, no doubt.

Meanwhile, as I mentioned this morning, leadership from the Centers for Disease Control and Prevention were in front of Congress today to explain the other two infectious-organism misfires that are happening coincident to this: the errors in the CDC's anthrax and influenza labs. Here is the video of the full session (2 hours, 40

minutes) in the House of Representatives. I haven't had the chance to watch it yet; I'll just leave it here for you: https://www.youtube.com/watch?v=bi4ziq86Ffw

http://www.eurekalert.org/pub_releases/2014-07/uoo-vrs071514.php

Viral relics show cancer's 'footprint' on our evolution

Viral relics show cancer's 'footprint' on our evolution Cancer has left its 'footprint' on our evolution, according to a study which examined how the relics of ancient viruses are preserved in the genomes of 38 mammal species.

Viral relics are evidence of the ancient battles our genes have fought against infection. Occasionally the retroviruses that infect an animal get incorporated into that animal's genome and sometimes these relics get passed down from generation to generation – termed 'endogenous retroviruses' (ERVs). Because ERVs may be copied to other parts of the genome they contribute to the risk of cancer-causing mutations.

Now a team from Oxford University, Plymouth University, and the University of Glasgow has identified 27,711 ERVs preserved in the genomes of 38 mammal species, including humans, over the last 10 million years. The team found that as animals increased in size they 'edited out' these potentially cancer-causing relics from their genomes so that mice have almost ten times as many ERVs as humans. The findings offer a clue as to why larger animals have a lower incidence of cancer than expected compared to smaller ones, and could help in the search for new anti-viral therapies.

A report of the research is published in the journal PLOS Pathogens.

'We set out to find as many of these viral relics as we could in everything from shrews and humans to elephants and dolphins,' said Dr Aris Katzourakis of Oxford University's Department of Zoology, lead author of the report. 'Viral relics are preserved in every cell of an animal: Because larger animals have many more cells they should have more of these endogenous retroviruses (ERVs) – and so be at greater risk of ERV-induced mutations – but we've found this isn't the case. In fact larger animals have far fewer ERVs, so they must have found ways to remove them.'

A combination of mathematical modelling and genome research uncovered some striking differences between mammal genomes: mice (c.19 grams) have 3331 ERVs, humans (c.59 kilograms) have 348 ERVs, whilst dolphins (c.281 kilograms) have just 55 ERVs.

'This is the first time that anyone has shown that having a large number of ERVs in your genome must be harmful – otherwise larger animals wouldn't have evolved ways of limiting their numbers,' said Dr Katzourakis. 'Logically we think this is linked to the increased risk of ERV-based cancer-causing mutations and how mammals have evolved to combat this risk. So when we look at the pattern of ERV distribution across mammals it's like looking at the 'footprint' cancer has left on our evolution.'

Dr Robert Belshaw of Plymouth University Peninsula Schools of Medicine and Dentistry, School of Biomedical and Healthcare Sciences, added: "Cancer is caused by errors occurring in cells as they divide, so bigger animals - with more cells - ought to suffer more from cancer. Put simply, the blue whale should not exist. However, larger animals are not more prone to cancer than smaller ones: this is known as Peto's Paradox (named after Sir Richard Peto, the scientist credited with first spotting this). A team of scientists at Oxford, Plymouth and Glasgow Universities had been studying endogenous retroviruses, viruses like HIV but which have become part of their host's genome and which in other animals can cause cancer. Surprisingly, they found that bigger mammals have fewer of these viruses in their genome. This suggests that similar mechanism might be involved in fighting both cancer and the spread of these viruses, and that these are better in bigger animals (like humans) than smaller ones (like laboratory mice)."

ERVs that are immediately harmful to an animal tend not be passed on, what makes them troublesome is that having arrived at one location in a genome the replication process means they can be copied across, 'jumping', to somewhere else. ERVs can, for example, 'jump' into the middle of gene machinery responsible for suppressing tumours, damaging it and ratcheting up the risk of mutations turning into cancer.

'We know that some cancers, such as t-cell leukaemia, are directly linked to retroviruses but a lot of the time ERVs contribute to the number of things that need to go wrong in cells for cancers to arise,' said Dr Katzourakis. 'As animals get bigger so the number of cells increases and there are more opportunities for things to go wrong, so there is an evolutionary pressure for larger animals to reduce the number of ERVs.'

Dr Gkikas Magiorkinis of Oxford University's Department of Zoology, an author of the report, said: 'We know that taller people have higher risk for some cancers, which fits our study about ERVs posing evolutionary pressure through cancer. Yet we still have no evidence that ERVs might have causal links with cancer in humans, even though they clearly cause cancers in other animals such as mice. We need to search in a more systematic way to see if ERVs cause cancer in humans, and our study suggests that viral pathogenic mechanisms in larger animals like humans would be more complex than those observed in smaller animals.'

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The research suggests that larger creatures must have more effective anti-viral genes and resources than smaller ones and, if these can be identified, in the future it may be possible to mimic these mechanisms to produce new anti-viral therapies.

The new study is relevant to Peto's Paradox, an observation made by Sir Richard Peto that the incidence of cancer does not appear to correlate with the number of cells in an organism. 'Our work doesn't solve Peto's paradox as a whole but is has solved it in respect of infection,' said Dr Katzourakis.

*Notes to editors *A full report of the research, entitled 'Larger Mammalian Body Size Leads to Lower retroviral Activity', is published in PLOS Pathogens embargoed until 19:00 BST/14:00 US ET 17 July 2014.*

**The work was supported by the Royal Society and the UK's Medical Research Council (MRC).*

http://www.eurekalert.org/pub_releases/2014-07/cp-bff071014.php

Brown fat found to be at the root of cancer-related wasting syndrome

Promising strategy that may stimulate weight gain and muscle strength

Many patients with advanced stages of cancer, AIDS, tuberculosis, and other diseases die from a condition called cachexia, which is characterized as a "wasting" syndrome that causes extreme thinness with muscle weakness. Cachexia is the direct cause of roughly 20% of deaths in cancer patients. While boosting food intake doesn't help, and no effective therapies are available, new research in the Cell Press journal Cell Metabolism points to a promising strategy that may stimulate weight gain and muscle strength.

The research relates to a process that has been gaining considerable attention as a way to combat obesity: the browning of white fat. While white fat normally stores calories, brown fat burns them and generates heat in the process. Therefore, efforts to turn white fat into brown fat may help people lose weight.

Erwin Wagner, of the Spanish National Cancer Research Centre in Madrid, and his colleagues found that in mice and patients with cancer-associated cachexia, white fat undergoes significant changes and turns into calorie-burning brown fat. The transformation leads to increased energy consumption and organ wasting.

The team also discovered that inflammation plays an important role in turning white fat into brown fat during cancer-associated cachexia, which suggests a potential therapeutic target. Indeed, anti-inflammatory therapies, including the nonsteroidal anti-inflammatory drug (NSAID) Sulindac, ameliorated the severity of cachexia in mice.

"Our data suggest that inhibition of the browning of white fat represents a promising approach to ameliorate the severity of cachexia in cancer patients," says Dr. Wagner. "In addition, identifying biomarkers of browning at early stages of cancer development could help to predict which patients are going to develop cachexia and are good candidates to benefit from a preventive treatment."

Cell Metabolism, Petruzzelli et al.: "A Switch from White to Brown Fat Increases Energy Expenditure in Cancer-Associated Cachexia."

http://www.bbc.com/news/magazine-28262541

The virus detective who discovered Ebola in 1976

Nearly 40 years ago, a young Belgian scientist travelled to a remote part of the Congolese rainforest - his task was to help find out why so many people were dying from an unknown and terrifying disease.

By Rob Brown BBC World Service

In September 1976, a package containing a shiny, blue thermos flask arrived at the Institute of Tropical Medicine in Antwerp, Belgium. Working in the lab that day was Peter Piot, a 27-year-old scientist and medical school graduate training as a clinical microbiologist.

"It was just a normal flask like any other you would use to keep coffee warm," recalls Piot, now Director of the London School of Hygiene and Tropical Medicine. But this thermos wasn't carrying coffee - inside was an altogether different cargo. Nestled amongst a few melting ice cubes were vials of blood along with a note.

It was from a Belgian doctor based in what was then Zaire, now the Democratic Republic of Congo - his handwritten message explained that the blood was that of a nun, also from Belgium, who had fallen ill with a mysterious illness which he couldn't identify.

This unusual delivery had travelled all the way from Zaire's capital city Kinshasa, on a commercial flight, in one of the passengers' hand luggage.

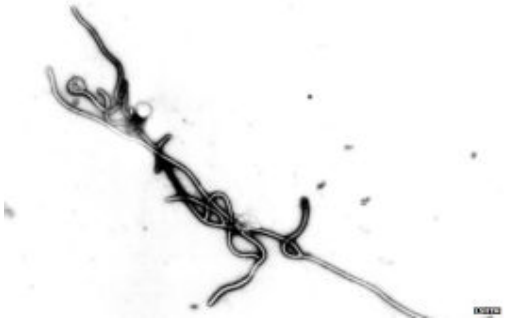
"When we opened the thermos, we saw that one of the vials was broken and blood was mixing with the water from the melted ice," says Piot.

He and his colleagues were unaware just how dangerous that was. As the blood leaked into the icy water so too did a deadly unknown virus.

The samples were treated like numerous others the lab had tested before, but when the scientists placed some of the cells under an electron microscope they saw something they didn't expect.

"We saw a gigantic worm like structure - gigantic by viral standards," says Piot. "It's a very unusual shape for a virus, only one other virus looked like that and that was the Marburg virus."

The Marburg virus was first recognised in 1967 when 31 people became ill with haemorrhagic fever in the cities of Marburg and Frankfurt in Germany and in Belgrade, the capital of Yugoslavia. This Marburg outbreak was associated with laboratory staff who were working with infected monkeys imported from Uganda - seven people died.



Piot knew how serious Marburg could be - but after consulting experts around the world he got confirmation that what he was seeing under the microscope wasn't Marburg - this was something else, something never seen before.

"It's hard to describe but the main emotion I had was one of real, incredible excitement," says Piot. "There was a feeling of being very privileged, that this was a moment of discovery."

News had reached Antwerp that the nun, who was under the care of the doctor in Zaire, had died. The team also learnt that many others were falling ill with this mysterious illness in a remote area in the north of the country - their symptoms included fever, diarrhoea and vomiting followed by bleeding and eventually death.

Two weeks later Piot, who had never been to Africa before, was on a flight to Kinshasa. "It was an overnight flight and I couldn't sleep. I was so excited about seeing Africa for the first time, about investigating this new virus and about stopping the epidemic."

The journey didn't end in Kinshasa - the team had to travel to the centre of the outbreak, a village in the equatorial rainforest, about 1,000km (620 miles) further north. "The personal physician of President Mobutu, the leader of Zaire at that time, arranged a C-130 transport aircraft for us," recalls Piot. They loaded a Landrover, fuel and all the equipment they needed on to the plane.

When the C-130 landed in Bumba, a river port situated on the northernmost point of the Congo River, the fear surrounding the mysterious disease was tangible. Even the pilots didn't want to hang around for long - they kept the airplane's engines running as the team unloaded their kit.

"As they left they shouted 'Adieu,'" says Piot. "In French, people say 'Au Revoir' to say 'See you again', but when they say 'Adieu' - well, that's like saying, 'We'll never see you again.'"

Standing on the tarmac watching the plane leave, facing a deadly unknown virus in an unfamiliar place, some people might have regretted the decision to go there.

"I wasn't scared. The excitement of discovery and wanting to stop the epidemic was driving everything. We heard far more people were dying from the disease than we originally thought and we wanted to get to work," Piot says.

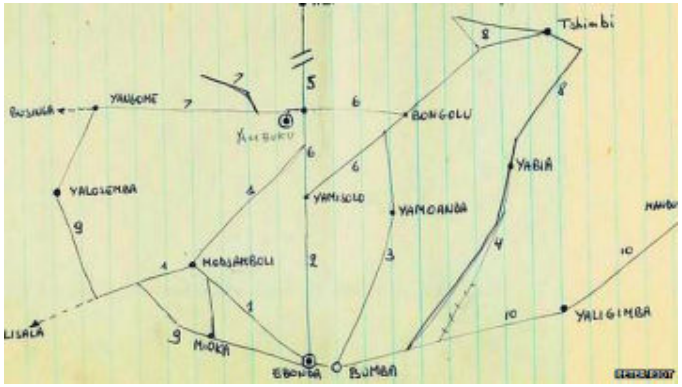
The curiosity and sense of adventure that brought Piot to this point had been ignited many years earlier when he was a young boy growing up in a small rural village in the Flanders region of Belgium.

A museum near Piot's home was dedicated to a local saint who worked with leprosy patients, and it was here that he got his first glimpse into the world of disease and microbiology. "I decided one day to cycle to the museum. The old pictures I saw there of those suffering from leprosy fascinated me," he says. "That sparked my interest in medicine - it gave me a thirst for scientific knowledge, a desire to help people and I hoped it would give me a passport to the world."

It did give Piot a passport to the world. The team's final destination was the village of Yambuku - about 120km (75 miles) from Bumba, where the plane had left them. Yambuku was home to an old Catholic mission - it had a hospital and a school run by a priest and nuns, all of them from Belgium.

"The area was beautiful. The mission was surrounded by lush rainforest and the earth was red - the nature was incredibly rich but the people were so poor," says Piot. "Joseph Conrad called that place 'The Heart of Darkness', but I thought there was a lot of light there." The beauty of Yambuku belied the horror that was unfolding for the people that lived there.

When Piot arrived, the first people he met were a group of nuns and a priest who had retreated to a guesthouse and established their own cordon sanitaire - a barrier used to prevent the spread of disease. There was a sign on the cord, written in the local Lingala language that read, "Please stop, anybody who crosses here may die."



"They had already lost four of their colleagues to the disease," says Piot. "They were praying and waiting for death."

To investigate the spread of the virus the team drew maps and plotted each village they visited

Piot jumped over the cordon and told them that the team would help them and stop the epidemic. "When you are 27, you have all this confidence," he says.

The nuns told the newly arrived scientists what had happened, they spoke about their colleagues and those in the village who had died and how they tried to help as best they could.

The priority was to stop the epidemic, but first the team needed to find out how this virus was moving from person to person - by air, in food, by direct contact or spread by insects. "We had to start asking questions. It was really like a detective story," says Piot.

These were the three questions they asked:

• How did the epidemic evolve? Knowing when each person caught the virus gave clues to what kind of infection this was - from here the story of the virus began to emerge.

• Where did the infected people come from? The team visited all the surrounding villages and mapped out the number of infections - it was clear that the outbreak was closely related to areas served by the local hospital.

• Who gets infected? The team found that more women than men caught the disease and particularly women between 18 and 30 years old - it turned out that many of the women in this age group were pregnant and many had attended an antenatal clinic at the hospital.

The mystery of the virus was beginning to unravel.

The team then discovered that the women who attended the antenatal clinic all received a routine injection. Each morning, just five syringes would be distributed, the needles would be reused and so the virus was spread between the patients.

"That's how we began to figure it out," recalls Piot. "You do it by talking, looking at the statistics and using logical deduction."

The team also noticed that people were getting ill after attending funerals. When someone dies from Ebola, the body is full of the virus - any direct contact, such as washing or preparation of the deceased without protection can be a serious risk.

The next step was to stop the transmission of the virus.

"We systematically went from village to village and if someone was ill they would be put into quarantine," says Piot. "We would also quarantine anyone in direct contact with those infected and we would ensure everyone knew how to correctly bury those who had died from the virus."

The closure of the hospital, the use of quarantine and making sure the community had all the necessary information eventually brought an end to the epidemic - but nearly 300 people died.

Piot and his colleagues had learned a lot about the virus during three months in Yambuku, but it still lacked a name. "We didn't want to name it after the village, Yambuku, because it's so stigmatising. You don't want to be associated with that," says Piot.

The team decided to name the virus after a river. They had a map of Zaire, although not a very detailed one, and the closest river they could see was the Ebola River. From that point on, the virus that arrived in a flask in Antwerp all those months earlier would be known as the Ebola virus.

In February 2014, Piot returned to Yambuku for only the second time since 1976, to mark his 65th birthday. He met Sukato Mandzomba, one of the few who caught the virus in 1976 and survived. "It was fantastic to meet him again, it was a very moving moment," says Piot.

Back then, Mandzomba was a nurse in the local hospital and could speak French so the pair had managed to build up a rapport. "He's still living in Yambuku and still working in the hospital - he's now running the lab there and it's impeccable. I was really impressed," Piot says.

It's 38 years since that initial outbreak and the world is now experiencing its worst Ebola epidemic ever. So far more than 600 people have died in the West African countries of Guinea, Liberia and Sierra Leone. The current situation has been called unprecedented, the spread of the disease across three countries making it more complicated to deal with than ever before.

In the absence of any vaccine or cure, the advice for this outbreak is much the same as it was in the 1970s. "Soap, gloves, isolating patients, not reusing needles and quarantining the contacts of those who are ill - in theory it should be very easy to contain Ebola," says Piot.

In practice though, other factors can make fighting an Ebola outbreak a difficult task. People who become ill and their families may be stigmatised by the community - resulting in a reluctance to come forward for help. Cultural beliefs lead some to think the disease is caused by witchcraft, while others are hostile towards health workers.

"We shouldn't forget that this is a disease of poverty, of dysfunctional health systems - and of distrust," says Piot. For this reason, information, communication and involvement of community leaders are as important as the classical medical approach, he argues.

Ebola changed Piot's life - following the discovery of the virus, he went on to research the Aids epidemic in Africa and became the founding executive director of the UNAIDS organisation. "It led me to do things I thought only happened in books. It gave me a mission in life to work on health in developing countries," he says. "It was not only the discovery of a virus but also of myself."

http://nyti.ms/UjYQAl

A Vasectomy May Increase Prostate Cancer Risk

Men with vasectomies may be at an increased risk for the most lethal form of prostate cancer, researchers have found. But aggressive cancer nonetheless remains rare in these patients.

By NICHOLAS BAKALAR

Earlier studies had hinted at a connection between vasectomies and prostate cancer. Many experts have dismissed the idea of a link: Men who have vasectomies may receive more medical attention, they said, and therefore may be more likely to receive a diagnosis.

The new study, published this month in The Journal of Clinical Oncology, sought to account for that possibility and for other variables.

Researchers at Harvard reviewed data on 49,405 men ages 40 to 75, of whom 12,321 had had vasectomies. They found 6,023 cases of prostate cancer among those men from 1986 to 2010.

The researchers found no association between a vasectomy and low-grade cancers. But men who had had a vasectomy were about 20 percent more likely to develop lethal prostate cancer, compared with those who had not.

The incidence was 19 in 1,000 cases, compared with 16 in 1,000, over the 24-year period.

The reason for the increase is unclear, but some experts have speculated that immunological changes, abnormal cell growth or hormonal imbalances following a vasectomy may also affect prostate cancer risk.

Dr. James M. McKiernan, interim chairman of the department of urology at Columbia, said the lack of a clear causal mechanism was a drawback of the new research.

“If someone asked for a vasectomy, I would have to tell them that there is this new data in this regard, but it’s not enough for me to change the standard of care,” he said. “I would not say that you should avoid vasectomy.”

The lead author, Lorelei A. Mucci, an associate professor of epidemiology at the Harvard School of Public Health, emphasized that a vasectomy does not increase the risk for prostate cancer over all.

“We’re really seeing the association only for advanced state and lethal cancers,” she said.

She agreed with Dr. McKiernan that the new data are not a reason to avoid a vasectomy.

“Having a vasectomy is a highly personal decision that men should make with their families and discuss with their physicians,” she said. “This is one piece of evidence that should be considered.”

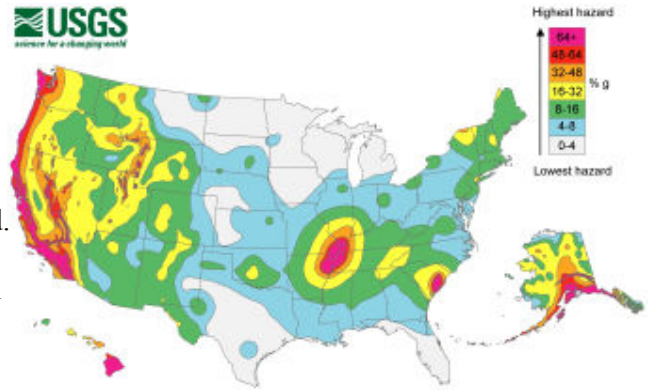
http://bit.ly/UjZtK7

USGS Updates Earthquake Map, 16 States at High Risk

Parts of 42 states are at risk of earthquakes during the next 50 years, according to a new report from the U.S. Geological Survey.

Jul 17, 2014 04:50 PM ET // by Laura Geggel, LiveScience

The report includes updated maps that show geologists' predictions of where and how often future earthquakes may occur, and how strongly they may shake the ground. Many of the at-risk states are in the country's western half, but the map also highlights hotspots in the Midwest and Southeast.



The 2014 USGS National Seismic Hazard Map displays the intensity of potential ground shaking from an earthquake in 50 years (which is the typical lifetime of a building).

There are 16 states that have regions labeled as being at high risk for seismic activity, because they have histories of earthquakes measuring a magnitude of 6.0 or greater: Alaska, Arkansas, California, Hawaii, Idaho, Illinois, Kentucky, Missouri, Montana, Nevada, Oregon, South Carolina, Tennessee, Utah, Washington and Wyoming. [Image Gallery: This Millennium's Destructive Earthquakes]

In making the new maps, geologists considered data from earthquakes that have struck since the maps were last updated, in 2008. For instance, the 5.8 Virginia temblor that struck in 2011 showed that seismic activity can happen in the Northeast. Seismic risk has also increased near Charleston, South Carolina, due to recent earthquakes in the area.

The map gave the Big Apple a slight reprieve. Geologists downgraded the risk that slow-moving waves from an earthquake would hit near New York City. Slow shaking is more likely to damage tall buildings than fast shaking, which is more likely to affect smaller structures.

In California, new information about faults in San Jose, Vallejo and San Diego have raised earthquake risks there. In contrast, the cities of Irvine, Santa Barbara and Oakland have reduced risks, thanks to new insights on the faults in those areas.

The new USGS maps are part of the National Earthquake Hazards Reduction Program, a partnership of four federal agencies created by Congress to reduce the risks to life and property caused by earthquakes. In addition to the USGS, the other

agencies include the Federal Emergency Management Agency, the National Institute of Standards and Technology and the National Science Foundation.
The information in the report could guide new building codes, geologists at the USGS said in a statement. The maps will also help set insurance rates and emergency preparedness plans. Private homeowners can consult them when deciding whether to reinforce their homes to make them more earthquake-safe.
"The standards for seismic safety in building codes are directly based upon USGS assessments of potential ground shaking from earthquakes, and have been for years," said Jim Harris, a member and former chairman of the Provisions Update Committee of the Building Seismic Safety Council.
Causes of Pakistan's New Island Revealed
As geologists continue to study earthquake hazards, they plan to incorporate risks from man-made activities, such as the disposal of wastewater into deep wells, they said in the statement.
"The cost of inaction in planning for future earthquakes and other natural disasters can be very high, as demonstrated by several recent damaging events across the globe," said Mark Petersen, chief of the USGS National Seismic Hazard Mapping Project. "It is important to understand the threat you face from earthquakes at home and the hazards for the places you might visit."

http://www.eurekalert.org/pub_releases/2014-07/uog-cpf071814.php

Consuming probiotics for a month helps diminish fat accumulation in the liver, new study says

Scientists at the University of Granada have made important strides in the fight against the Non-Alcoholic Fatty Liver Disease, which is closely related to obesity and diabetes

Spanish scientists have demonstrated through an experiment on obese rats that the consumption of probiotics during thirty days helps diminish the accumulation of fat in the liver. This new finding, published today by the journal PLOS ONE, is a great step forward on the fight agains the Non-Alcolohic Fatty Liver Disease (NAFLD), which is closely related to obesity and diabetes.
Researchers from the 'Nutrition Biochemistry: Theurapetic Applications' group (CTS-461) and the José Mataix Institute for Nutrition and Food Technology at the University of Granada have demonstrated that the administration of three probiotic strains diminishes the accumulation of fat in the liver of obese rats.
The accumulation of fat in the liver is called steatosis and it constitutes the first stage in the NAFLD disease, which is closely related to obesity and diabetes. Given that the prevalence of these two pathologies does not cease to increase, NAFLD has also become a health problem that affects millions of people throughout the world.

Living or dead microorganisms

Probiotics are microorganisms (bacteria or yeasts) with healthy effects upon individuals that consume them in adequate doses. They were traditionally considered to be living microorganisms, but the concept was widened since some dead microorganisms, or even their components, can display probiotic properties.
University of Granada researchers worked with three strains which are custodied at the Collection Nationale de Cultures de Microorganismes (CNCM) of the Pasteur Institute: Lactobacillus paracasei CNCM I-4034, Bifidobacterium breve CNCM I-4035 and Lactobacillus rhamnosus CNCM I-4036. During their first experiment, conducted on healthy volunteers, researchers demonstrated that all three of them are perfectly tolerable and safe for human consumption.
In this current study, the strains were administered during thirty days in the diet of Zucker rats. These rats develop obesity due to a mutation in the gene that codifies the receptor or leptine, a homone that transmits a sensation of satiety to the organism. Zucker rats are among the best characterized genetic models.
In their article, the authors describe that the administration of probiotics led to an accumulation of lipids (most of them triacylglycerides) in the liver which was significantly lower than that occurring in rats fed with a placebo.
"This new finding went hand in hand with lower values in proinflamatory molecules (tumor-a necrosis factor, interleukin 6 and liposacarid) in the serum of rats fed with probiotics. These effects were not observed in those
According to these researchers, this liver disease will not be cured with probiotics, but these microorganisms can certainly be used as support therapy in joint use with other treatment.
This study has been financed by the private company HERO SPAIN S.A.

http://scitechdaily.com/astronomers-discover-evidence-giant-planets-form/

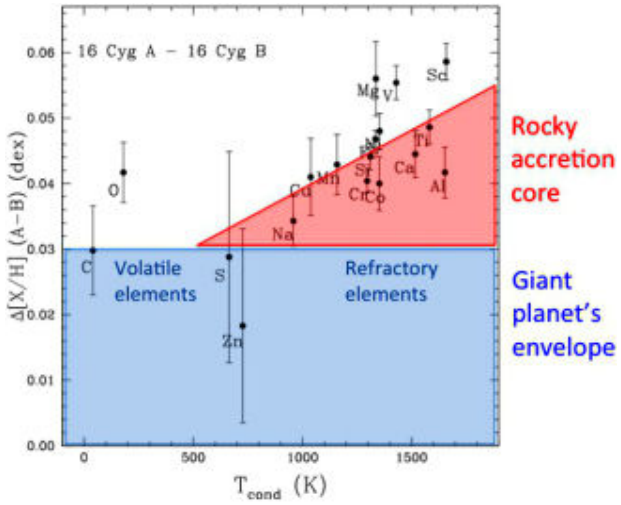
Astronomers Discover Evidence of How Giant Planets Form

Evidence of How Giant Planets Like Jupiter Form

One of the main models to form giant planets is called “core accretion”. In this scenario, a rocky core forms first by aggregation of solid particles until it reaches a few Earth masses when it becomes massive enough to accrete a gaseous envelope. For the first time, astronomers have detected evidence of this rocky core, the first step in the formation of a giant planet like our own Jupiter.
The astronomers used the Canada-France-Hawaii Telescope (CFHT) to analyze the starlight of the binary stars 16 Cygni A and 16 Cygni B. The system is a perfect laboratory to study the formation of giant planets because the stars were born together and are therefore very similar, and both resemble the Sun. However, observations during the last decades show that only one of the two stars, 16 Cygni B, hosts a giant planet which is about 2.4 times as massive as Jupiter. By

decomposing the light from the two stars into their basic components and looking at the difference between the two stars, the astronomers were able to detect signatures left from the planet formation process on 16 Cygni B.

The fingerprints detected by the astronomers are twofold. First, they found that the star 16 Cygni A is enhanced in all chemical elements relative to 16 Cygni B. This means that 16 Cygni B, the star that hosts a giant planet, is metal deficient. As both stars were born from the same natal cloud, they should have exactly the same chemical composition. However, planets and stars form at about the same time, hence the metals that are missing in 16 Cygni B (relative to 16 Cygni A) were probably removed from its protoplanetary disk to form its giant planet, so that the remaining material that was falling into 16 Cygni B in the final phases of its formation was deficient in those metals.



Using Canada-France-Hawaii Telescope observations of 16 Cygni, astronomers discovered evidence of how giant planets like Jupiter form. **Canada-France-Hawaii Telescope**

The second fingerprint is that on top of an overall deficiency of all analyzed elements in 16 Cygni B, this star has a systematic deficiency in the refractory elements such as iron, aluminum, nickel, magnesium, scandium, and silicon. This is a remarkable discovery because the rocky core of a giant planet is expected to be rich in refractory elements. The formation of the rocky core seems to rob refractory material from the proto-planetary disk, so that the star 16 Cygni B ended up with a lower amount of refractories. This deficiency in the refractory elements can be explained by the formation of a rocky core with a mass of about 1.5 – 6 Earth masses, which is similar to the estimate of Jupiter's core.

"Our results show that the formation of giant planets, as well as terrestrial planets like our own Earth, leaves subtle signatures in stellar atmospheres", says Marcelo Tucci Maia (Universidade de São Paulo), the lead author of the paper. "It is fascinating that our differential technique can measure these subtle differences in chemical abundances; we achieve a precision that was unthinkable until now", adds team member Jorge Meléndez (Universidade de São Paulo). Ivan Ramírez (University of Texas) concludes: "16 Cyg is a remarkable system, but certainly not unique. It is special because it is nearby; however, there are many other binary stars with twin components on which this experiment could be performed. This could help us find planet-host stars in binaries in a much more straightforward manner compared to all other planet-finding techniques we have available today."

The team is composed of the PhD student Marcelo Tucci Maia, Prof. Dr. Jorge Meléndez (Universidade de São Paulo) and Dr. Iván Ramírez (University of Texas at Austin). This research will appear in the paper "High precision abundances in the 16 Cyg binary system: a signature of the rocky core in the giant planet", by M. Tucci Maia, J. Meléndez and I. Ramírez, in the Astrophysical Journal Letters.

Publication: Marcelo Tucci Maia, et al., "High precision abundances in the 16 Cyg binary system: a signature of the rocky core in the giant planet," 2014, ApJ, 790, L25; doi:10.1088/2041-8205/790/2/L25

PDF Copy of the Study: High precision abundances in the 16 Cyg binary system: a signature of the rocky core in the giant planet Source: Canada-France-Hawaii Telescope

http://bit.ly/1rfbnlJ

Dogs Were a Prehistoric Woman's Best Friend, Too

Women in a forested area 8,000 years ago were not only in close contact with dogs, but they were also eating the same food the dogs ate and suffering from one or more illnesses the dogs had.

Jul 18, 2014 11:40 AM ET // by Jennifer Viegas

A new study published in the Journal of Archaeological Science reveals that dogs weren't just prehistoric man's best friend. At least some women during the Early Neolithic period, and likely their children too, also lived very canine-centric lives.

"It is possible that females were more involved in caring for the dogs -- possibly more often the ones who fed them, organized living quarters for them, and cleaned up after them," lead author Andrea Waters-Rist told Discovery News.

Waters-Rist, a Leiden University archaeologist, added: "One can envision a camp in the boreal forest with people and dogs living side by side, and dogs being used in many everyday tasks, with dogs being as important to the group as they are to many people today."

Waters-Rist and her team analyzed remains from two 8,000-year-old cemeteries near Lake Baikal, Siberia. The researchers determined that women from both cemeteries had, at some point in their lives, suffered from a parasitic infection called hydatid disease, or echinococcosis. "It's been recognized for centuries - mentioned in ancient Greco-Roman and Jewish texts - and in modern times it is a relatively common infection in Northern Eurasian reindeer herders who use dogs to help with herding, and in indigenous Alaskan groups reliant on sled dogs," Waters-Rist explained.

Cysts from the parasites, which look like calcified, egg-like objects, were found in the abdomens of the women. The researchers suspect that the cysts were probably growing in the liver of each person.

Echinococcosis in humans almost always occurs as a result of direct contact with dogs. People can also get it after ingesting food or water that has been contaminated by dog feces that contain the parasitic eggs. "As these cysts take many years to form and may not have always preserved," Waters-Rist said, "it suggests that many more people were likely infected. So it is a piece of the puzzle in our reconstruction of the importance of dogs in the lives of ancient peoples."

Robert Losey, a University of Alberta anthropologist, told Discovery News that he previously documented "intentional burial of dogs and wolves" at the same Siberian cemeteries. "These dogs were much like modern Siberian huskies," Losey said. "Upon their deaths, they were carefully placed in graves just like the human dead."

Some dogs in the Siberian cemeteries were buried with implements such as spoons and stone knives. One dog was even interred wearing a necklace.

The people living at the site appear to have been hunter-gatherers who fished for both their own supper and that of their dogs. The scientists know the dogs and people were eating similar diets based on chemical analysis of their bones.

Dogs and humans at other locations worldwide could have been equally close during prehistoric times, but proof of such connections can be harder to find where populations were low. Losey explained that dog burials tend to be more common finds in areas where diets were rich in aquatic foods, because such spots generally had denser human populations.

The Siberian dog burials strongly suggest that the canines were valued for more than just their hunting, guarding, and other probable work efforts.

"Altogether, several lines of evidence - the intentional burial of dogs in cemeteries, their similar diets, and now a shared disease - demonstrate that these ancient Siberian foragers likely had close physical and emotional ties with their domesticated dogs," Waters-Rist said.

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Changing Antarctic winds create new sea level threat

New research shows projected changes in the winds circling the Antarctic may accelerate global sea level rise significantly more than previously estimated.

Changes to Antarctic winds have already been linked to southern Australia's drying climate but now it appears they may also have a profound impact on warming ocean temperatures under the ice shelves along the coastline of West and East Antarctica.

"When we included projected Antarctic wind shifts in a detailed global ocean model, we found water up to 4°C warmer than current temperatures rose up to meet the base of the Antarctic ice shelves," says lead author Dr Paul Spence of the UNSW Climate Change Research Centre and ARC Centre of Excellence for Climate System Science (ARCCSS).

"The sub-surface warming revealed in this research is on average twice as large as previously estimated, with almost all of coastal Antarctica affected. This relatively warm water provides a huge reservoir of melt potential right near the grounding lines of ice shelves around Antarctica. It could lead to a massive increase in the rate of ice sheet melt, with direct consequences for global sea level rise."

The study by Dr Spence and colleagues from Australian National University and UNSW, is published in the journal Geophysical Research Letters.

Prior to this research, most sea level rise studies focused on the rate of ice shelf melting due to the general warming of the ocean over large areas.

Using super computers at Australia's National Computational Infrastructure (NCI) Facility the researchers were able to examine the impacts of changing winds on currents down to 700m around the coastline in greater detail than ever before.

Previous global models did not adequately capture these currents and the structure of water temperatures at these depths. Unexpectedly, this more detailed approach suggests changes in Antarctic coastal winds due to climate change and their impact on coastal currents could be even more important on melting of the ice shelves than the broader warming of the ocean.

"When we first saw the results it was quite a shock. It was one of the few cases where I hoped the science was wrong," says Dr Spence. "But the processes at play are quite simple, and well-resolved by the ocean model, so this has important implications for climate and sea-level projections. What is particularly concerning is how easy it is for climate change to increase the water temperatures beside Antarctic ice sheets."

The research may help to explain a number of sudden and unexplained increases in global sea levels that occurred in the geological past.

"It is very plausible that the mechanism revealed by this research will push parts of the West Antarctic Ice Sheet beyond a point of no return," says Dr Axel Timmerman, Professor of Oceanography at University of Hawaii and an IPCC lead author who has seen the paper. "This work suggests the Antarctic ice sheets may be less stable to future climate change than previously assumed."

Recent estimates suggest the West Antarctic Ice Sheet alone could contribute 3.3 metres to long-term global sea level rise. With both West and East Antarctica affected by the change in currents, abrupt rises in sea level in the future become more likely.

According to another of the paper's authors, Dr Nicolas Jourdain from ARCCSS, the mechanism that leads to rapid melting may be having an impact on the Western Antarctic right now. It may help explain why the melt rate of some of the glaciers in that region are accelerating more than scientists expected.

"Our research indicates that as global warming continues, parts of East Antarctica will also be affected by these wind-induced changes in ocean currents and temperatures," says Dr Jourdain. "Dramatic rises in sea level are almost inevitable if we continue to emit greenhouse gases at the current rate."

http://nyti.ms/1n5u8WW

Pathogen Mishaps Rise as Regulators Stay Clear

The recently documented mistakes at federal laboratories involving anthrax, flu and smallpox have incited public outrage at the government's handling of dangerous pathogens.

By DENISE GRADYJULY 19, 2014

But the episodes were just a tiny fraction of the hundreds that have occurred in recent years across a sprawling web of academic, commercial and government labs that operate without clear national standards or oversight, federal reports show.

Spurred by the anthrax attacks in the United States in 2001, an increase in "high-level containment" labs set up to work with risky microbes has raised the number to about 1,500 from a little more than 400 in 2004, according to the Government Accountability Office.

Yet there has never been a national plan for how many of them are needed, or how they should be built and operated. The more of these labs there are, the G.A.O. warned Congress last week, the greater the chances of dangerous blunders or sabotage, especially in a field where oversight is "fragmented and largely self-policing."

As the labs have multiplied, so have mishaps. According to a 2012 article by researchers from the Centers for Disease Control and Prevention, the number of reported accidents involving microbes that can cause severe illnesses grew rapidly - from just 16 in 2004 to 128 in 2008 and 269 in 2010, the last year reported. Many of the accidents involved leaks, spills or other releases of infectious material inside the laboratories, potentially infecting workers and often requiring extensive decontamination.

Another report, by the Department of Homeland Security in 2008, provided a rare glimpse into the types of accidents that have occurred at high-level labs around the country, often at universities.

Lab workers at different sites accidentally jabbed themselves with needles contaminated by anthrax or West Nile virus. An air-cleaning system meant to filter dangerous microbes out of a lab failed, but no one knew because the alarms had been turned off. A batch of West Nile virus, improperly packed in dry ice, burst open at a Federal Express shipping center. Mice infected with bubonic plague or Q fever went missing. And workers exposed to Q fever, brucellosis or tuberculosis did not realize it until they either became ill or blood tests detected the exposure.

The good news is that relatively few lab workers have become ill from accidental exposures: only 11 from 2004 to 2010, according to the C.D.C. report. None died, and none infected other people.

Richard H. Ebright, a molecular biologist and laboratory director from Rutgers University, said he had "no confidence" in the safety of the many labs that have sprung up since 2001. He suggested there was a culture of complacency at some of them, as well as hubris among some researchers who believe they do not need oversight or management.

The most recent revelations have underscored potentially serious lapses at the government's premier institutions. In June, dozens of C.D.C. employees may have been exposed to live anthrax. In another case disclosed this month, a C.D.C. lab accidentally contaminated a relatively benign flu sample with a dangerous H5N1 bird flu strain that has killed 386 people since 2003 - and then shipped it to a lab at the Department of Agriculture. In yet another episode this month, vials of smallpox and other infectious agents were discovered in a government laboratory on the campus of the National Institutes of Health after being stored and apparently forgotten about 50 years ago.

Six or seven government agencies were involved in the growth spurt of labs across the country focusing on dangerous pathogens, with no overall strategic plan, according to Nancy Kingsbury, the managing director of applied research and methods at the G.A.O., who testified last week before a House Energy and Commerce subcommittee.

For years, the accountability office has warned that there was no one federal agency overseeing all the laboratories. In fact, it has said, the real number of high-level labs is not even known because the only ones required to register with the government are those handling "select agents" - microbes that can cause serious illness in people, animals or crops. Other high-level labs handle pathogens that may be dangerous but are not listed as select agents, the office said, adding that not much is known about them.

Both Dr. Kingsbury and Dr. Ebright, who also testified before Congress last week, said there should be one independent national agency to oversee work with select agents. Dr. Ebright said that many of the labs should be shut down, and that no more than 25 to 50 were needed nationwide.

Dr. Thomas Frieden, director of the C.D.C., has also said the number of high-level labs, dangerous pathogens and people with access to them should be reduced to

"the absolute minimum necessary." Testifying on Wednesday, he said the more such labs there were, the greater the risk of accidents.

The recent mistakes at federal labs have opened the door to a much broader criticism of the risks posed by the expanding research into risky pathogens, especially the efforts to create dangerous strains of flu not currently circulating, or to manipulate already deadly flu viruses to make them more contagious.

Researchers who conduct that work, sometimes labeled "gain of function" research, say its purpose is, in part, to help scientists recognize changes in natural viruses that may help predict which ones are becoming more deadly or more contagious. But it provoked a public outcry in 2011 because of fears that a lab accident might release the altered viruses and start a lethal pandemic. The studies were halted for about a year while governments and research organizations tried to develop safety rules, but the work has since resumed in several laboratories.

Scientists who oppose the research issued a statement last week urging that the experiments be curtailed until their risks and benefits can be reconsidered.

They expressed particular concern about the possibility of accidents involving newly created strains of highly transmissible, dangerous viruses, saying they could cause outbreaks that would be difficult or impossible to control. Once transmission of a new flu strain becomes established, the statement said, it can infect a quarter of the world's population within two years.

One of the signers, Marc Lipsitch, a professor of epidemiology and director of the Center for Communicable Disease Dynamics at the Harvard School of Public Health, said, "These experiments knowingly put large numbers of human lives at risk."

Then on Wednesday, the European Center for Disease Prevention and Control, funded by the European Union, also expressed concerns about the flu research, stating, "Recent incidents remind us that laboratory accidents and laboratory escapes can happen with dangerous pathogens, even if the highest security standards are applied."

Focusing specifically on recent work at the University of Wisconsin by Yoshihiro Kawaoka - who used genetic engineering to create a bird-flu virus similar to the one that killed millions of people in 1918 - the group said accidents would pose a risk to lab workers and the public. Dr. Kawaoka said in an email message that the accidents at the C.D.C. were "very troubling." Even so, he said, the flu studies have to continue because "these pathogens exist in nature, and they could be used as bioweapons."

He said that at his lab, "we continue to take every precaution to ensure risks are as low as possible." And he added that to be approved for the research, his lab had to submit to unannounced inspections, and had one in the first half of July.

Ron Fouchier, a virologist who does similar work on flu viruses at the Erasmus Medical Center in the Netherlands, said the recent lab errors had no bearing on his work.

"Just because there were incidents in one institute does not mean others have the same problem," Dr. Fouchier said by email. He said the fact that no one had contracted anthrax from the accident at the C.D.C. proved that adequate safety measures were taken. "One cannot bring down the number of incidents in labs to zero, but one can reduce the risks to negligible," he wrote.

Dr. Fouchier dismissed as irrelevant the finding of forgotten vials of smallpox at the National Institutes of Health.

"Box found," he wrote. "Contained. Destroyed. Done."

http://www.eurekalert.org/pub_releases/2014-07/bidm-nfs071514.php

New findings show strikingly early seeding of HIV viral reservoir

Discovery presents new challenges for HIV eradication efforts

BOSTON – The most critical barrier for curing HIV-1 infection is the presence of the viral reservoir, the cells in which the HIV virus can lie dormant for many years and avoid elimination by antiretroviral drugs. Very little has been known about when and where the viral reservoir is established during acute HIV-1 infection, or the extent to which it is susceptible to early antiretroviral therapy (ART).

Now a research team led by investigators at Beth Israel Deaconess Medical Center (BIDMC) in collaboration with the U.S. Military HIV Research Program has demonstrated that the viral reservoir is established strikingly early after intrarectal simian immunodeficiency virus (SIV) infection of rhesus monkeys and before detectable viremia. The findings appear online in the journal Nature.

"Our data show that in this animal model, the viral reservoir was seeded substantially earlier after infection than was previously recognized," explains senior author Dan H. Barouch, MD, PhD, Director of the Center for Virology and Vaccine Research at BIDMC and steering committee member of the Ragon Institute of MGH, MIT and Harvard. "We found that the reservoir was established in tissues during the first few days of infection, before the virus was even detected in the blood."

This discovery coincides with the recently reported news of the HIV resurgence in the "Mississippi baby," who was believed to have been cured by early administration of ART. "The unfortunate news of the virus rebounding in this child further emphasizes the need to understand the early and refractory viral reservoir that is established very quickly following HIV infection in humans," adds Barouch, a Professor of Medicine at Harvard Medical School.

In this new study, the scientific team initiated suppressive ART in groups of monkeys on days 3, 7, 10 and 14 after intrarectal SIV infection. Animals treated on

day 3 following infection showed no evidence of virus in the blood and did not generate any SIV-specific immune responses. Nevertheless, after six months of suppressive ART, all of the animals in the study exhibited viral resurgence when treatment was stopped.

While early initiation of ART did result in a delay in the time to viral rebound (the time it takes for virus replication to be observed in the blood following cessation of ART) as compared with later treatment, the inability to eradicate the viral reservoir with very early initiation of ART suggests that additional strategies will be needed to cure HIV infection.

"The strikingly early seeding of the viral reservoir within the first few days of infection is sobering and presents new challenges to HIV-1 eradication efforts," the authors write. "Taken together, our data suggest that extremely early initiation of ART, extended ART duration, and probably additional interventions that activate the viral reservoir will be required for HIV-1 eradication."

Study coauthors include first author James Whitney of BIDMC and the Ragon Institute of MGH, MIT and Harvard; BIDMC investigators Srisowmya Sanisetty, Pablo Penaloz-MacMaster, Jinyan Liu, Mayuri Shetty, Lily Parenteau, Crystal Cabral, Jennifers Shields, Stephen Blackmore, Jeffrey Y. Smith, Amanda L. Brinkman, Lauren E. Peter, Sheeba I. Mathew, Kaitlin M. Smith, Erica N. Borducchi; Aliso L. Hill and Daniel I. S. Rosenbloom of Harvard University; Mark G. Lewis of Bioqual, Rockville, MD; Jillian Hattersley, Bei Li, Joseph Hesselgesser, Romas Geleziunas of Gileas Sciences, Foster City, CA; and Merlin L. Robb, Jerome H. Kim and Nelson L. Michael of the Walter Reed Army Institute of Research.

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http://www.eurekalert.org/pub_releases/2014-07/s-ssd071814.php

Singapore scientists discover genetic cause of common breast tumours in women

Multi-disciplinary research team discovers that a gene known as MED12 is altered in nearly 60 percent of fibroadenomas

Singapore - A multi-disciplinary team of scientists from the National Cancer Centre Singapore, Duke-NUS Graduate Medical School Singapore, and Singapore General Hospital have made a seminal breakthrough in understanding the molecular basis of fibroadenoma, one of the most common breast tumours diagnosed in women. The team, led by Professors Teh Bin Tean, Patrick Tan, Tan Puay Hoon and Steve Rozen, used advanced DNA sequencing technologies to identify a critical gene called MED12 that was repeatedly disrupted in nearly 60% of fibroadenoma cases. Their findings have been published in the top-ranked journal Nature Genetics.

Fibroadenomas are the most common benign breast tumours in women of reproductive age, affecting thousands of women in Singapore each year. Worldwide, it is estimated that millions of women are diagnosed with fibroadenoma annually. Frequently discovered in clinical workups for breast cancer diagnosis and during routine breast cancer screening, clinicians often face of challenge of distinguishing fibroadenomas from breast cancer.

To facilitate this diagnostic question, the team embarked on a study to identify if there are any genetic abnormalities in fibroadenomas that may be used to differentiate them. By analysing all the protein-coding genes in a panel of fibroadenomas from Singapore patients, the team identified frequent mutations in a gene called MED12 in a remarkable 60% of fibroadenomas. Prof Tan Puay Hoon said, "It is amazing that these common breast tumours can be caused by such a precise disruption in a single gene. Our findings show that even common diseases can have a very exact genetic basis. Importantly, now that we know the cause of fibroadenoma, this research can have many potential applications."

Prof Tan added, "For example, measuring the MED12 gene in breast lumps may help clinicians to distinguish fibroadenomas from other types of breast cancer. Drugs targeting the MED12 pathway may also be useful in patients with multiple and recurrent fibroadenomas as this could help patients avoid surgery and relieve anxiety."

The team's findings have also deepened the conceptual understanding of how tumours can develop. Like most breast tumours including breast cancers, fibroadenomas consist of a mixed population of different cell types, called epithelial cells and stromal cells. However, unlike breast cancers where the genetic abnormalities arise from the epithelial cells, the scientists, using a technique called laser capture microdissection (LCM), showed that the pivotal MED12 mutations in fibroadenomas are found in the stromal cells.

Assoc Prof Steve Rozen said, "Stromal cells function to provide a supportive tissue around organs, and in breast cancers, are typically thought of as uninvolved or at least secondary bystanders in tumour formation. Our study shows that far from that, fibroadenomas and possibly other tumours may actually arise from genetic lesions in stromal cells. Targeting such stromal cells may be an important avenue for therapy in the future."

Reflecting its importance, the study also sheds light on the cause of uterine fibroids, another common benign tumour in women where similar MED12 mutations have been observed. Prof Patrick Tan said, "Combined with our data, the fact that MED12 mutations are shared, highly frequent, and specific to fibroadenomas and uterine fibroids strongly attests to a role for abnormal responses to female hormones in the birth of these tumours."

The scientists are already planning further studies to explore this possibility by investigating the role of MED12 in other categories of breast tumours.

The study also involved investigators from the Cancer Science Institute of Singapore, Genome Institute of Singapore, A*STAR, and National University Hospital. According to Prof Teh Bin Tean, "Our study's success was only possible due to a multi-institutional, multi-disciplinary collaboration centred on the concept of team science. The group, called BRGO (Breast Research Group at Outram), leverages on the diverse expertise of scientists and clinicians coming from fields such as molecular biology, bioinformatics, pathology, breast surgery and oncology."

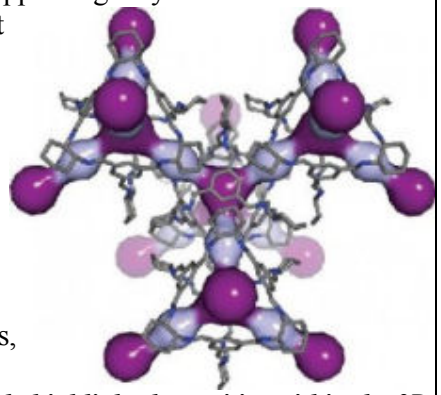
Funding for this work was provided by the Singapore National Medical Research Council, the Singapore Millennium Foundation, the Lee Foundation, the Tanoto Foundation, the National Cancer Centre Singapore's NCC Research Fund, the Duke-NUS Graduate Medical School, the Cancer Science Institute, Singapore and the Verdant Foundation, Hong Kong.

http://www.eurekalert.org/pub_releases/2014-07/dnnl-ang071714.php

A noble gas cage

New material traps gases from nuclear fuel better and uses less energy than currently available options

Richland, Wash. -- When nuclear fuel gets recycled, the process releases radioactive krypton and xenon gases. Naturally occurring uranium in rock contaminates basements with the related gas radon. A new porous material called CC3 effectively traps these gases, and research appearing July 20 in Nature Materials shows how: by breathing enough to let the gases in but not out.



In this computer simulation, light and dark purple highlight the cavities within the 3D pore structure of CC3. **Nature Materials 2014**

The CC3 material could be helpful in removing unwanted or hazardous radioactive elements from nuclear fuel or air in buildings and also in recycling useful elements from the nuclear fuel cycle. CC3 is much more selective in trapping these gases compared to other experimental materials. Also, CC3 will likely use less energy to recover elements than conventional treatments, according to the authors.

The team made up of scientists at the University of Liverpool in the U.K., the Department of Energy's Pacific Northwest National Laboratory, Newcastle University in the U.K., and Aix-Marseille Universite in France performed simulations and laboratory experiments to determine how -- and how well -- CC3 might separate these gases from exhaust or waste.

"Xenon, krypton and radon are noble gases, which are chemically inert. That makes it difficult to find materials that can trap them," said coauthor Praveen Thallapally of PNNL. "So we were happily surprised at how easily CC3 removed them from the gas stream."

Noble gases are rare in the atmosphere but some such as radon come in radioactive forms and can contribute to cancer. Others such as xenon are useful industrial gases in commercial lighting, medical imaging and anesthesia.

The conventional way to remove xenon from the air or recover it from nuclear fuel involves cooling the air far below where water freezes. Such cryogenic separations are energy intensive and expensive. Researchers have been exploring materials called metal-organic frameworks, also known as MOFs, that could potentially trap xenon and krypton without having to use cryogenics. Although a leading MOF could remove xenon at very low concentrations and at ambient temperatures admirably, researchers wanted to find a material that performed better.

Thallapally's collaborator Andrew Cooper at the University of Liverpool and others had been researching materials called porous organic cages, whose molecular structures are made up of repeating units that form 3-D cages. Cages built from a molecule called CC3 are the right size to hold about three atoms of xenon, krypton or radon.

To test whether CC3 might be useful here, the team simulated on a computer CC3 interacting with atoms of xenon and other noble gases. The molecular structure of CC3 naturally expands and contracts. The researchers found this breathing created a hole in the cage that grew to 4.5 angstroms wide and shrunk to 3.6 angstroms. One atom of xenon is 4.1 angstroms wide, suggesting it could fit within the window if the cage opens long enough. (Krypton and radon are 3.69 angstroms and 4.17 angstroms wide, respectively, and it takes 10 million angstroms to span a millimeter.)

The computer simulations revealed that CC3 opens its windows big enough for xenon about 7 percent of the time, but that is enough for xenon to hop in. In addition, xenon has a higher likelihood of hopping in than hopping out, essentially trapping the noble gas inside.

The team then tested how well CC3 could pull low concentrations of xenon and krypton out of air, a mix of gases that included oxygen, argon, carbon dioxide and nitrogen. With xenon at 400 parts per million and krypton at 40 parts per million, the researchers sent the mix through a sample of CC3 and measured how long it took for the gases to come out the other side.

Oxygen, nitrogen, argon and carbon dioxide -- abundant components of air -- traveled through the CC3 and continued to be measured for the experiment's full 45 minute span. Xenon however stayed within the CC3 for 15 minutes, showing that CC3 could separate xenon from air.

In addition, CC3 trapped twice as much xenon as the leading MOF material. It also caught xenon 20 times more often than it caught krypton, a characteristic known as selectivity. The leading MOF only preferred xenon 7 times as much. These experiments indicated improved performance in two important characteristics of such a material, capacity and selectivity.

"We know that CC3 does this but we're not sure why. Once we understand why CC3 traps the noble gases so easily, we can improve on it," said Thallapally.

To explore whether MOFs and porous organic cages offer economic advantages, the researchers estimated the cost compared to cryogenic separations and determined they would likely be less expensive.

"Because these materials function well at ambient or close to ambient temperatures, the processes based on them are less energy intensive to use," said PNNL's Denis Strachan.

The material might also find use in pharmaceuticals. Most molecules come in right- and left-handed forms and often only one form works in people. In additional experiments, Cooper and colleagues in the U.K. tested CC3's ability to distinguish and separate left- and right-handed versions of an alcohol. After separating left- and right-handed forms of CC3, the team showed in biochemical experiments that each form selectively trapped only one form of the alcohol.

This work was supported by the Department of Energy Office of Nuclear Energy.

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