http://www.eurekalert.org/pub_releases/2012-02/uog-ici020612.php

Increased clumsiness in former welders

Welders who are exposed to manganese from welding fumes, risk developing increased clumsiness – and the result may remain decades after exposure has ceased.

This is the finding of a study at the University of Gothenburg, Sweden, of former shipyard workers.

It is estimated that 35,000 people in Sweden work full-time with welding, while many more carry out welding as one of several workplace activities. Previous research has shown that the concentration of manganese in the air during welding often lies at levels that can give immediate negative effects on the central nervous system, but the long-term effects of exposure to manganese have been essentially unexplored.

Effects on fine motor skills

Scientists at the Sahlgrenska Academy, University of Gothenburg, have now shown in a study of former shipyard workers in Gothenburg that long-term exposure to manganese can give permanent effects on fine motor skills almost 20 years after the exposure has ceased.

Test on Gothenburg welders

Scientist Gunilla Wastensson of the Department of Occupational and Environmental Medicine at the Sahlgrenska Academy has examined 17 former shipyard welders who worked at the shipyards in Gothenburg. The average period that had passed since they stopped welding was 18 years. The average period during which the participants had worked with welding was 28 years. They were given several tests to measure manual dexterity and motor speed, eye-hand coordination, tremor and balance. Their test results were compared to 21 other shipyard workers who had worked with other tasks, such as filers and electricians.

Total individual manganese exposure

The investigation showed that shipyard welders performed less well than the other shipyard workers in a test of manual dexterity and motor speed. The scientists also calculated a measure of total manganese exposure for each individual.

"The investigation showed that individuals with higher total manganese exposure had a poorer performance. We interpret this as a possible remaining effect of previous exposure to manganese, which is remarkable, given that so long a period had passed since they stopped welding", says Gunilla Wastensson.

The study is the first to examine the effects a considerable period after the exposure to manganese has ceased. The results are worrying, but Gunilla Wastensson emphasises that they must be confirmed in further studies. "Recent improvements in the work environment mean that the levels are lower now, but further measures to improve the situation associated with exposure to manganese at work are important", she says.

MANGANESE

Manganese is a metal that occurs naturally in the environment and in our bodies, where it is important in processes such as the turnover of carbohydrates and fats. People who are occupationally exposed for long periods to dust and fumes that contain high concentrations of manganese run the risk of developing, in rare cases, manganism. This is a disease with symptoms similar to those of Parkinson disease. It is caused by an accumulation of manganese in particular regions of the brain known as the basal ganglia, which are important for controlling body movement. Manganese is slowly excreted once exposure to the metal ends. The threshold limit value for manganese in air has been severely reduced in recent years, and is now 0.2 mg/m3 for total dust, and 0.1 mg/m3 for respirable dust. There is, however, a serious risk that the threshold limit value for manganese is exceeded at many welding locations. A proposal has been put forward in the US to reduce the threshold limit value to 0.02 mg/m3.

http://www.eurekalert.org/pub_releases/2012-02/uow-mr020612.php

Metabolic 'breathalyzer' reveals early signs of disease

The future of disease diagnosis may lie in a "breathalyzer"-like technology currently under development at the University of Wisconsin-Madison.

MADISON – New research published online in February in the peer-reviewed journal Metabolism demonstrates a simple but sensitive method that can distinguish normal and disease-state glucose metabolism by a quick assay of blood or exhaled air.

Many diseases, including diabetes, cancer, and infections, alter the body's metabolism in distinctive ways. The new work shows that these biochemical changes can be detected much sooner than typical symptoms would appear – even within a few hours – offering hope of early disease detection and diagnosis.

"With this methodology, we have advanced methods for tracing metabolic pathways that are perturbed in disease," says senior author Fariba Assadi-Porter, a UW-Madison biochemist and scientist at the Nuclear Magnetic Resonance Facility at Madison. "It's a cheaper, faster, and more sensitive method of diagnosis."

The researchers studied mice with metabolic symptoms similar to those seen in women with polycystic ovary syndrome (PCOS), an endocrine disorder that can cause a wide range of symptoms including infertility, ovarian cysts, and metabolic dysfunction. PCOS affects approximately 1 in 10 women but currently can only be diagnosed after puberty and by exclusion of all other likely diseases – a time-consuming and frustrating process for patients and doctors alike.

"The goal is to find a better way of diagnosing these women early on, before puberty, when the disease can be controlled by medication or exercise and diet, and to prevent these women from getting metabolic syndromes like diabetes, obesity, and associated problems like heart disease," Assadi-Porter says.

The researchers were able to detect distinct metabolic changes in the mice by measuring the isotopic signatures of carbon-containing metabolic byproducts in the blood or breath. They injected glucose containing a single atom of the heavier isotope carbon-13 to trace which metabolic pathways were most active in the sick or healthy mice. Within minutes, they could measure changes in the ratio of carbon-12 to carbon-13 in the carbon dioxide exhaled by the mice, says co-author Warren Porter, a UW-Madison professor of zoology.

One advantage of the approach is that it surveys the workings of the entire body with a single measure. In addition to simplifying diagnosis, it could also provide rapid feedback about the effectiveness of treatments.

"The pattern of these ratios in blood or breath is different for different diseases – for example cancer, diabetes, or obesity – which makes this applicable to a wide range of diseases," explains Assadi-Porter.

The technology relies on the fact that the body uses different sources to produce energy under different conditions. "Your body changes its fuel source. When we're healthy we use the food that we eat," Porter says. "When we get sick, the immune system takes over the body and starts tearing apart proteins to make antibodies and use them as an energy source." That shift from sugars to proteins engages different biochemical pathways in the body, resulting in distinct changes in the carbon isotopes that show up in exhaled carbon dioxide. If detected quickly, these changes may signal the earliest stages of disease.

The researchers found similar patterns using two independent assays – nuclear magnetic resonance spectroscopy on blood serum and cavity ring-down spectroscopy on exhaled breath. The breath-based method is particularly exciting, they say, because it is non-invasive and even more sensitive than the blood-based assays.

In the mice, the techniques were sensitive enough to detect statistically significant differences between even very small populations of healthy and sick mice.

The current cavity ring-down spectroscopy analysis uses a machine about the size of a shoebox, but the researchers envision a small, hand-held "breathalyzer" that could easily be taken into rural or remote areas. They co-founded a company, Isomark, LLC, to develop the technology and its applications. They hope to explore the underlying biology of disease and better understand whether the distinctive biochemical changes they can observe are causative or side effects.

Funding for the new study came from the National Institutes of Health, Wisconsin Institutes for Discovery, Rodale Foundation, and the Farmers Advocating for Organics fund. The other co-authors are Julia Haviland, Marco Tonelli, and Dermot Haughey, all at UW-Madison.

The full article, which may require a subscription, is online at http://dx.doi.org/10.1016/j.metabol.2011.12.010.

http://www.eurekalert.org/pub_releases/2012-02/dci-tc020312.php

3 'targeted' cancer drugs raise risk of fatal side effects

Treatment with three relatively new "targeted" cancer drugs has been linked to a slightly elevated chance of fatal side effects

BOSTON - Treatment with three relatively new "targeted" cancer drugs has been linked to a slightly elevated chance of fatal side effects, according to a new analysis led by scientists at Dana-Farber Cancer Institute. They added that the risk remains low, but should be taken into account by physicians and patients.

The incidence of fatal complications was 1.5 percent in patients who received any of the three drugs, which block the vascular endothelial growth factor (VEGF) tyrosine kinase receptors in cancer cells, according to the study published February 6 in the Journal of Clinical Oncology. This is compared to a 0.7 percent incidence in patients given standard treatments or placebos.

The study looked at three drugs: sorafenib (Nexavar), sunitinib (Sutent), and pazopanib (Votrient). Sorafenib is approved to treat kidney and liver cancer, sunitinib to treat kidney cancer and gastrointestinal stromal tumor (GIST), and pazopanib to treat kidney cancer.

The authors of the study, led by Dana-Farber's Toni Choueiri, MD, suggest that physicians give full consideration of the potential risk before using the targeted drugs with patients at slightly high risk for bleeding or heart attacks - the most common fatal adverse events seen in clinical trials. They also recommended that physicians and patients be aware of the risks and to consider if those patients need to be closely monitored.

"There is no doubt for the average patient, these drugs have benefits and are FDA-approved for these indications," said Choueiri. "While the absolute incidence of these fatal side effects is very small, the relative risks are higher and patients and practitioners need to be aware of it."

For example, he said, it might be necessary to temporarily stop treating a patient with the drug or to cancel an elective surgery while a patient is taking one of these drugs. Choueiri added that these drugs should be used cautiously in patients who have had heart attacks. "The patient should be given all the information, and then he or she can balance the pros and cons in deciding whether to take the next step into treatment."

Choueiri said he believed the study is the first meta-analysis of published controlled trials to show a significantly increased risk of death from treatment with these VEGF-tyrosine kinase inhibitors. The majority of patients who died suffered fatal bleeding; the second most common cause was heart attack or heart failure; liver failure was also seen.

The 10 clinical trials subjected to the meta-analysis included 4,679 patients treated with the drugs.

Vascular endothelial growth factor receptor is a tyrosine kinase molecule that responds to chemical signals secreted by tumors to encourage the formation of new blood vessels for the purpose of providing nutrients to support tumor growth. However, humans need vascular endothelial growth factor (VEGF) at low levels to maintain critical to several physiologic processes in the body, including wound-healing, cardiac homeostasis, and formation of new blood vessels in normal tissues. As a result, blocking VEGF to treat cancer can interfere with these normal functions, increasing the odds of adverse effects.

Fabio A.B. Schutz, MD, of Dana-Farber, is the first author of the paper. The other authors are Youjin Je, ScD, of Harvard School of Public Health, and Christopher Richards, MD, of Beth Israel Deaconess Medical Center.

The study was supported by the Trust Family Research Fund for Kidney Cancer.

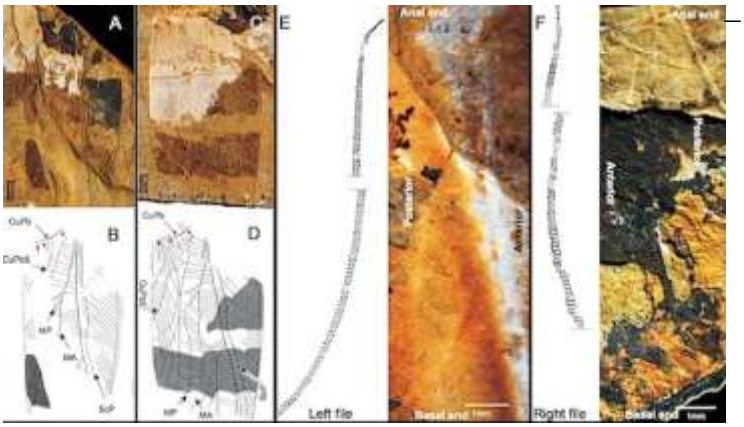
http://www.eurekalert.org/pub_releases/2012-02/uob-fcr020312.php

Fossil cricket reveals Jurassic love song

A cricket song last heard 165 million years ago has been played again.

Some 165 million years ago, the world was host to a diversity of sounds. Primitive bushcrickets and croaking amphibians were among the first animals to produce loud sounds by stridulation (rubbing certain body parts together). Modern-day bushcrickets – also known as katydids – produce mating calls by rubbing a row of teeth on one wing against a plectrum on the other wing but how their primitive ancestors produced sound and what their songs actually sounded like was unknown until now.

On discovering several insect fossils, a group of Chinese palaeontologists, including Jun-Jie Gu and Professor Dong Ren from the Capital Normal University in Beijing, contacted Dr Fernando Montealegre-Zapata and Professor Daniel Robert, both experts in the biomechanics of singing and hearing in insects, in Bristol's School of Biological Sciences. The group also teamed up with Dr Michael Engel of the University of Kansas, USA, a leading expert on insect evolution.



Fossils of A. musicus wings and illustrations of its wing ridges. **Images: Gu et al./PNAS**

The Chinese researchers provided an exceptionally detailed bushcricket fossil from the Mid Jurassic period. The specimen had such well-preserved wing features that the details of its stridulating organs were clearly visible under an optical microscope. Such information has never been obtained before from insect fossils. It was identified as a new fossil species and named Archaboilus musicus by the Beijing-Kansas team.

Dr Montealegre-Z and Professor Robert examined the anatomical construction of the fossil's song apparatus, and compared it to 59 living bushcricket species. They concluded that this animal must have produced musical songs, broadcasting pure, single frequencies.

Professor Robert said: "This discovery indicates that pure tone communication was already exploited by animals in the middle Jurassic, some 165 million years ago. For Archaboilus, as for living bushcricket species, singing constitutes a key component of mate attraction. Singing loud and clear advertises the presence, location and quality of the singer, a message that females choose to respond to – or not. Using a single tone, the male's call carries further and better, and therefore is likely to serenade more females. However, it also makes the male more conspicuous to predators if they have also evolved ears to eavesdrop on these mating calls."

The research, published today in PNAS, implies that the acoustic environment was already quite busy 165 million years ago with many animals (such as amphibians and other arthropods) singing at the same time, possibly chorusing, within the additional background noise produced by waterfalls, streams and wind.

Amazingly, based on the detailed morphology of Archaboilus' wings, Dr Fernando Montealegre-Z could reconstruct the songs emitted by these ancient insects.

Following biomechanical principles that he discovered some years ago, Dr Montealegre-Z established that A. musicus sang a tone pitched at 6.4kHz and that every bout of singing lasted 16 milliseconds. This turned out to be enough information to acoustically reconstruct the song itself, possibly the most ancient known musical song documented to date.

To hear the song, download file from: ***https://fluff.bris.ac.uk/fluff/u/inxhj/fqxIALCbZk8r_RBMfny__QRy/***

This paleobioacoustical analysis also provides a unique insight into the ecology of an extinct insect.

Dr Montealegre-Z said: "Using a low-pitched song, A. musicus was acoustically adapted to long-distance communication in a lightly cluttered environment, such as a Jurassic forest. Today, all species of katydids that use musical calls are nocturnal so musical calls in the Jurassic were also most likely an adaptation to nocturnal life. Being nocturnal, Archaboilus musicus probably escaped from diurnal predators like Archaeopteryx, but it cannot be ruled out that Jurassic insectivorous mammals like Morganucodon and Dryolestes also listened to the calls of Archaboilus and preyed on them.

"This Jurassic bushcricket thus sheds light on the potential auditory capacity of other animals, and helps us learn a little more about the ambiance of a world long gone. It also suggests the evolutionary mechanisms that drove modern bushcrickets to develop ultrasonic signals for sexual pairing and for avoiding an increasingly relevant echolocating predator, but that only happened 100 million years later, possibly with the appearance of bats."

Paper *'Wing stridulation in a jurassic katydid (insecta, orthoptera) produced low-pitched musical calls to attract females' by Gu, J. J., Montealegre-Z, F., Robert, D., Engel, M. S., Qiao, G. X. and Ren, D. in Proc. Natl. Acad. Sci. USA DOI:10.1073/pnas.111837210*

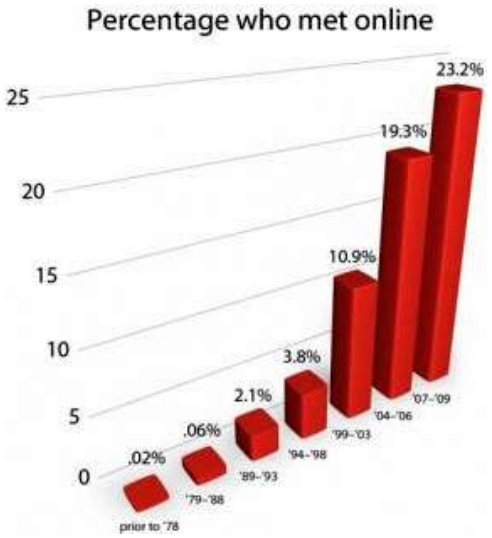
http://www.eurekalert.org/pub_releases/2012-02/uor-odr020112.php

Online dating research shows cupid's arrow is turning digital

Online dating has not only shed its stigma, it has surpassed all forms of matchmaking in the United States other than meeting through friends, according to a new analysis of research on the burgeoning relationship industry.

The digital revolution in romance is a boon to lonely-hearters, providing greater and more convenient access to potential partners, reports the team of psychological scientists who prepared the review. But the industry's claims to offering a "science-based" approach with sophisticated algorithm-based matching have not been substantiated by independent researchers and, therefore, "should be given little credence," they conclude.

"Online dating is definitely a new and much needed twist on relationships," says Harry Reis, one of the five co-authors of the study and professor of psychology at the University of Rochester. Behavioral economics has shown that the dating market for singles in Western society is grossly inefficient, especially once individuals exit high school or college, he explains. "The Internet holds great promise for helping adults form healthy and supportive romantic partnerships, and those relationships are one of the best predictors of emotional and physical health," says Reis.



The graph shows the percentage of Americans who met their partners online as a function of the year they met. The data is adapted from a study by Michael Rosenfeld from Stanford University and Reuben Thomas from City College of New York and is based on a nationally representative sample of 3,009 partnered respondents.
University of Rochester.

But online love has its pitfalls, Reis cautions. Comparing dozens and sometimes hundreds of possible dates may encourage a "shopping" mentality in which people become judgmental and picky, focusing exclusively on a narrow set of criteria like attractiveness or interests. And corresponding by computer for weeks or months before meeting face-to-face has been shown to create unrealistic expectations, he says.

The 64-page analysis reviews more than 400 psychology studies and public interest surveys, painting a full and fascinating picture of an industry that, according to one industry estimate, attracted 25 million unique users around the world in April 2011 alone. The report was commissioned by the Association for Psychological Science and will be published in the February edition of its journal Psychological Science in the Public Interest.

Other highlights from the analysis include:

Online dating has become the second-most-common way for couples to meet, behind only meeting through friends. According to research by Michael Rosenfeld from Stanford University and Reuben Thomas from City College of New York, in the early 1990s, less than 1 percent of the population met partners through printed personal advertisements or other commercial intermediaries. By 2005, among single adults Americans who were Internet users and currently seeking a romantic partner, 37 percent had dated online. According to research by Michael Rosenfeld, a professor of sociology at Stanford University, in 2007-2009, 22 percent of heterosexual couples and 61 percent of same-sex couples had found their partners through the Web. Those percentages are likely even larger today, the authors write.

Attitudes have changed radically. Through the 1980s and into the 1990s, a stigma was associated with personal advertisements that initially extended to online dating. But today, "online dating has entered the mainstream, and it is fast shedding any lingering social stigma," the authors write.

Men and women behave differently online.

* A 2010 study of 6,485 users of a major online dating site found that men viewed three times more profiles than women did (597,169 to 196,363).

* Men were approximately 40 percent more likely to initiate contact with a woman after viewing her profile than women were after viewing a man's profile (12.5 to 9 percent).

Online sites may encourage "soulmate" search. The authors caution that matching sites' emphasis on finding a perfect match, or soulmate, may encourage an unrealistic and destructive approach to relationships. "People with strong beliefs in romantic destiny (sometimes called soulmate beliefs) - that a relationship between two people either is or is not 'meant to be' - are especially likely to exit a romantic relationship when problems arise … and to become vengeful in response to partner aggression when they feel insecure in the relationship," the authors write.

Online dating sites are not "scientific". Despite claims of using a "science-based" approach with sophisticated algorithm-based matching, the authors found "no published, peer-reviewed papers – or Internet postings, for that matter – that explained in sufficient detail … the criteria used by dating sites for matching or for selecting which profiles a user gets to peruse." Instead, research touted by online sites is conducted in-house with study methods and data collection treated as proprietary secrets, and, therefore, not verifiable by outside parties.

Online dating fundamentally changes access to information. "In the words of one online dater: 'Where else can you go in a matter of 20 minutes [and] look at 200 women who are single and want to go on dates?' "

Along with Reis, other co-authors include Eli Finkel, associate professor of social psychology at Northwestern University and lead author on the paper; Paul Eastwick, assistant professor of psychology at Texas A&M University; Benjamin Karney, professor of psychology at the University of California at Los Angeles; and Susan Sprecher, professor of sociology and psychology at Illinois State University.

http://www.eurekalert.org/pub_releases/2012-02/luhs-ebt020612.php

Easy-to-use blood thinners likely to replace Coumadin

For atrial fibrillation patients at risk for stroke

MAYWOOD, Ill. - Within a few years, a new generation of easy-to-use blood-thinning drugs will likely replace Coumadin for patients with irregular heartbeats who are at risk for stroke, according to a journal article by Loyola University Medical Center physicians. Unlike Coumadin, the new drugs do not require patients to come in to the clinic on a regular basis to check the dose. Nor do the drugs require extensive dietary restrictions.

First author Sarkis Morales-Vidal, MD, and colleagues describe the new drugs in a review article in the February issue of the journal Expert Reviews. Co-authors are Michael J. Schneck, MD, Murray Flaster, MD, and José Biller, MD. All are in the Department of Neurology, Stroke Program, of Loyola University Chicago Stritch School of Medicine. Biller is department chair.

The new drugs include rivaroxaban (Xarelto®), dabigatran etexilate (Pradaxa®) and apixaban (Eliquis®). They do not share the disadvantages of Coumadin, and may provide equal or superior prevention against clots, Morales and colleagues write.

Atrial fibrillation is the most common form of irregular heartbeat, and a major cause of stroke in the elderly. Electrical signals, which regulate the heartbeat, become erratic. Instead of beating regularly, the upper chambers of the heart quiver. Not all the blood gets pumped out, so clots can form. The clots can migrate to the

brain and cause strokes. More than 3 million Americans have atrial fibrillation, and the number is increasing, due in part to the aging population.

Coumadin's generic name is warfarin. For more than 30 years, the drug had been the only anticoagulant for primary and secondary stroke prevention in patients with atrial fibrillation. But the Food and Drug Administration recently approved dabigatran and rivaroxaban to reduce the risk of stroke and blood clots in patients with atrial fibrillation that is not caused by a heart valve problem. The FDA is considering an application to approve apixaban for the same use.

Coumadin must be carefully monitored. If the dose is too high, a patient could experience excessive bruising and be at higher risk for brain hemorrhages. If the dose is too low, the drug would be ineffective in preventing blood clots. Patients typically must come in at least once a month for a blood test to determine whether the dose needs to be adjusted. Some patients have to come in as often as twice a week. Coumadin patients also must restrict their diets. For example, they should consume only small amounts of cranberry juice and alcohol and not eat large amounts of foods that are rich in vitamin K, such as spinach, brussels sprouts and green tea.

Disadvantages of the new medications include the limited clinical experience and lack of antidotes, the researchers wrote. The newer drugs are more expensive than Coumadin, but reduce the cost of patient monitoring and blood testing, Morales said.

Dabigatran is an effective alternative to Coumadin for stroke prevention in patients with non-valvular atrial fibrillation. Rivaroxaban is another promising alternative for those patients. Apixaban appears to be better than aspirin for stroke prevention in atrial fibrillation patients who are not candidates for Coumadin therapy, Morales and colleagues wrote. The authors predict that within the next few years, the new drugs will likely replace Coumadin for long-term anticoagulation in selective patients with non-valvular atrial fibrillation.

http://www.eurekalert.org/pub_releases/2012-02/cu-zcc020612.php

Zinc control could be path to breast cancer treatment

Zinc control mechanisms could be key to aggressive breast cancer treatments

The body's control mechanisms for delivering zinc to cells could be key to improving treatment for some types of aggressive breast cancer.

New research by Cardiff University and King's College London has identified the switch which releases zinc into cells, with important implications for a number of diseases.

Zinc has long been known to play a vital part in human health. Too much zinc, or too little, can cause cell death. A growing body of evidence links zinc to disease states including neurodegeneration, inflammation, diabetes and cancer.

Zinc levels in cells are controlled by protein molecules called zinc transporters. These move zinc in and out of the cell to ensure correct levels are maintained. Until now, scientists have not understood how the transporters release the zinc. The Cardiff and King's research team have identified a switch, known as CK2, a protein which opens one transporter, called ZIP7, and allows the zinc to flow.

Earlier research by the team has already linked zinc delivery to types of breast cancer. Higher levels of intracellular zinc and the ZIP7 transporter were found in tamoxifen-resistant breast cancers. CK2 was also known to be more common in cancers which encourage cell growth. The discovery that CK2 opens ZIP7 suggests that drugs which block this release of zinc could also block cancer development. Early results from clinical trials of CK2 inhibitors suggest they are performing well.

Dr Kathryn Taylor, of Cardiff University's School of Pharmacy and Pharmaceutical Sciences, said: "We know that zinc, in the right quantities, is vital for development, our immune systems and many other aspects of human health. But when something goes wrong with the body's zinc delivery system, it looks as though disease can result. In particular, our research has shown a link to highly aggressive forms of breast cancer. Our better understanding of how exactly zinc is delivered suggests if we can block malfunctioning transporter channels, we can potentially halt the growth of these forms of cancer. We believe this makes zinc, and zinc delivery, a high priority for future cancer research."

Professor Christer Hogstrand from the Diabetes and Nutritional Sciences Division at King's College London, said: "Our discovery provides a mechanistic explanation for how the cell uses zinc to regulate different functions. The evidence that zinc is released on command in the cell and then regulates cellular processes seems to set it apart from other transition metals, such as copper and iron, in the way that it is used by the body. These findings should open the door for new research into the roles of zinc in health and disease."

The research, funded by a Wellcome Trust University Research Award to Dr Taylor, is published tomorrow (February 7) in the leading journal Science Signaling.

http://www.scientificamerican.com/article.cfm?id=cracks-in-the-plaques-mys

Cracks in the Plaques: Mysteries of Alzheimer's Slowly Yielding to New Research

Science is bringing some understanding of the heritability, prevalence and inner workings of one of the most devastating diseases

By Daisy Yuhas | Monday, February 6, 2012 | 3

This has been a big week in Alzheimer's news as scientists put together a clearer picture than ever before of how the disease affects the brain. Three recently published studies have detected the disease with new technologies, hinted at its prevalence, and described at last how it makes its lethal progress through the brain.

The existence of two forms of Alzheimer's - early- and late-onset - has long baffled scientists. Of the estimated five million Americans who suffer from Alzheimer's, only a few thousand are diagnosed with an early-onset form of the affliction, which affects people before the age of 65. This rare early-onset form is thought to be hereditary and scientists have associated multiple genetic mutations contributing to its occurrence.

Late-onset Alzheimer's, although more common, has been the bigger mystery. One variant of the APOE gene- - sometimes known as the Alzheimer's gene - is linked to the late-onset disease. But the APOE gene, unlike dominant early-onset genes, does not determine whether a person will ultimately have dementia.

Now there's evidence that late-onset Alzheimer's has a genetic basis similar to that of early-onset Alzheimer's. By sequencing select genes associated with the latter, along with frontotemporal dementia, researchers at Washington University in Saint Louis and other institutions found that patients with late-onset Alzheimer's carry some of the same genetic mutations as those with the early-onset form. The evidence, published on Wednesday in PLoS ONE, bolsters the argument that the forms of Alzheimer's that appear at different life stages should be classified as the same disease. As to why the disease appears earlier in some cases, the scientists speculated that those patients diagnosed relatively early in life carry more genetic risk factors for the disease.

This study's use of rapid genetic sequencing, the authors noted, may provide a model for more precise identification of dementias. Within the study, the researchers identified patients who may have been misdiagnosed as having Alzheimer's; the genes of these patients suggested that they had another type of dementia. Given the heritable component, patients with a family history could be screened to detect and diagnose Alzheimer's early.

Other genetic research unveiled in the past week or so has shed light on the biological processes that underlie how Alzheimer's affects the brain. Certain mutations may lead to an increased production of a protein called amyloid beta in the region of the brain that creates memory. This excess amyloid beta, naturally secreted by brain cells, then becomes a complex called an oligomer. These oligomers may interrupt the signals transmitted between neurons. As in other neurodegenerative diseases like Parkinson's or Huntington's, the spread of oligomers appears to be driving the disease process.

Oligomer-linked diseases are relatively common, in part because oligomers can also play an essential biological role in the brain. A recent investigation using fruit flies reveals that the presence of a specific oligomer is actually required for the flies to form long-term memories.

In an early stage of Alzheimer's, the naturally secreted amyloid beta protein builds up as oligomers in the brain, which then go on to form larger aggregates called plaques. Later in the disease, another aberrant form of a protein called tau starts to build up, in the entorhinal cortex. Normally, tau helps provide structure crucial to neuron functioning. The buildup of tau, however, causes the protein to tangle and eventually kill brain cells. What was unknown until recently, however, was how the tau protein spreads through different brain regions.

Two studies - one to be published in Neuron and the other published in PLoS ONE on Wednesday - have answered this question using brain samples from mice genetically engineered to express tau as it occurs in the human brain. Using a staining technique to highlight tau's distribution in the brain, they compared samples from mice of different ages to analyze how tau moved through brain cells over time. They found the protein spread from neuron to neighboring neuron, traveling along synapses.

Understanding how this protein moves may allow scientists to stop tau in its tracks. "This opens up a whole new world of biology," says Columbia University's Karen Duff, an author on the study published in PLoS ONE. Tau is implicated in 30 different forms of dementia. In addition, the movement of tau may be similar to the spread of oligomers associated with Parkinson's and Huntington's. Nonetheless, we are still a long way from a therapeutic solution and stopping tau, which comes at a relatively late stage of Alzheimer's, might be a very limited therapy.

As the world's population continues to age, Alzheimer's becomes a threat to more of us with every passing day. Although we may not yet have new treatments from this work, the take-away on these findings is clear: If

we really are going to win the war, or even a battle, against Alzheimer's, we need basic research that can delve into the complex biology that contorts proteins and kills brain cells to find treatments for this disease.

http://medicalxpress.com/news/2012-02-uga-discovery-fracture-putty-broken.html

UGA discovery uses 'fracture putty' to repair broken bone in days

Studies show promise to significantly shorten the healing time and revolutionize the course of fracture treatment

Broken bones in humans and animals are painful and often take months to heal. Studies conducted in part by University of Georgia Regenerative Bioscience Center researchers show promise to significantly shorten the healing time and revolutionize the course of fracture treatment.

"Complex fractures are a major cause of amputation of limbs for U.S. military men and women," said Steve Stice, a Georgia Research Alliance Eminent Scholar, animal and dairy scientist in the UGA College of Agricultural and Environmental Sciences and director of the UGA Regenerative Bioscience Center.

"For many young soldiers, their mental health becomes a real issue when they are confined to a bed for three to six months after an injury," he said. "This discovery may allow them to be up and moving as fast as days afterward." Stice is working with Dr. John Peroni to develop a fast bone healing process. "This process addresses both human and veterinary orthopedic needs," said Peroni, an associate professor of large animal surgery in the UGA College of Veterinary Medicine and a member of the RBC.

Peroni and Stice are leading a large animal research project funded by the U.S. Department of Defense. The project includes scientists and surgeons from the Baylor University College of Medicine, Rice University and the University of Texas, who conducted the early studies.

Engineering new bone

"Healing of critical-size defects is a major challenge to the orthopedic research community," Peroni said. "Large-bone defects must be stabilized and necessitate technologies that induce rapid bone formation in order to replace the missing tissue and allow the individual to return to rapid function. To date, no single material can suffice."

The group they lead is a multidiscipline and multi-institutional group actively working on bone tissue engineering. "Our group has been working productively together on numerous projects through the last several years," Stice said, "So, a collegial relationship and successful collaborative working relationship is already established." Between 2009 and 2011, the collaborations received a $1.4 million grant from the DOD for the use of stem cells in fracture healing to be tested in sheep.

"In our experiences with large animal models, following the guidelines established by our animal care and use committee," Stice said, "we have been successful in formulating a product that contains mesenchymal stem cells and allows them to survive in the environment of the fracture long enough to elicit the rapid formation of new bone." This year, the group showed bone can be generated in sheep in less than four weeks. The speed in which bone is formed is one of the truly unique features of this study.

Fracture putty

To start the bone regeneration process, the RBC used adult stem cells that produce a protein involved in bone healing and generation. They then incorporated them into a gel, combining the healing properties into something Stice calls "fracture putty."

With Peroni's assistance, the Houston-based team used a stabilizing device and inserted putty into fractures in rats. Video of the healed animals at two weeks shows the rats running around and standing on their hind legs with no evidence of injury. The RBC researchers are testing the material in pigs and sheep, too.

"The small-animal work has progressed, and we are making good progress in large animals," he said.

More work is needed to get to human medical trials, but the threat of losing federal funding for biomedical work through the DOD means they will have to find new ways to fund the project.

Next steps

"The next step is to show that we can rapidly and consistently heal fractures in a large animal," Peroni said, "then to convert it to clinical cases in the UGA [College of Veterinary Medicine] clinics where clinicians treat animals with complex fractures all the time."

Once they have something that works for animals, it will be passed over to the DOD for human use.

Peroni, who is chairman of the North American Veterinary Regenerative Medicine Association, is hopeful this material will be promoted to the veterinary and human medical fields through the educational efforts of NAVRMA and the RBC. However, the RBC isn't the only group working on a faster fix for broken bones.

"Our approach is biological with the putty," Stice said. "Other groups are looking at polymers and engineering approaches like implants and replacements which may eventually be combined with our approach. We are looking at other applications, too, using this gel, or putty, to improve spinal fusion outcomes."

One of the best hopes for the fracture putty is in possible facial cranial replacements, an injury often seen on the battlefield. The project ends in mid-2012. "By then we are to deliver the system to the DOD," Stice said.

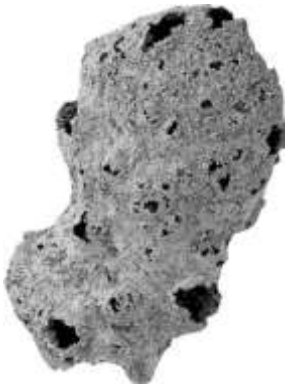
Provided by University of Georgia

http://www.physorg.com/news/2012-02-namibia-sponge-fossils-world-animals.html

Namibia sponge fossils are world's first animals: study

Scientists digging in a Namibian national park have uncovered sponge-like fossils they say are the first animals, a discovery that would push the emergence of animal life back millions of years.

The tiny vase-shaped creatures' fossils were found in Namibia's Etosha National Park and other sites around the country in rocks between 760 and 550 million years old, a 10-member team of international researchers said in a paper published in the South African Journal of Science.



The fossil Otavia.

That means animals, previously thought to have emerged 600 million to 650 million years ago, actually appeared 100 million to 150 million years before that, the authors said. It also means the hollow globs - about the size of a dust speck and covered in holes that allowed fluid to pass in and out of their bodies - were our ancestors, said co-author Tony Prave, a geologist at the University of St Andrews in Scotland.

"If one looks at the family tree and projects this backward to where you have what's called the stem group, the ancestor of all animals, then yes, this would be our great-great-great-great-great-great-great grandmother," he told AFP.

Prave said fossil evidence that animals emerged as long as 760 million years ago fit together neatly with what geneticists had hypothesised by looking at "molecular clocks", a means of gauging a species' age by looking at the percentage difference between its DNA and that of another species.

"The aspect of this that's rather satisfying, at least intellectually, is that it is in broad agreement with what geneticists would tell us based on looking at molecular clocks when we should see the first advent of large multi-cellular life forms," he said. *(c) 2012 AFP*

http://bit.ly/zJHcfM

Coelacanths are not living fossils. Like the rest of us, they evolve

It was supposed to be extinct. Yet here it lay, with fins round and fleshy, scales as hard as bone and a tail unlike any living fish.

By Lucas Brouwers | February 6, 2012

Axelrodichthys araripensis, an extinct coelacanth from South America. **Photo by Ghedoghedo.**

"Lass, this discovery will be on the lips of every scientist in the world", James Smith said to Marjorie Courtenay-Latimer, curator of the East London Museum. Smith had good reasons to make such a grand claim. This was a coelacanth.

Naturalists had known about coelacanths for a long time – but only as fossils. It was Louis Agassiz who first described the group in 1839. Paleontologists had found dozens of different coelacanth species since then, but always in rocks older than 70 million years. The lack of coelacanth fossils in younger strata led them to conclude that coelacanths had gone extinct a long time ago. But the fish that now lay before Smith was no fossil. This creature had been caught only weeks ago, as bycatch by a fishing trawler off the coast of South Africa.

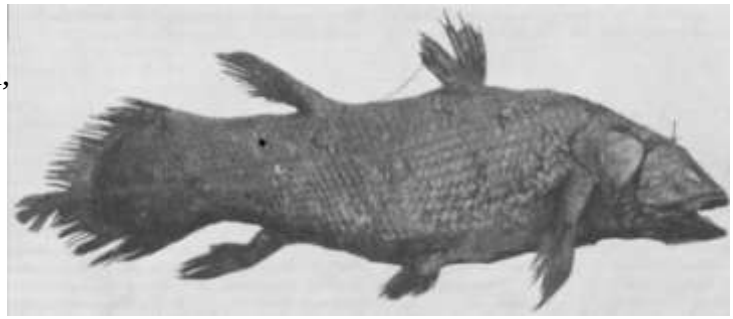
It was 1939, and the discovery of the first living coelacanth was on the lips of scientists around the world. The press heralded the fish as a 'missing link', 'prehistoric fish' and 'living fossil'. In doing so, they branded the coelacanths as a backwards fish for years to come.

The same stereotypes have haunted the coelacanth to this very day. In most popular accounts, the coelacanth is portrayed as a a forgotten survivor that has been left at the evolutionary wayside. In this modern fable, coelacanths had been trapped in a private bubble of time for millions of years until they re-emerged in the 20th century.

But the truth is that evolution leaves no fish behind. Coelacanths are as much affected by evolution as finches, ferns and flying lemurs. They have their own evolutionary history – we only need to look for it. This is what Japanese and African coelacanth researchers did not long ago when they took stock of the genetic

diversity amongst coelacanths in the Indian Ocean. Through their research, they uncovered a small part of the coelacanth's history of change.

Coelacanths have popped up in several places in the Indian Ocean over the years, but the majority of them has been found in the Comoros archipelago. In the late eighties, Hans Fricke filmed how coelacanths inhabit rocky crevices and caves around the Comoros. At night he saw them drifting along the up- and downwelling currents, using their fins as stabilizers, to sneak up on unsuspecting fish. A short stroke with its fan-like tail, a sudden and forceful bite and its prey is gone.

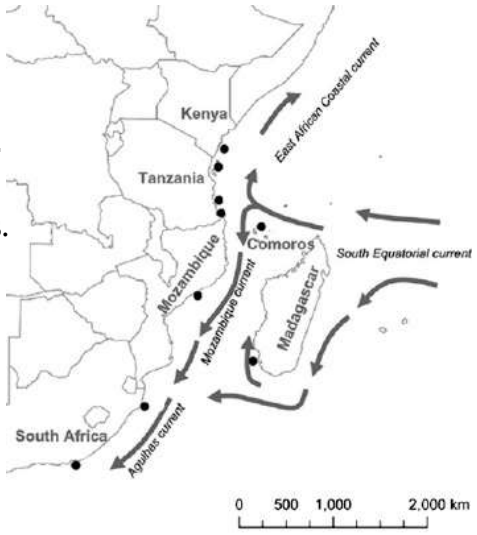


This stuffed coelacanth, described by Smith in 1939, achieved worldwide fame. Source.

Other coelacanths have been captured off the coast of Madagascar, South Africa, Mozambique and Kenya, but these fish have been dismissed as strays. Biologists reasoned that coelacanths would not be able to survive on the flat and sandy sea floors near Mozambique and South Africa. They presumed that strong ocean currents had swept the creatures away from the Comoros. These dead-end drifters were destined for death.

But there's evidence that these stragglers represent distinct coelacanth populations. Geologists have identified several marine canyons near South Africa and Mozambique in which coelacanths could live. A dozen coelacanths have been caught near Tanzania every year since 2003. It's unlikely that these are all strays. Indeed – when marine biologists let a remotely operated submersible descend in Tanzanian waters, they were able to capture footage of nine living coelacanths. Could this be the second home of coelacanths in the Indian Ocean?

In the paper that was published a few months ago, researchers have compare the DNA of Tanzanian and Comoran coelacanths. They found that some Tanzanian fish carry unique genetic variants. These variants were not found in any Comoran fish or anywhere else. This was especially true for coelacanths captured off northern Tanzania. The team believe their results indicate that coelacanths from northern Tanzania form a separate breeding population from the coelacanths from the South and the Comoros. These last two populations are much closer to each other genetically.



The researchers think the last common ancestor of the Tanzanian and Comoran coelacanths lived at least 200,000 years ago. For your sense of time: this was around the same time when the first modern human walked the earth. The researchers arrived at this estimate with a simple technique, known as the molecular clock: the more genetic differences exist between two lineages, the longer ago they diverged. But calibrating the clock can be tricky. Using a different calibration point, the researchers dated the split between the two populations to a few millions years ago.

Coelacanths have popped up in many places along the East African coast. **Figure from first reference.**

Whatever the exact figure is, fact is that the Indian Ocean harbours distinct populations of coelacanths. If the Comoros Archipelago is the ancestral home of coelacanths, some fish have packed their things and settled somewhere else. Given enough time these populations might evolve into distinct species. We know this has happened in the past, for there are two species of coelacanth alive today. Aside from the West Indian Coelacanth, there exists a second species of coelacanth that was discovered at a local fish market two decades ago, near Indonesia.

Scientists have just started to collect and sequence coelacanth DNA. The amount of DNA analyzed in genetic studies (including this one) has been tiny so far. As more sequences will become available, more evidence of the continued evolution of the coelacanth will come to light.

Let's leave the silly concept of 'living fossils' behind. Watch the movie above, and see the coelacanth sail the currents with subtle movements of its fins. Marvel at the mysterious headstand these creatures perform. Peer into its eyes, and see how the light is reflected back at you. These creatures are no fossils. They are very much alive.

As Smith wrote in the paper that announced the discovery of a second specimen:

"Numbers of successful modern fishes appear less well equipped for survival than the coelacanth. [..] Coelacanths can scarcely be regarded as degenerate fish. They are apparently full of vigour."

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http://www.eurekalert.org/pub_releases/2012-02/jaaj-aom020212.php

Administration of meningococcal vaccine with other routine infant vaccines appears effective

Administration of routine infant immunizations with a vaccine for B Neisseria meningitidis, was effective and produced minimal interference with the response to the routine vaccinations

CHICAGO – Administration of routine infant immunizations with a vaccine for serogroup B Neisseria meningitidis, a bacterium that is a cause of serious disease such as sepsis and meningitis, was effective against meningococcal strains and produced minimal interference with the response to the routine vaccinations, according to a study in the February 8 issue of JAMA.

Certain serogroup B Neisseria meningitidis (MenB) vaccines proved effective in clinical trials and controlled a clonal MenB outbreak in New Zealand; however, the high strain specificity of these vaccines limited their usefulness, especially in infants and young children, according to background information in the article.

Nicoletta Gossger, M.D., of the University of Oxford, United Kingdom, and colleagues assessed the immunogenicity (the ability to produce an immune response) and reactogenicity (producing adverse reactions) of a vaccine developed to provide broader protection, a multicomponent serogroup B meningococcal vaccine (4CMenB), in a large group of infants, given in 2 different schedules, with or separately from routine vaccines. The multicenter, randomized controlled study included 1,885 infants enrolled at age 2 months from August 2008 to July 2010 in Europe. Participants were randomized to receive (1) 4CMenB at 2, 4, and 6 months with routine vaccines (7-valent pneumococcal and combined diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, Haemophilus influenzae type b vaccines); (2) 4CMenB at 2, 4, and 6 months and routine vaccines at 3, 5, and 7 months; (3) 4CMenB with routine vaccines at 2, 3, and 4 months; or (4) routine vaccines alone at 2, 3, and 4 months. The primary outcome the researchers measured was the percentage of participants with human complement serum bactericidal activity (hSBA) titer (concentration) of 1:5 or greater against 3 MenB strains specific for vaccine antigens (NZ98/254, 44/76-SL, and 5/99).

After immunization with 4CMenB and routine vaccines together at either 2, 4, and 6 or 2, 3, and 4 months, 99 percent or more of participants had hSBA titers of 1:5 or greater for strains 44/76-SL and 5/99. For NZ98/254, this proportion was 79 percent for vaccination at 2, 4, and 6 months with routine vaccines, 86.1 percent for vaccination at 2, 4, and 6 months without routine vaccines, and 81.7 percent for vaccination at 2,3, and 4 months with routine vaccines. The predefined criteria of a sufficient immune response was met for all three strains.

Responses to routine vaccines given with 4CMenB were noninferior (outcome not worse than treatment compared to) to routine vaccines alone for all antigens, except for the responses to pertactin (a pertussis antigen) and the pneumococcal vaccine serotype 6B. "Fever was seen following 26 percent to 41 percent of 4CMenB doses when administered alone, compared with 23 percent to 36 percent after routine vaccines given alone and 51 percent to 61 percent after 4CMenB and routine vaccines administered together," the authors write.

"In conclusion, 4CMenB was immunogenic, generally well tolerated, and showed minimal interference with routine vaccines in the first year of life. The flexibility in schedule allows it to be incorporated into a range of country-specific immunization schedules and for primary immunization to be completed in early infancy. If licensed, the decisions regarding vaccine introduction will require detailed assessment of potential vaccine coverage at a regional level and monitoring after implementation to determine the accuracy of such predictions. Nevertheless, this vaccine could potentially provide improved protection for infants against meningococcal disease beyond the protection provided by currently licensed vaccines."

(JAMA. 2012;307[6]:573-582. Available pre-embargo to the media at www.jamamedia.org)
Editor's Note: *This study was funded by Novartis Vaccines and Diagnostics. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, etc.*

Editorial: Inching Toward a Serogroup B Meningococcal Vaccine for Infants

In an accompanying editorial, Amanda C. Cohn, M.D., and Nancy E. Messonnier, M.D., of the Centers for Disease Control and Prevention, Atlanta, write that "the potential of 4CMenB vaccine to reduce serogroup B meningococcal disease is substantial, but it cannot be compared with the success of conjugate vaccine programs."

"4CMenB vaccine may not reduce nasopharyngeal [pertaining to the cavity of the nose and the nasal parts of the pharynx] carriage or produce herd immunity, as the serogroup C conjugate vaccine did in the United Kingdom. Booster doses may be required to sustain protection but may not confer the same degree of immunologic memory as conjugate vaccines. Countries will have to weigh the benefits of serogroup B vaccination against the costs of adding vaccines to the infant schedule. However, the anticipated licensure of this vaccine in Europe and other countries means that for the first time vaccines to prevent all 5 of the serogroups that cause most meningococcal disease worldwide will be available."

(JAMA. 2012;307[6]:614-615. Available pre-embargo to the media at www.jamamedia.org)
Editor's Note: *The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.*

http://www.eurekalert.org/pub_releases/2012-02/acoc-ndg020112.php

New DVT guidelines: No evidence to support 'economy class syndrome'

Oral contraceptives, sitting in a window seat, advanced age, and pregnancy increase DVT risk in long-distance travelers

New evidence-based guidelines from the American College of Chest Physicians (ACCP) address the many risk factors for developing a deep vein thrombosis (DVT), or blood clot, as the result of long-distance travel.

These risk factors include the use of oral contraceptives, sitting in a window seat, advanced age, and pregnancy. The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, published in the February issue of the journal CHEST, also suggest there is no definitive evidence to support that traveling in economy class can lead to the development of a DVT, therefore, dispelling the myth of the so-called "economy class syndrome."

"Traveling in economy class does not increase your risk for developing a blood clot, even during long-distance travel; however, remaining immobile for long periods of time will," said guideline co-author Mark Crowther, MD, Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

"Long-distance travelers sitting in a window seat tend to have limited mobility, which increases their risk for DVT. This risk increases as other factors are present." DVT is a serious condition that can lead to a potentially fatal blockage in the lung known as a pulmonary embolism (PE).

DVT/PE Risk Factors For Long-Distance Travel

Although developing a DVT/PE as the result of long-distance travel is unlikely in most cases, the guidelines note that for long-distance flights, the following factors may increase your risk of developing a DVT/PE and related complications:

- ***Previous DVT/PE or known thrombophilic disorder***
- ***Malignancy***
- ***Recent surgery or trauma***
- ***Immobility***
- ***Advanced age***
- ***Estrogen use, including oral contraceptives***
- ***Pregnancy***
- ***Sitting in a window seat***
- ***Obesity***

Conversely, the guidelines suggest there is no definitive evidence to support that dehydration, alcohol intake, or sitting in economy class (compared with sitting in business class) increases your risk for developing a DVT/PE resulting from long-distance flights.

Recommendations For DVT/PE Prevention In Long-Distance Travelers

For travelers on flights of 6 hours or more who have an increased risk for DVT/PE, the ACCP recommends frequent ambulation, calf muscle stretching, sitting in an aisle seat if possible, or the use of below-knee graduated compression stockings (GCS). For long-distance travelers who are not at increased risk for DVT/PE, the guidelines suggest against the use of GCS. In addition, the guidelines suggest against the use of aspirin or anticoagulant therapy to prevent DVT/PE in long-distance travelers. For travelers who are considered to be at particularly high risk for DVT/PE, the use of antithrombotic agents should be considered on an individual basis because the adverse effects may outweigh the benefits.

"Symptomatic DVT/PE is rare in passengers who have returned from long flights; however the association between air travel and DVT/PE is strongest for flights longer than 8 to 10 hours," said Dr. Crowther. "Most passengers who do develop a DVT/PE after long-distance travel have one or more risk factors."

Patient-Focused Antithrombotic Guidelines

In addition to long-distance travel, the ACCP guidelines include more than 600 recommendations for the prevention, diagnosis, and treatment of thrombosis, addressing a comprehensive list of clinical conditions. These clinical conditions include medical, surgery, orthopedic surgery, atrial fibrillation, stroke, cardiovascular disease, pregnancy, and neonates and children, among others. Key advances in this edition of the guidelines include a stronger focus on risk stratification of patients, which suggests clinicians should consider a patient's risk for DVT/PE before administering or prescribing a prevention therapy.

"There has been a significant push in health care to administer DVT prevention for every patient, regardless of risk. As a result, many patients are receiving unnecessary therapies that provide little benefit and could have adverse effects," said Guidelines Panel Chair Gordon Guyatt, MD, FCCP. "The decision to administer DVT prevention therapy should be based on the patients' risk and the benefits of prevention or treatment." The new guidelines also take a more patient-focused approach by considering patient values and preferences regarding antithrombotic therapy and prevention.

The guidelines are endorsed by the following medical associations: the American Association for Clinical Chemistry, American College of Clinical Pharmacy, American Society of Health-System Pharmacists, American Society of Hematology, International Society of Thrombosis and Hemostasis, and the American College of Obstetrics and Gynecology (pregnancy article only).

For more information about the guidelines and accompanying clinician resources, visit http://www.chestnet.org and follow #AT9 on Twitter. Patient resources related to the guidelines are available through OneBreath, an initiative of The CHEST Foundation, the philanthropic arm of the ACCP.

http://www.eurekalert.org/pub_releases/2012-02/jaaj-sea020212.php

Study evaluates antibiotic option for treating bladder infection in women

Short-term use of cefpodoxime for treatment of women with uncomplicated cystitis did not meet criteria for noninferiority for achieving clinical cure compared with ciprofloxacin

CHICAGO – Short-term use of the antibiotic cefpodoxime for the treatment of women with uncomplicated cystitis (bladder infection) did not meet criteria for noninferiority for achieving clinical cure compared with ciprofloxacin, a drug in the fluoroquinolone class of antibiotics for which there have been concerns about overuse and a resulting increase in resistance rates, according to a study in the February 8 issue of JAMA. The criteria for noninferiority was if the efficacy of cefpodoxime had been shown to be within a pre-specified margin of 10 percent of the efficacy of ciprofloxacin.

Fluoroquinolones have high rates of efficacy and minimal adverse drug reactions when used in a 3-day regimen as recommended to treat uncomplicated cystitis. However, increasing rates of antimicrobial resistance among fluoroquinolones have been reported. To prevent further emergence of fluoroquinolone resistance, there are calls for restricting fluoroquinolones to those specific instances of uncomplicated cystitis when other first-line urinary tract infection (UTI) antimicrobials are not suitable, according to background information in the article. "Cefpodoxime, with its broad spectrum of antimicrobial activity, would provide a useful alternative to fluoroquinolones for the treatment of cystitis if demonstrated to be similar in efficacy to fluoroquinolones and without adverse ecological effects (such as the selection of drug-resistant organisms)."

Thomas M. Hooton, M.D., of the University of Miami, and colleagues conducted a clinical trial to assess whether cefpodoxime would have clinically acceptable efficacy and tolerance compared with ciprofloxacin. The study, conducted from 2005 to 2009, included 300 women ages 18 to 55 years with acute uncomplicated cystitis. Outcomes were assessed at 5 to 9 days and 28 to 30 days after completion of therapy. Intent-to-treat and per-protocol analyses were performed; 15 women in the ciprofloxacin group (n = 150) and 17 women in the cefpodoxime group (n = 150) were lost to follow-up. Patients were randomized to 250 mg of ciprofloxacin orally twice daily for 3 days or 100 mg of cefpodoxime proxetil orally twice daily for 3 days. Overall clinical cure was defined as not requiring antimicrobial treatment during follow-up through the 30-day follow-up visit. The hypothesis that cefpodoxime would be noninferior to ciprofloxacin by a 10 percent margin was formulated prior to data collection.

The researchers found that the overall clinical cure rate with the intent-to-treat approach in which patients lost to follow-up were attributed as having clinical cure was 93 percent (139/150) for ciprofloxacin compared with 82 percent (123/150) for cefpodoxime. The test of noninferiority was not statistically significant. In an alternative intent-to-treat analysis in which patients who were lost to follow-up were considered to have not

responded to treatment, the clinical cure rate was 83 percent (124/150) for ciprofloxacin compared with 71 percent (106/150) for cefpodoxime. Among women who reported no previous UTI in the past year before enrollment, the overall clinical cure rate was 96 percent for ciprofloxacin and 83 percent for cefpodoxime, a magnitude of difference that was not seen among women who reported 1 or more UTIs in the past year before enrollment.

The clinical cure rate at the first follow-up visit (average, 5 days after treatment) was 93 percent for ciprofloxacin compared with 88 percent for cefpodoxime. The microbiological cure rate at the first follow-up visit (average, 5 days after treatment) was 96 percent for ciprofloxacin compared with 81 percent for cefpodoxime. At first follow-up, 16 percent of women in the ciprofloxacin group compared with 40 percent of women in the cefpodoxime group had vaginal E coli colonization (the presence of organisms on some surface or in some bodily fluid that are not causing symptoms). The differential effect of the two drugs on vaginal E coli colonization may have played a role in the difference in clinical outcomes.

"Among women with uncomplicated cystitis, a 3-day regimen of cefpodoxime compared with ciprofloxacin did not meet criteria for noninferiority for achieving clinical cure," the authors write. They add that this finding, along with concerns about possible ecological adverse effects associated with other broad-spectrum β-lactams (a class of antimicrobials that includes cefpodoxime), do not support the use of cefpodoxime as a first-line fluoroquinolone-sparing antimicrobial for acute uncomplicated cystitis.

(JAMA. 2012;307[6]:583-589. Available pre-embargo to the media at www.jamamedia.org)

Editor's Note: *This work was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases. The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Hooton reported that he has been a consultant for Pinnacle Pharmaceuticals, Pfizer Inc., and Alita Pharmaceuticals. No other author reported disclosures.*

http://www.eurekalert.org/pub_releases/2012-02/uab-pds020212.php

Parkinson's disease: Study of live human neurons reveals the disease's genetic origins

UB researchers identify how the parkin gene works and how mutations cause Parkinson's disease

BUFFALO, N.Y. - Parkinson's disease researchers at the University at Buffalo have discovered how mutations in the parkin gene cause the disease, which afflicts at least 500,000 Americans and for which there is no cure.

The results are published in the current issue of Nature Communications. The UB findings reveal potential new drug targets for the disease as well as a screening platform for discovering new treatments that might mimic the protective functions of parkin. UB has applied for patent protection on the screening platform.

"This is the first time that human dopamine neurons have ever been generated from Parkinson's disease patients with parkin mutations," says Jian Feng, PhD, professor of physiology and biophysics in the UB School of Medicine and Biomedical Sciences and the study's lead author.

As the first study of human neurons affected by parkin, the UB research overcomes a major roadblock in research on Parkinson's disease and on neurological diseases in general. The problem has been that human neurons live in a complex network in the brain and thus are off-limits to invasive studies, Feng explains.

"Before this, we didn't even think about being able to study the disease in human neurons," he says. "The brain is so fully integrated. It's impossible to obtain live human neurons to study."

But studying human neurons is critical in Parkinson's disease, Feng explains, because animal models that lack the parkin gene do not develop the disease; thus, human neurons are thought to have "unique vulnerabilities. Our large brains may use more dopamine to support the neural computation needed for bipedal movement, compared to quadrupedal movement of almost all other animals," he says.

Since in 2007, when Japanese researchers announced they had converted human cells to induced pluripotent stem cells (iPSCs) that could then be converted to nearly any cells in the body, mimicking embryonic stem cells, Feng and his UB colleagues saw their enormous potential. They have been working on it ever since.

"This new technology was a game-changer for Parkinson's disease and for other neurological diseases," says Feng. "It finally allowed us to obtain the material we needed to study this disease."

The current paper is the fruition of the UB team's ability to "reverse engineer" human neurons from human skin cells taken from four subjects: two with a rare type of Parkinson's disease in which the parkin mutation is the cause of their disease and two healthy subjects who served as controls.

"Once parkin is mutated, it can no longer precisely control the action of dopamine, which supports the neural computation required for our movement," says Feng.

The UB team also found that parkin mutations prevent it from tightly controlling the production of monoamine oxidase (MAO), which catalyzes dopamine oxidation.

"Normally, parkin makes sure that MAO, which can be toxic, is expressed at a very low level so that dopamine oxidation is under control," Feng explains. "But we found that when parkin is mutated, that regulation is gone, so MAO is expressed at a much higher level. The nerve cells from our Parkinson's patients had much higher levels of MAO expression than those from our controls. We suggest in our study that it might be possible to design a new class of drugs that would dial down the expression level of MAO."

He notes that one of the drugs currently used to treat Parkinson's disease inhibits the enzymatic activity of MAO and has been shown in clinical trials to slow down the progression of the disease.

Parkinson's disease is caused by the death of dopamine neurons. In the vast majority of cases, the reason for this is unknown, Feng explains. But in 10 percent of Parkinson's cases, the disease is caused by mutations of genes, such as parkin: the subjects with Parkinson's in the UB study had this rare form of the disease.

"We found that a key reason for the death of dopamine neurons is oxidative stress due to the overproduction of MAO," explains Feng. "But before the death of the neurons, the precise action of dopamine in supporting neural computation is disrupted by parkin mutations. This paper provides the first clues about what the parkin gene is doing in healthy controls and what it fails to achieve in Parkinson's patients."

He noted in this study that these defects are reversed by delivering the normal parkin gene into the patients' neurons, thus offering hope that these neurons may be used as a screening platform for discovering new drug candidates that could mimic the protective functions of parkin and potentially even lead to a cure for Parkinson's.

While the parkin mutations are only responsible for a small percentage of Parkinson's cases, Feng notes that understanding how parkin works is relevant to all Parkinson's patients. His ongoing research on sporadic Parkinson's disease, in which the cause is unknown, also points to the same direction.

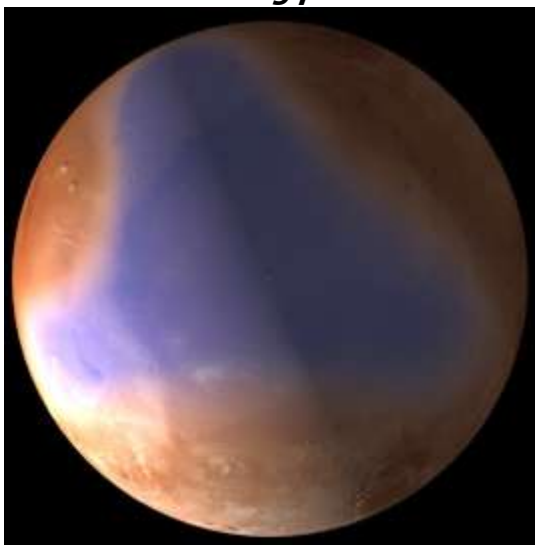
In addition to Feng, co-authors are Houbo Jiang, PhD, Yong Ren, PhD, Eunice Y. Yuen, all research assistant professors at UB; Ping Zhong, PhD, research scientist, Mahboobe Ghaedi, PhD, postdoctoral associate, Zhixing Hu, PhD, postdoctoral associate, and Zhen Yan, PhD, professor, all of the UB Department of Physiology and Biophysics. Other co-authors are Gissou Azabdaftari, MD, of the Roswell Park Cancer Institute, and Kazuhiro Nakaso, MD, of Tottori University in Japan.

http://www.physorg.com/news/2012-02-mars-radar-strong-evidence-ocean.html

Mars Express radar gives strong evidence for former Mars ocean

ESA's Mars Express has returned strong evidence for an ocean once covering part of Mars.

PhysOrg.com - Using radar, it has detected sediments reminiscent of an ocean floor within the boundaries of previously identified, ancient shorelines on Mars. The MARSIS radar was deployed in 2005 and has been collecting data ever since.



Jérémie Mouginot, Institut de Planétologie et d'Astrophysique de Grenoble (IPAG) and the University of California, Irvine, and colleagues have analysed more than two years of data and found that the northern plains are covered in low-density material."We interpret these as sedimentary deposits, maybe ice-rich," says Dr. Mouginot. "It is a strong new indication that there was once an ocean here."

The existence of oceans on ancient Mars has been suspected before and features reminiscent of shorelines have been tentatively identified in images from various spacecraft. But it remains a controversial issue.

New results from the MARSIS radar on Mars Express give strong evidence for a former ocean of Mars. The radar detected sediments reminiscent of an ocean floor inside previously identified, ancient shorelines on the red planet. The ocean would have covered the northern plains billions of years ago. **Credits: ESA, C. Carreau**

Two oceans have been proposed: 4 billion years ago, when warmer conditions prevailed, and also 3 billion years ago when subsurface ice melted following a large impact, creating outflow channels that drained the water into areas of low elevation.

"MARSIS penetrates deep into the ground, revealing the first 60–80 metres of the planet's subsurface," says Wlodek Kofman, leader of the radar team at IPAG.

"Throughout all of this depth, we see the evidence for sedimentary material and ice."

The sediments revealed by MARSIS are areas of low radar reflectivity. Such sediments are typically low-density granular materials that have been eroded away by water and carried to their final destination.

This later ocean would however have been temporary. Within a million years or less, Dr. Mouginot estimates, the water would have either frozen back in place and been preserved underground again, or turned into vapour and lifted gradually into the atmosphere.

"I don't think it could have stayed as an ocean long enough for life to form."

In order to find evidence of life, astrobiologists will have to look even further back in Mars' history when liquid water existed for much longer periods.

Nevertheless, this work provides some of the best evidence yet that there were once large bodies of liquid water on Mars and is further proof of the role of liquid water in the martian geological history.

"Previous Mars Express results about water on Mars came from the study of images and mineralogical data, as well as atmospheric measurements. Now we have the view from the subsurface radar," says Olivier Witasse, ESA's Mars Express Project Scientist.

"This adds new pieces of information to the puzzle but the question remains: where did all the water go?"

Mars Express continues its investigation. *Provided by European Space Agency*

http://medicalxpress.com/news/2012-02-green-tea-disability-elderly.html

Green tea found to reduce disability in the elderly

A lot of research has been done over the past several years looking into the health benefits of green tea.

Medical Xpress - As a result, scientists have found that regular consumption of the beverage leads to a reduction in several maladies often associated with aging, such as osteoporosis, stroke and cognitive impairment. But until now, according to the authors of a new study on its benefits, no such studies have been undertaken to determine if regular tea drinking provides other benefits, such as a reduction in functional disabilities. Because of this, a research project was undertaken by a team from Tokyo's Graduate School of Medicine, and they have found that older people who drink more green tea tend to have less functional disabilities than do those who don't. They have published their findings in The American Journal of Clinical Nutrition.

The team describes functional disabilities as those that interfere with living a normal life, such as being able to dress or bathe without assistance, or to perform household chores, or go for a walk. To find out if drinking green tea regularly helps people ward off such disabilities as they age, the team surveyed 13,998 adults age 65 and over and followed their eating, drinking and health habits over a three year period. They also accessed Japan's Long-term Care Insurance database to help in gathering statistics.

After compiling all the data, the team found that people who drank more of the green tea, tended to have the least number of functional disabilities. Put into numbers, they found that approximately 13% of those tested that drank one cup or less of the tea every day wound up with a functional disability, whereas only 7% of those who drank five cups or more each day became so.

The research team isn't claiming they've found absolute proof that drinking a lot of green tea every day will ward of functional disabilities, but that instead their research suggests that it seems likely. They say that those who drank more green tea every day also tended to live healthier lifestyles, such as eating more fish, fruits and vegetables, staying more active and maintaining a more well-rounded social life that included family. However, they note, even after discounting such factors, those that drank more tea still did better than did those who did not. Researchers in general aren't really clear about why green tea has health benefits, but suspect it has something to do with a compound in it called EGCG, an antioxidant that appears to ward off cell damage that can lead to disease.

More information: Green tea consumption and the risk of incident functional disability in elderly Japanese: the Ohsaki Cohort 2006 Study, Am J Clin Nutr, First published January 25, 2012, doi: 10.3945/ajcn.111.023200

Abstract

Background: Previous studies have reported that green tea consumption is associated with a lower risk of diseases that cause functional disability, such as stroke, cognitive impairment, and osteoporosis. Although it is expected that green tea consumption would lower the risk of incident functional disability, this has never been investigated directly.

Objective: The objective was to determine the association between green tea consumption and incident functional disability in elderly individuals.

Design: We conducted a prospective cohort study in 13,988 Japanese individuals aged ≥65 y. Information on daily green tea consumption and other lifestyle factors was collected via questionnaire in 2006. Data on functional disability were retrieved from the public Long-term Care Insurance database, in which subjects were followed up for 3 y. We used Cox proportional hazards regression analysis to investigate the association between green tea consumption and functional disability.

Results: The 3-y incidence of functional disability was 9.4% (1316 cases). The multiple-adjusted HR (95% CI) of incident functional disability was 0.90 (0.77, 1.06) among respondents who consumed 1–2 cups green tea/d, 0.75 (0.64, 0.88) for

those who consumed 3–4 cups/d, and 0.67 (0.57, 0.79) for those who consumed ≥5 cups/d in comparison with those who consumed <1 cup/d (P-trend < 0.001).
Conclusion: Green tea consumption is significantly associated with a lower risk of incident functional disability, even after adjustment for possible confounding factors.

http://www.eurekalert.org/pub_releases/2012-02/bc-pwd020612.php

Pneumonia wonder drug: Zinc saves lives

Respiratory tract infections, including pneumonia, are the most common cause of death in children under the age of five.

In a study looking at children given standard antibiotic therapy, new research published in BioMed Central's open access journal BMC Medicine shows how zinc supplements drastically improved children's chances of surviving the infection. The increase in survival due to zinc (on top of antibiotics) was even greater for HIV infected children.

In a double-blind, randomized, placebo-controlled trial, 350 children, aged from six months to five years old, were treated with standard antibiotic therapy at Mulago Hospital. Half the children were given zinc and the other half a placebo.

The researchers from Makerere University found that while there was no difference between zinc and placebo in the time it took to recover from the infection (measured by time it took to return to a normal temperature, reparatory rate and oxygen saturation) the risk of death between the groups was very different. 4% of the children taking zinc died compared to 12% of the children without zinc. This means that an extra eight out of 100 children could have been saved by taking zinc. Among the HIV infected children this rose to 26 out of every 100.

Prof James Tumwine explained, "Zinc is known to bolster the immune system and zinc deficiency is rife all over the developed, and developing, world. In Uganda, where this study was performed, zinc deficiency in some areas can be as high as 70%. We would only need to give 13 of these children with pneumonia zinc on top of their antibiotics to save one life. This equates to about 4 USD – a small price to pay."

Notes to Editors *1. Zinc adjunct therapy reduces case fatality in severe childhood pneumonia: a randomized double blind placebo-controlled trial Maheswari G Srinivasan, Grace Ndeezi, Cordelia Katureebe Mboijana, Sarah Kiguli, Gabriel S Bimenya, Victoria Nankabirwa and James K Tumwine BMC Medicine (in press)*

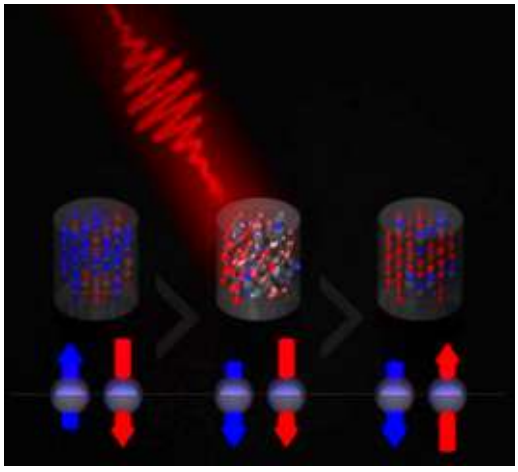
http://www.physorg.com/news/2012-02-physicists-magnetic-breakthrough.html

Physicists 'record' magnetic breakthrough

Scientists demonstrate a new way of magnetic recording which allows information to be processed hundreds of times faster than current technology.

An international team of scientists has demonstrated a revolutionary new way of magnetic recording which will allow information to be processed hundreds of times faster than by current hard drive technology.

The researchers found they could record information using only heat - a previously unimaginable scenario. They believe this discovery will not only make future magnetic recording devices faster, but more energy-efficient too. The results of the research, which was led by the University of York's Department of Physics, are reported in the February edition of Nature Communications.



York physicist Thomas Ostler said: "Instead of using a magnetic field to record information on a magnetic medium, we harnessed much stronger internal forces and recorded information using only heat. This revolutionary method allows the recording of Terabytes (thousands of Gigabytes) of information per second, hundreds of times faster than present hard drive technology. As there is no need for a magnetic field, there is also less energy consumption."

Visualisation of ultrafast heat-induced magnetic switching. Before the laser pulse, the two components of the ferrimagnetic material Fe (Blue) and Gd (Red) are aligned anti-parallel to each other. The 60 femtosecond duration laser pulse rapidly heats the material and this alone induces a transient ferromagnetic-like state, where the Fe and Gd moments are aligned in parallel. After the laser pulse the moments relax to their usual state completing a single switching event in less than 5 picoseconds. **Credit: Richard Evans, University of York**

The multinational team of scientists included researchers from Spain, Switzerland, Ukraine, Russia, Japan and the Netherlands. Experimental work was carried out at the Paul Scherrer Institut in Switzerland, the Ioffe Physical Technical Institute of the Russian Academy of Sciences and Radboud University Nijmegen, Netherlands.

Dr Alexey Kimel, from the Institute of Molecules and Materials, Radboud University Nijmegen, said: "For centuries it has been believed that heat can only destroy the magnetic order. Now we have successfully demonstrated that it can, in fact, be a sufficient stimulus for recording information on a magnetic medium."

Modern magnetic recording technology employs the principle that the North pole of a magnet is attracted to the South pole of another and two like poles repulse. Until now it has been believed that in order to record one bit of information – by inverting the poles of a magnet – there was a need to apply an external magnetic field. The stronger the applied field, the faster the recording of a magnetic bit of information.

However, the team of scientists has demonstrated that the positions of both the North and South poles of a magnet can be inverted by an ultrashort heat pulse, harnessing the power of much stronger internal forces of magnetic media.

More information: *The paper "Ultrafast heating as a sufficient stimulus for magnetization reversal in a ferrimagnet" is published in Nature Communications on Tuesday, 7 February. http://dx.doi.org/ ... ms1666 Provided by University of York*

http://www.wired.com/wiredscience/2012/02/schmallenberg-virus/

Fast-Spreading Animal Virus Leaps Europe, UK Borders

A newly identified disease is moving rapidly through livestock in Europe and has authorities both worried and puzzled.

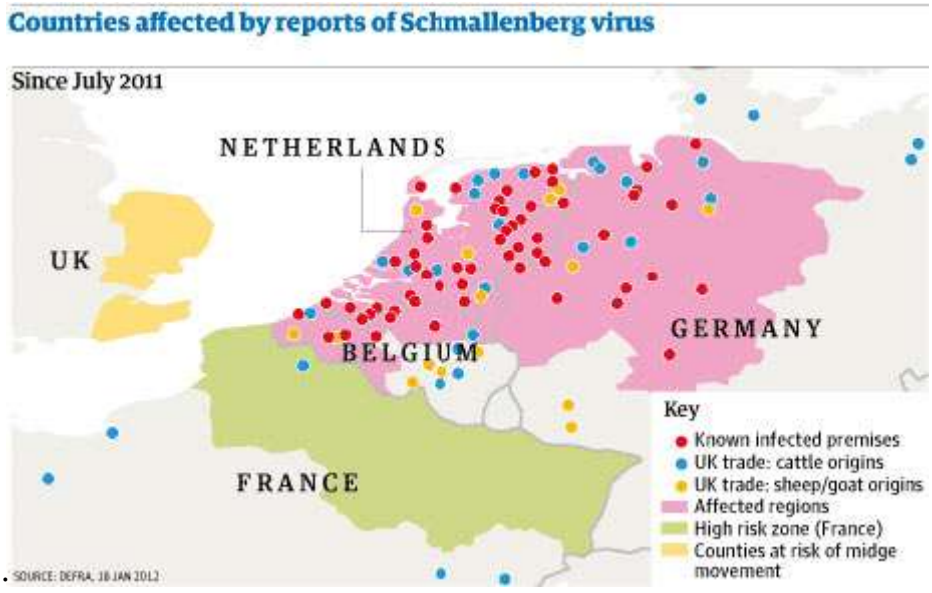
By Maryn McKenna

The disease, dubbed Schmallenberg virus for a town in west-central Germany where one of the first outbreaks occurred, makes adult animals only mildly ill, but causes lambs, kids and calves to be born dead or deformed. The United Kingdom's Animal Health and Veterinary Laboratories Agency (AVHLA) said today that the virus has been found on 29 farms in England; in the past few weeks they found it in sheep, but today announced that they have identified it in cattle as well. In mainland Europe, it has been identified on several hundred farms in the Netherlands, Germany and Belgium, and most recently in France. The European Center for Disease Prevention and Control has said that the new virus's closest relatives do not cause disease in humans - but that other more distantly related viruses do:

The new virus belongs to the Bunyaviridae family, genus Orthobunyavirus, Simbu serogroup (preliminary information, based solely on genetic information)… Genetic characterisation has shown that the new virus is closest to the following Simbu serogroup viruses: Shamonda-, Aino- and Akabane-viruses, which do not cause disease in humans.

However, at least 30 orthobunyaviruses are zoonotic and may cause disease in humans, with symptoms ranging from mild to severe - e.g. La Crosse encephalitis virus, California Encephalitis virus, Cache Valley virus, Batai virus, Tahyna virus, Inkoo virus, Snowshoe Hare virus, Iquitos virus and Oropouche virus.

The viral vector - the thing which spreads it - is believed to be midges, small flying biting insects (Culicoides) and maybe also mosquitoes (Culicidae). The disease doesn't pass from adult animal to another animal, but apparently does from a mother animal to its offspring in utero, and that is why it is showing up now: It's lambing season. With Europe enduring its coldest winter in decades, there are no virus-carrying insects flying around now. Instead, the animals that are giving birth to deformed and dead offspring were infected last summer and fall. No one has been able to say so far whether the organism can survive in insects over the winter (the way West Nile virus, for instance, may).



The disease has now been confirmed on farms in the UK, as well as Germany, the Netherlands and Belgium. **Source: Defra, 18 January**

The insect vector is also believed to be how the disease got to the UK. The seven counties where it has been found so far - Norfolk, Suffolk, Essex, Kent, East Sussex, West Sussex and Hertfordshire - are all in the southeast. They are the first places in the UK to catch winds from the Continent, and therefore the first where anything carried by the wind, including insects, might drop out.

The international disease-warning mailing list ProMED has collected links to all the maps of outbreaks published so far: France Netherlands Belgium Germany. Agricultural media are starting to record the economic fallout, including a Russian ban on European livestock and the possibility of a ban on shipping live animals, including to livestock shows and sales. And the CDC journal Emerging Infectious Diseases has just posted ahead of print the ***first paper on the new disease***.

Meanwhile, the British Veterinary Record seizes on the outbreaks to make a larger point: Finding new diseases such as Schmallenberg depends on having good disease surveillance - but in the UK, funding is about to be sharply cut. It is precisely this kind of emerging disease threat that scanning surveillance aims to detect – and it is also this kind of disease threat that might not be detected promptly if, for whatever reason, arrangements for surveillance fall short of the mark…

Schmallenberg virus is not the first new disease to be detected by scanning surveillance, nor will it be the last. It was scanning surveillance that identified the emergence of BSE in the late 1980s and, in more recent years, it has been responsible for, among other things, the early detection of pandemic H1N1 influenza in pigs, four notifiable avian disease outbreaks, bovine TB in non-bovine species, antimicrobial resistance in Salmonella and virulent psoroptic mange in cattle. The AHVLA has noted that the value of its surveillance programme has greatly exceeded the cost in recent years, with monetised benefits having been estimated at over £200 million a year.

For more, here's ***a Guardian story*** with a map of European hot-spots and one from the ***East Anglian Daily Times*** on the most recent developments.

http://bit.ly/zEZCM

Most fish in the sea evolved on land

Family histories don't come much more bizarre. Three-quarters of the fish in the sea can trace their origins back to a freshwater ancestor.

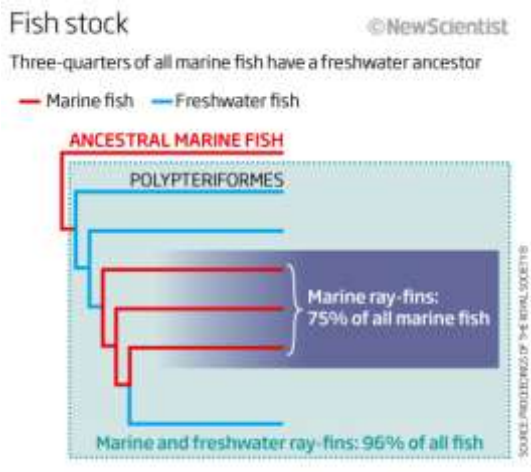
00:01 08 February 2012 by Colin Barras

The finding highlights how important rivers and lakes are as a source of new species, just as that supply is under threat from disappearing freshwater habitats. Fish first evolved in the sea. The oceans have been teeming with them for almost half a billion years, so there is no reason to doubt that the fish living there today did all their evolving in salt water - until you take a closer look at their family tree.

Greta Vega and John Wiens at Stony Brook University in New York noticed something peculiar while studying the evolutionary tree of ray-finned fish, a mega-group comprising 96 per cent of all freshwater and marine fish species on the planet. They realised that all the fossils belonging to the ancestral group that gave rise to ray-fins some 300 million years ago – known as the polypteriformes – came from freshwater deposits. In fact, according to Vega and Wiens's tree, the ray-fins may not have taken to the sea in large numbers until about 170 million years ago. Their descendants now make up three-quarters of all marine fish (see diagram).

We've seen this kind of topsy-turvy evolution before. Most whales, dolphins and porpoises, live in the sea, but like the ray-finned fish, they all evolved in rivers.

Michael Benton of the University of Bristol, UK, says that combined with what we know about whales and dolphins, the new study may point to a more general pattern: that most major groups of vertebrates came from land-based ecosystems. But we'll need many more studies to confirm that, he says.



What could be driving such a pattern? Wiens says it is possible that seas may be more prone to extinctions than land, rivers or lakes; while rivers and lakes form an "arc of survival" that can reseed the oceans when marine species are lost.

"I don't think our results show that seas are strongly inhospitable, but they may become so at certain points in time," he says. Unfortunately, the strong ocean acidification that is predicted for the near future means we may be heading for one of those times now, he adds.

Today, however, rivers and lakes may not be healthy enough to help re-supply the oceans. "Freshwater ecosystems suffer from a higher rate of species loss than any other major ecosystem," says Peter Bosshard, policy director at International Rivers, a non-profit NGO based in Berkeley, California. "This study shows that by damming, diverting and polluting the world's rivers, we may deplete the seed bank of future generations."

Journal reference: Proceedings of the Royal Society B, DOI: 10.1098/rspb.2012.0075

http://www.eurekalert.org/pub_releases/2012-02/hfss-npb020612.php

New procedure bests standard of care for fixing damaged cartilage

A new study has demonstrated that a procedure wherein healthy cartilage is transplanted to fix an area of damaged cartilage is superior to the standard of care for repairing cartilage defects

A new study has demonstrated that a procedure wherein healthy cartilage is transplanted to fix an area of damaged cartilage (osteoarticular cartilage transplantation or OATS procedure) is superior to the standard of care for repairing cartilage defects. It is thought that fixing such lesions may ultimately help to prevent the onset of osteoarthritis, and get athletic individuals back to sporting activities reliably. The study by Hospital for Special Surgery researchers was reported at the annual meeting of the American Academy of Orthopaedic Surgeons, Feb. 7-11.

"Studies have shown that there is only about a 40% return to sport after the microfracture procedure which is the standard of care treatment in the U.S. Over 90% of patients return to sport with the OATS procedure, said Riley J. Williams, III, M.D., a sports medicine orthopedic surgeon at Hospital for Special Surgery (HSS) in New York City and senior investigator of the study. "For those who have isolated cartilage lesions of the femur and are interested in a return to sport in a timely and predictable fashion, the OATS procedure, relative to microfracture, represents a better option."

For years, researchers have known that erosion of articular cartilage, the soft lining or cushion at the end of bones, can lead to symptomatic osteoarthritis. The cartilage can be damaged from normal wear and tear or from a traumatic injury. Once the cartilage is damaged, it continues to deteriorate. Athletes with progressive osteoarthritis are often forced to stop playing their sport of choice.

Over the years, researchers have developed a number of procedures for repairing cartilage in patients who range from roughly 16 to 50 years of age. The current standard of care is microfracture, an arthroscopic procedure that involves using a tiny pick to punch holes into the base of the damaged cartilage area. This promotes bleeding and allows bone marrow cells to come to the surface of the damaged tissue. As a result, the cells then change into fibrocartilage cells and heal the defect. A study from the HSS Cartilage Registry showed that only about 40% of athletes return to sport after this procedure. "40% is such an abysmal rate of return to sport, which is why we keep looking for other repair methods to help our patients," said Dr. Williams, who is also director of the HSS Institute for Cartilage Repair.

Another more recently developed procedure is OATS, which involves transferring healthy cartilage tissue from one part of a person's knee to the damaged area. The transplanted graft includes cartilage and underlying bone and can be performed arthroscopically. A single plug of cartilage may be transferred or multiple plugs may be transferred in a procedure called mosaicplasty. Each plug is a few millimeters in diameter, and when multiple plugs are moved to the damaged area, it creates a mosaic appearance.

Several European studies have shown that the OATS procedure provides a higher return to sport and a longer lasting result, but HSS researchers wanted to verify the results in the U.S. population. "There is an essential difference between American sports and European sports. When you talk about European sports, you are really talking about soccer," said Dr. Williams, whereas most U.S. patients mostly participate in American football, basketball, running, as well as soccer.

To test the two procedures in the U.S. population, HSS investigators recruited 48 patients who had "potholes" in their cartilage in the area known as the femoral condyle, an area located at the end of the thighbone in the upper half of the knee. For the control group, the researchers identified 48 patients in the HSS Cartilage Registry who were matched for gender and underwent microfracture for a similar cartilage repair, same lesion size and location.

Clinicians evaluated patients prior to surgery and at one, two, three and five years of follow-up. They used a variety of tools commonly used to measure outcomes in patients undergoing these types of procedures. They used the short-form (SF)-36 health survey, a 36-question scale that includes a gamut of questions about general health and is widely used across all fields of medicine. They used two knee specific questionnaires: the international knee documentation committee (IKDC) scores and the Knee Outcome Survey (KOS). And they used the Marx Activity Level that is scored on a scale from 0 to 16 and gauges a person's ability to do four activities: running, cutting, decelerating, and pivoting.

They found no difference in the knee outcome surveys or SF-36 form, but they did identify significant differences in the Marx Activity Level. Patients who underwent the OATS procedure had higher scores than patients who underwent microfracture at one year from baseline (score 5.21 vs. 4.11), two years (7.29 vs. 3.71), three years (7.75 vs. 2.91) and five years (8.55 vs. 2.89).

"The Marx activity rating scale correlates directly to the amount of physical activity that you can do at the time of the assessment," said Dr. Williams. "Patients who underwent the OATS were able to do more sports and more athletic activities compared to the microfracture group at the same time point. We now have another procedure which is likely to result in a return to sport more predictably."

He said the results are not surprising given that the OATS repair results in a natural cartilage repair whereas microfracture results in a repair comprised mainly of fibrocartilage that has been shown to be biomechanically inferior to articular cartilage.

Dr. Williams is the head team physician for the Nets NBA basketball team and the Major League Soccer's New York Red Bulls. Other investigators involved in the research are Thomas Wickiewicz, M.D., Russell Warren, M.D., and Scott Rodeo, M.D., from Hospital for Special Surgery; Heather Harnly, M.D., a former HSS fellow who is now at Robert Wood Johnson University Hospital, East Brunswick, New Jersey; and Aaron Krych, M.D., a former HSS fellow who is now at the Mayo Clinic, Rochester, Minn.

http://bit.ly/xIaEtE

Men get creative with grammar when they want to impress fertile women

Men who find themselves in the company of fertile women are more likely to make creative attempts at sentence structure to signify their mating fitness, a study has found.

Researchers discovered that when young men talk with a woman who is in the fertile period of her menstrual cycle, they react to small changes in her facial skin tone, vocal pitch and scent. The changes activate their mating goals and cause them to shift the way they speak.

Conversational partners often align their linguistic choices to demonstrate affiliation, but when men talk to fertile women they are less likely to copy their sentence structure – and more likely to try to stand out, the researchers found. Their study, led by Michael Kaschak, an associate professor of psychology at Florida State University in Tallahassee, is published in the journal PLoS ONE.

In one experiment, they studied 123 male college students as they took turns interacting with five female college students at different times in their menstrual cycles. After getting to know each other, the men and women had to give one-line descriptions of a group of drawings.

When the women were at the low point of their menstrual cycle, the men mimicked their sentence constructions 62% of the time. When they were at their peak, the men did so 49.7% of the time.

The results reflected the idea that men may use "non-conforming behaviour" to stand out to potential mates, the researchers said, but was "at odds with a wide range of data suggesting that attraction to a conversational partner should lead to an increase in matching behavior".

Dr Kaschak said that "being creative is a way of showing one's mental acumen. Within the context of our experiment, non-aligning sentence structures may be used as a way of showing creativity or non-conformity so that you can stand out a bit. "We'll need to do more research to pin down the motivations more precisely – for example, is it creativity, non-conformity, or some combination of both, that is motivating the behaviour?"

Although he did not ask the men in the study if they knew what they were doing, Dr Kaschak said that "structural repetition effects are virtually always unconscious; participants have no idea that they are repeating the syntactic structures of their conversation partner. I'd bet that the same is true for the men in our studies."

Nenagh Kemp, a lecturer in the School of Psychology at the University of Tasmania, said there was ample evidence that under normal circumstances, someone else's choice of sentence construction can influence our own. "If we hear someone else describe a scene as "The teacher is reading a book to the children", we'll be more likely to describe a subsequent scene with the same grammatical pattern, for example, saying "The farmer is giving some hay to the horses", rather than "The farmer is giving the horses some hay"."

The research extended current thinking about the attractiveness of non-conforming behaviour by showing how men would switch between different grammatical constructions when engaging with women.

"It seems that men can show off their potential as a partner by structuring their sentences a little bit differently, and that this propensity varies according to how receptive the woman appears."

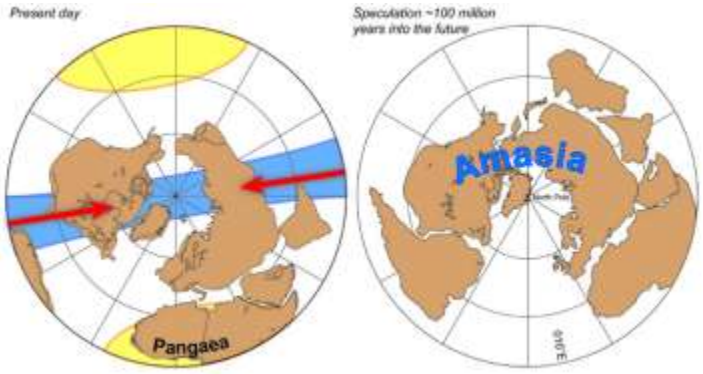
http://www.physorg.com/news/2012-02-amasia-supercontinent-arctic-ocean-caribbean.html

Amasia: As next supercontinent forms, Arctic Ocean, Caribbean will vanish first

Yale scientists theorize that the present-day Arctic Ocean and Caribbean Sea will vanish as North and South America fuse during a mutual northward migration that leads to a collision with Europe and Asia.

PhysOrg.com - Geologists at Yale University have proposed a new theory to describe the formation of supercontinents, the epic process by which Earth's major continental blocks combine into a single vast landmass. The new model radically challenges the dominant theories of how supercontinents might take shape.

In a paper published Feb. 9 in the journal Nature, Yale researchers introduce a process called orthoversion, in which each succeeding supercontinent forms 90 degrees from the geographic center of its ancient predecessor. Under the theory, the present-day Arctic Ocean and Caribbean Sea will vanish as North and South America fuse during a mutual northward migration that leads to a collision with Europe and Asia.

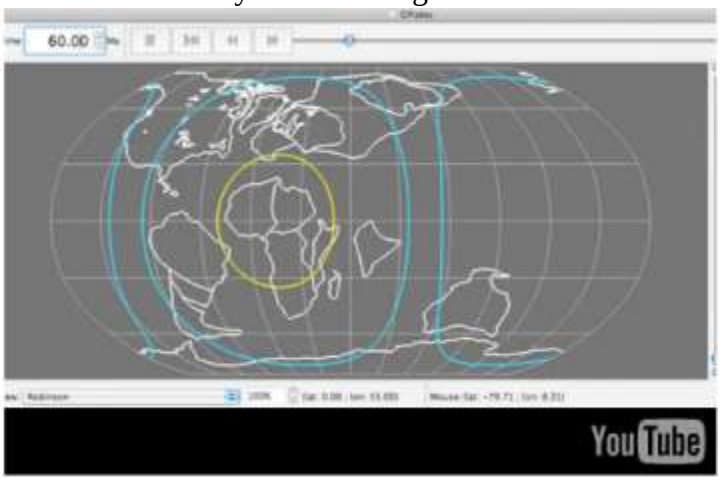


"After those water bodies close, we're on our way to the next supercontinent," said Ross N. Mitchell, the Yale doctoral student who is the paper's first author. "You'd have the Americas meeting Eurasia practically at the North Pole."

The researchers do not speculate in the paper when the next supercontinent, named Amasia for its union of America with Eurasia, will emerge, but the event is far distant - between 50 million and 200 million years away, Mitchell said.

The new theory contrasts with the standard theories about supercontinent formation, introversion and extroversion, which hold that supercontinents form either 0 or 180 degrees away from the geographic center of the previous supercontinent. Under these earlier theories, the Atlantic Ocean will disappear and the next supercontinent will form with a center more or less in the same spot as the last supercontinent's center (present-day Africa), or, alternately, the Pacific Ocean will disappear and the next supercontinent will form with a center on the opposite side of the globe.

Mitchell and colleagues arrived at the new theory after an extensive analysis of the magnetism of ancient rocks. After each historical supercontinent assembled, it underwent a series of back-and-forth rotations around a stable axis along the equator. From one supercontinent to the next, the axes were offset from each other by about 90 degrees, the Yale team showed - consistent with orthoversion, but not with either introversion or extroversion.



"This kind of analysis gives us a way to arrange continents in both latitude and longitude, providing a better understanding in patterns of biological dispersal and the dynamics of Earth's deep interior," said Yale doctoral student Taylor M. Kilian, the study's second author.

***From the supplementary information of the paper authored by Ross N. Mitchell, Taylor M. Kilian & David A. D. Evans, "Supercontinent cycles and the calculation of absolute palaeolongitude in deep time,"* Nature 482: 208--211 (09 February 2012). http://dx.doi.org/10.1038/nature10800**

The most recent supercontinent, Pangea, formed about 300 million years ago with Africa at its center. It began breaking apart into the seven continents of today with the birth of the Atlantic Ocean about 100 million years later. Researchers believe Pangea is the third or fourth supercontinent in Earth's history. Its immediate predecessors were Rodinia (which formed about 1 billion years ago) and Nuna (which formed about 1.8 billion years ago). The paper's senior author, Professor David A.D. Evans of Yale, has devoted most of his career to studying the internal arrangements of the Earth's continental blocks.

Under the orthoversion model, either Asia or North America would become the center of Amasia, in a spot currently occupied by the Arctic Ocean. A newly formed mountain range will stitch them together.

"Such speculations far into the future cannot be tested by waiting around 100 million years, of course," Evans said, "but we can use the patterns gleaned from ancient supercontinents to think deeply about humanity's current existence in time and space within the grand tectonic dance of the Earth."

More information: *Supercontinent cycles and the calculation of absolute palaeolongitude in deep time, Nature 482, 208–211 (09 February 2012) doi:10.1038/nature10800*

Abstract

Traditional models of the supercontinent cycle predict that the next supercontinent - 'Amasia' - will form either where Pangaea rifted (the 'introversion'1 model) or on the opposite side of the world (the 'extroversion'2, 3, 4 models). Here, by contrast, we develop an 'orthoversion'5 model whereby a succeeding supercontinent forms 90° away, within the great circle of subduction encircling its relict predecessor. A supercontinent aggregates over a mantle downwelling but then

influences global-scale mantle convection to create an upwelling under the landmass6. We calculate the minimum moment of inertia about which oscillatory true polar wander occurs owing to the prolate shape of the non-hydrostatic Earth5, 7. By fitting great circles to each supercontinent's true polar wander legacy, we determine that the arc distances between successive supercontinent centres (the axes of the respective minimum moments of inertia) are 88° for Nuna to Rodinia and 87° for Rodinia to Pangaea - as predicted by the orthoversion model. Supercontinent centres can be located back into Precambrian time, providing fixed points for the calculation of absolute palaeolongitude over billion-year timescales. Palaeogeographic reconstructions additionally constrained in palaeolongitude will provide increasingly accurate estimates of ancient plate motions and palaeobiogeographic affinities. *Provided by Yale University*

http://www.scientificamerican.com/article.cfm?id=gene-therapy-blindness

Sight Seen: Gene Therapy Restores Vision in Both Eyes

Two doses of gene therapy restore vision to three women who were born nearly blind

By Ferris Jabr | Wednesday, February 8, 2012 | 6

Gene therapy has markedly improved vision in both eyes in three women who were born virtually blind. The patients can now avoid obstacles even in dim light, read large print and recognize people's faces. The operation, researchers predict, should work even better in children and adolescents blinded by the same condition.

The advance, reported in the February 8 issue of Science Translational Medicine, extends earlier work by the same group. Between 2008 and 2011, Jean Bennett of the University of Pennsylvania's Mahoney Institute of Neurological Sciences and her colleagues used gene therapy to treat blindness in 12 adults and children with Leber's congenital amaurosis (LCA), a rare inherited eye disease that destroys vision by killing photoreceptors - light-sensitive cells in the retina at the back of the eye. Typically, afflicted children start life with poor vision, which worsens as more and more photoreceptors die.

The treatment grew out of the understanding that people with the disorder become blind because of genetic mutations in retinal cells. One mutated gene that causes the disorder is named RPE65. An enzyme encoded by RPE65 helps break down a derivative of vitamin A called retinol into a substance that photoreceptors need to detect light and send signals to the brain. Mutant forms of RPE65 prevent the production of this enzyme in a "nursery" layer of cells called the retinal pigment epithelium, which is attached to the retina and nourishes photoreceptors by breaking down retinol, among other cellular services.

In the initial study, retina specialist and Bennett's co-author Albert Maguire of Penn Medicine injected a harmless virus carrying normal copies of RPE65 into an area of the retinal pigment epithelium, which subsequently began producing the enzyme. In each of the 12 patients, Maguire treated one eye - the one with worse vision. Six patients improved so much they no longer met the criteria for legal blindness.

In the new study, Maguire injected the functional genes into the previously untreated eye in three of the women from the first group. Bennett followed the patients for six months after their surgeries. The women's vision in their previously untreated eye improved as soon as two weeks after the operation: They could navigate an obstacle course, even in dim light, avoiding objects that had tripped them up before, as well as recognize people's faces and read large signs. Bennett showed that not only were the women's eyes much more sensitive to light, their brains were much more responsive to optical input as well. Functional magnetic imaging showed regions of their visual cortices that had remained offline before gene therapy began to light up.

Surprisingly, Bennett reports, the second round of gene therapy further strengthened the brain's response to the initially treated eye as well as the newly treated one. "That wasn't something we had been expecting, but it makes sense because the two eyes act in concert, and some aspects of vision rely on binocularity." In the new paper, the authors suggest that neuroplasticity plays a role: It is possible that regions of the visual cortex responding to the newly flowing channel of information from the second eye bolster activity in areas of the visual cortex responding to the initially treated eye.

An institutional review board required that Bennett work with adults in the follow-up study, but she thinks the therapy will work even better in younger patients who have not lost as many photoreceptors. She says the results "really bode well" for restoring meaningful vision to people with LCA and other forms of inherited blindness.

http://www.scientificamerican.com/article.cfm?id=fasting-might-boost-chemo

Fasting Might Boost Chemo's Cancer-Busting Properties

A new animal study suggests that short-term starvation might improve outcomes for cancer patients undergoing chemotherapy

By Katherine Harmon | Wednesday, February 8, 2012 | 9

Cancer treatment can be brutal for patients. Many of the tools we have - chemotherapy, radiation - are big, blunt weapons that deal punishing blows to healthy tissues along with cancerous ones. So the hunt has been on for more and more finely targeted therapies that will attack malignant cells yet minimize damage to patients'

bodies. But a new study shows that we might be able to catch cancer cells off guard by using an ancient and body-wide tactic: fasting.

Fasting has long been practiced as part of various cultural traditions and has, more recently, gained favor in alternative and complementary medicine practices. But researchers are still figuring out whether nutritional deprivation can prevent or cure some diseases - and if so, how.

The new study found that in mice with cancer, fasting prior to chemotherapy often led to more tumor shrinkage than chemo alone. And in some cases, the combination apparently eliminated certain kinds of cancer. This fasting–chemo combo, the researchers suggest, "could extend the survival of advanced stage cancer patients by both retarding tumor progression and reducing side effects," they noted in their study, published online Wednesday in Science Translational Medicine. It might be able to help early-stage patients, too, they say.

One–two punch?

The new work builds on a 2008 mouse study that found fasting helped to protect healthy cells against chemotherapy's toxic effects. That finding raised flags in the cancer field. "The concern was we were also protecting the cancer cells," says Valter Longo, a professor of biology and gerontology at the University of Southern California Davis School of Gerontology and co-author of the new paper. So he and his colleagues embarked on five years of research to see whether that was the case, testing different fasting and chemotherapy regimens on a variety of cancers - glioma, melanoma, neuroblastoma, breast and ovarian - in mice. "We not only saw that the cancer was not protected but that it was sensitized" to the chemo, he says.

In the new work, fasting mice were allowed to drink water but were not given food for at least two days. When mice with breast cancer, glioma or melanoma were subjected to two rounds of 48-hour fasting before their chemo, their tumors shrunk more than those in mice that received chemotherapy alone.

Mice that had metastasized cancer and were put on the fasting-chemo plan showed a 40 percent greater reduction in their metastases than those that had been fed before receiving chemotherapy. They also seemed to live longer after getting this treatment. With two cycles of fasting and a high dose of chemo, 42 percent of mice with one of two types of metastatic neuroblastoma lived for more than 180 days, whereas all of their well-fed, chemo-treated mice had already died by then. Fasting and chemo together had an even more dramatic effect in a third type of metastatic neuroblastoma: about a quarter of mice lived for more than 300 days, at which point they still seemed to be cancer free.

Fasting appears to protect normal cells from chemotherapy's toxic effects by rerouting energy from growing and reproducing to internal maintenance. But cancer cells do not undergo this switch to self-repair and so continue to be susceptible to drug-induced damage - making for what the researchers call a differential stress resistance. Fasting, then, the authors wrote, should enhance the power of chemotherapies without having to resort to "the more typical strategy of increasing the toxicity of drugs."

The findings give a new boost to an old approach to medical research: generalized medicine. Personalized medicine will come around eventually, Longo says. But in the meantime, he is focused on finding treatments that can work across diseases. "Especially with cancer, we have an opportunity to look at what is common," he says. "What is it that, by definition, all cancer cells will have difficulty doing?" he asks. The fasting research suggests that the answer is adaptation.

As a cancer grows and its cells mutate, they become more specifically adapted to the environment - a tactic that often spell success for the malignancy. But, Longo says, "if you start changing the environment" by fasting, it has more trouble surviving chemo assaults than healthy tissue cells. Cancer cells, at least in breast cancer experiments, seemed to be fighting to stay alive in the starvation–chemo environment by eating up even more energy, which stresses the malignant cells and causes more damage in them.

Mary Helen Barcellos-Hoff, a professor at the New York University Langone Medical Center who was not involved in the new research, wonders if fasting is also having other effects in the body that is making it less hospitable to cancer, say by increasing immune system sensitivity to the cancer or helping to squelch vascularization of tumors. "I really think modifying the microenvironment to make it less permissive is really one of the untapped potentials for future cancer therapies, she says."

But as Longo notes, fasting - for two to three days in mice, which would be the equivalent of four to five days in humans - alters the body in myriad ways. "You look at their blood, everything changes," from the factors that control blood vessel growth to acids, he says. So now he and his team are going back to look for different signs of what is changing the fasting and chemo in hopes of further optimizing the timing and treatments.

From mice to people

The medical research field is strewn with promising cures-turned-casualties that had to be scrapped after showing promise in mice and failing to work in humans. The cancer battleground is one of the most littered. "Unfortunately we can cure cancer in mice, and we have a much harder time in humans," Barcellos-Hoff says.

The new study might help to quell some of the common reservations about promise in people. "One of the thing that's impressive about it is they used so many models of mouse cancer," Barcellos-Hoff says. The researchers tested more than a dozen different types of cancer lines in mice.

The other concern in translating this research to humans is that people with cancer - and especially those already undergoing treatment - have often already lost a substantial amount of weight. So prescribing days without food could be dangerous, especially for those who already have low blood pressure, diabetes or other metabolic conditions.

Most mice in the fasting groups were able to gain their weight back in five days or so. But humans, of course, are very different animals. Small fasting studies in cancer patients - some involving as long as 62 hours without food before treatment and 24 hours without food afterward - so far have produced only small side effects, Longo says, such as fatigue and headaches. And as Barcellos-Hoff notes, "I think humans would be much grouchier after two days without food." But so far the method seems to be relatively well tolerated in small, carefully controlled studies. And "chemotherapy does make you feel really bad," Barcellos-Hoff says. So fasting "is a lot less unpleasant than many of the things cancer patients are subjected to."

But the results from human trials are not conclusive yet, and Barcellos-Hoff emphasizes that even if it has looked promising in mouse studies, fasting alone (without chemotherapy) should not be something patients attempt on their own. Especially for a patient who already has decent odds of survival, undertaking an unproved approach can be quite risky.

And although many diets and alternative treatment regimens exist, Longo cautions, "if you do it without the science, you can end up doing more damage than good." For example, when a fast is too long the immune system starts to suffer, potentially leaving a patient even less protected.

"Everything has to be timed so that it maximizes the damage to the cancer," he says. Research into that is still ongoing. Even just finding out whether fasting with chemo will be as successful in humans as it is in mice might not come quickly. "You have so many cancers and so many chemos that it's almost like a never-ending process," Longo says.

http://www.bbc.co.uk/nature/16944753

Zebra stripes evolved to keep biting flies at bay

Why zebras evolved their characteristic black-and-white stripes has been the subject of decades of debate among scientists.

By Victoria Gill Science reporter, BBC Nature

Now researchers from Hungary and Sweden claim to have solved the mystery. The stripes, they say, came about to keep away blood-sucking flies. They report in the Journal of Experimental Biology that this pattern of narrow stripes makes zebras "unattractive" to the flies. They key to this effect is in how the striped patterns reflect light.

"We started off studying horses with black, brown or white coats," explained Susanne Akesson from Lund University, a member of the international research team that carried out the study. "We found that in the black and brown horses, we get horizontally polarised light." This effect made the dark-coloured horses very attractive to flies.

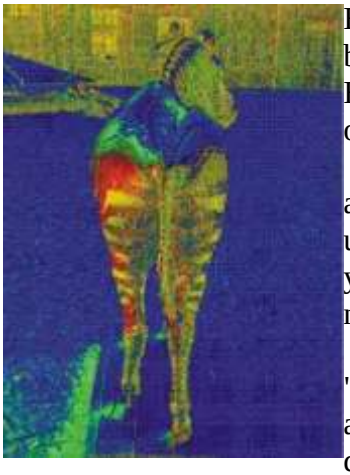
The team placed the sticky model horses in a fly-infested field

It means that the light that bounces off the horse's dark coat - and travels in waves to the eyes of a hungry fly - moves along a horizontal plane, like a snake slithering along with its body flat to the floor.

Dr Akesson and her colleagues found that horseflies, or tabanids, were very attracted by these "flat" waves of light. "From a white coat, you get unpolarised light [reflected]," she explained. Unpolarised light waves travel along any and every plane, and are much less attractive to flies. As a result, white-coated horses are much less troubled by horseflies than their dark-coloured relatives.

Having discovered the flies' preference for dark coats, the team then became interested in zebras. They wanted to know what kind of light would bounce off the striped body of a zebra, and how this would affect the biting flies that are a horse's most irritating enemy.

"We created an experimental set-up where we painted the different patterns onto boards," Dr Akesson told BBC Nature. She and her colleagues placed a blackboard, a whiteboard, and several boards with stripes of varying widths into one of the fields of a horse farm in rural Hungary. "We put insect glue on the boards and counted the number of flies that each one attracted," she explained.



The striped board that was the closest match to the actual pattern of a zebra's coat attracted by far the fewest flies, "even less than the white boards that were reflecting unpolarised light," Dr Akesson said. "That was a surprise because, in a striped pattern, you still have these dark areas that are reflecting horizontally polarised light. "But the narrower (and more zebra-like) the stripes, the less attractive they were to the flies."

To test horseflies' reaction to a more realistic 3-D target, the team put four life-size "sticky horse models " into the field - one brown, one black, one white and one black-and-white striped, like a zebra. The researchers collected the trapped flies every two days, and found that the zebra-striped horse model attracted the fewest.

Coloured images revealed how light was polarised as it bounced off a zebra's coat

Prof Matthew Cobb, an evolutionary biologist from the University of Manchester pointed out that the experiment was "rigorous and fascinating" but did not exclude the other hypotheses about the origin of zebras' stripes. "Above all, for this explanation to be true, the authors would have to show that tabanid fly bites are a major selection pressure on zebras, but not on horses and donkeys found elsewhere in the world... none of which are stripy," he told BBC Nature. "[They] recognise this in their study, and my hunch is that there is not a single explanation and that many factors are involved in the zebra's stripes.

There are many theories about why zebras are striped
Scientists have proposed that the mass of stripes in a large herd confuses predators
Others have shown that stripes may help the animals regulate their temperature, and that zebras recognise other individuals by their stripes
Studies of zebra embryos show that, early in development, they are black and they develop their white stripes later

http://www.eurekalert.org/pub_releases/2012-02/cwru-dqr020512.php

Drug quickly reverses Alzheimer's symptoms in mice

Case Western Reserve researchers discover FDA-approved drug rapidly clears amyloid from the brain and reverses cognitive defects

Neuroscientists at Case Western Reserve University School of Medicine have made a dramatic breakthrough in their efforts to find a cure for Alzheimer's disease. The researchers' findings, published in the journal Science, show that use of a drug in mice appears to quickly reverse the pathological, cognitive and memory deficits caused by the onset of Alzheimer's. The results point to the significant potential that the medication, bexarotene, has to help the roughly 5.4 million Americans suffering from the progressive brain disease.

Bexarotene has been approved for the treatment of cancer by the U.S. Food and Drug Administration for more than a decade. These experiments explored whether the medication might also be used to help patients with Alzheimer's disease, and the results were more than promising.

Alzheimer's disease arises in large part from the body's inability to clear naturally-occurring amyloid beta from the brain. In 2008 Case Western Reserve researcher Gary Landreth, PhD, professor of neurosciences, discovered that the main cholesterol carrier in the brain, Apolipoprotein E (ApoE), facilitated the clearance of the amyloid beta proteins. Landreth, a professor of neurosciences in the university's medical school, is the senior author of this study as well.

Landreth and his colleagues chose to explore the effectiveness of bexarotene for increasing ApoE expression. The elevation of brain ApoE levels, in turn, speeds the clearance of amyloid beta from the brain. Bexarotene acts by stimulating retinoid X receptors (RXR), which control how much ApoE is produced.

In particular, the researchers were struck by the speed with which bexarotene improved memory deficits and behavior even as it also acted to reverse the pathology of Alzheimer's disease. The present view of the scientific community is that small soluble forms of amyloid beta cause the memory impairments seen in animal models and humans with the disease. Within six hours of administering bexarotene, however, soluble amyloid levels fell by 25 percent; even more impressive, the effect lasted as long as three days. Finally, this shift was correlated with rapid improvement in a broad range of behaviors in three different mouse models of Alzheimer's.

One example of the improved behaviors involved the typical nesting instinct of the mice. When Alzheimer's-diseased mice encountered material suited for nesting – in this case, tissue paper – they did nothing to create a

space to nest. This reaction demonstrated that they had lost the ability to associate the tissue paper with the opportunity to nest. Just 72 hours after the bexarotene treatment, however, the mice began to use the paper to make nests. Administration of the drug also improved the ability of the mice to sense and respond to odors.

Bexarotene treatment also worked quickly to stimulate the removal of amyloid plaques from the brain. The plaques are compacted aggregates of amyloid that form in the brain and are the pathological hallmark of Alzheimer's disease. Researchers found that more than half of the plaques had been cleared within 72 hours. Ultimately, the reduction totaled 75 percent. It appears that the bexarotene reprogrammed the brain's immune cells to "eat" or phagocytose the amyloid deposits. This observation demonstrated that the drug addresses the amount of both soluble and deposited forms of amyloid beta within the brain and reverses the pathological features of the disease in mice.

This study identifies a link between the primary genetic risk factor for Alzheimer's disease and a potential therapy to address it. Humans have three forms of ApoE: ApoE2, ApoE3, and ApoE4. Possession of the ApoE4 gene greatly increases the likelihood of developing Alzheimer's disease. Previously, the Landreth laboratory had shown that this form of ApoE was impaired in its ability of clear amyloid. The new work suggests that elevation of ApoE levels in the brain may be an effective therapeutic strategy to clear the forms of amyloid associated with impaired memory and cognition.

"This is an unprecedented finding," says Paige Cramer, PhD candidate at Case Western Reserve School of Medicine and first author of the study. "Previously, the best existing treatment for Alzheimer's disease in mice required several months to reduce plaque in the brain."

Added Professor Landreth: "This is a particularly exciting and rewarding study because of the new science we have discovered and the potential promise of a therapy for Alzheimer's disease. We need to be clear; the drug works quite well in mouse models of the disease. Our next objective is to ascertain if it acts similarly in humans. We are at an early stage in translating this basic science discovery into a treatment."

Daniel Wesson, PhD, assistant professor of neurosciences at Case Western Reserve School of Medicine and co-author of the study agreed. "Many often think of Alzheimer's as a problem of remembering and learning, but the prevalent reality is this disease spreads throughout the brain, resulting in serious insults to numerous functions," he said. "The results of this study, showing the preservation of behaviors across a wide spectrum, and accompanying brain function, are tremendously exciting and suggest great promise in the utility of this approach in treatment of Alzheimer's disease."

Bexarotene has a good safety and side-effect profile. The Case Western Reserve researchers hope these attributes will help speed the transition to clinical trials of the drug. Professor Landreth said modest resources funded this self-described "far-fetched idea." Crucial support came from the Blanchette Hooker Rockefeller Foundation, the Thome Foundation, and the National Institutes of Health.

The Science study was co-authored by John R. Cirrito, Jessica L. Restivo, Whitney D. Goebel, Washington University School of Medicine; C.Y. Daniel Lee, Colleen Karlo, Adriana E. Zinn, Brad T. Casali, Case Western Reserve University School of Medicine; Donald A. Wilson, New York University School of Medicine, and Michael J. James, Kurt R. Brunden, Perelman School of Medicine, University of Pennsylvania.

After the embargo has lifted, visit Case Western Reserve University's YouTube channel to view a short video about the School of Medicine discovery: ***http://www.youtube.com/user/case****.*

http://www.eurekalert.org/pub_releases/2012-02/sri-srs020912.php

Scripps research scientists identify most lethal known species of prion protein

Findings suggest new view of 'mad cow' and other neurodegenerative diseases

JUPITER, FL - Scientists from the Florida campus of The Scripps Research Institute have identified a single prion protein that causes neuronal death similar to that seen in "mad cow" disease, but is at least 10 times more lethal than larger prion species. This toxic single molecule or "monomer" challenges the prevailing concept that neuronal damage is linked to the toxicity of prion protein aggregates called "oligomers." The study was published this week in an advance, online edition of the journal Proceedings of the National Academy of Sciences.

"By identifying a single molecule as the most toxic species of prion proteins, we've opened a new chapter in understanding how prion-induced neurodegeneration occurs," said Scripps Florida Professor Corinne Lasmézas, who led the new study. "We didn't think we would find neuronal death from this toxic monomer so close to what normally happens in the disease state. Now we have a powerful tool to explore the mechanisms of neurodegeneration."

In the study, the newly identified toxic form of abnormal prion protein, known as TPrP, caused several forms of neuronal damage ranging from apoptosis (programmed cell death) to autophagy, the self-eating of

cellular components, as well as molecular signatures remarkably similar to that observed in the brains of prion-infected animals. The study found the most toxic form of prion protein was a specific structure known as alpha-helical.

New Paths to Explore

In addition to the insights it offers into prion diseases such as "mad cow" and a rare human form Creutzfeldt-Jakob disease, the study opens the possibility that similar neurotoxic proteins might be involved in neurodegenerative disorders such as Alzheimer's and Parkinson diseases.

In prion disease, infectious prions (short for proteinaceous infectious particles), thought to be composed solely of protein, have the ability to reproduce, despite the fact that they lack DNA and RNA. Mammalian cells normally produce what is known as cellular prion protein or PrP; during infection with a prion disease, the abnormal or misfolded protein converts the normal host prion protein into its disease form.

Lasmézas explains that prion diseases are similar to Alzheimer's and other protein misfolding diseases in that they are caused by the toxicity of a misfolded host protein. Recent work, as reported in The New York Times, also found that diseases such as Alzheimer's resemble prion diseases by spreading from cell to cell.

The new study adds another twist. "Until now, it was thought that oligomers of proteins are toxic in all these diseases," Lasmézas said. "Since we found for the first time that an abnormally folded monomer is highly toxic, it opens up the possibility that this might be true also for some other protein misfolding diseases as well."

The first author of the study, "Highly Neurotoxic Monomeric α-Helical Prion Protein," is Minghai Zhou of Scripps Research. Other authors include Gregory Ottenberg and Gian Franco Sferrazza also of Scripps Research. For more information on the study, see http://www.pnas.org/content/early/2012/02/07/1118090109.abstract The study was supported by the State of Florida.

http://www.eurekalert.org/pub_releases/2012-02/uoc--nmm020912.php

New method makes culture of complex tissue possible in any lab

Scientists at the University of California, San Diego have developed a new method for making scaffolds for culturing tissue in three-dimensional arrangements that mimic those in the body.

This advance, published online in the journal Advanced Materials, allows the production of tissue culture scaffolds containing multiple structurally and chemically distinct layers using common laboratory reagents and materials. According to the UC San Diego researchers, this process is more affordable and widely feasible than previous methods that required expensive equipment and expertise.

The new approach is remarkably simple: solutions of the components of each layer, including polymers, are mixed with varying concentrations of a common inert reagent to control density. The solutions are layered so that the difference in density segregates each solution, and then polymerized so that they form a gel. The structure of each layer can be altered by varying the concentration of polymers, and the discreteness of the transition between layers can be altered by allowing the solutions to diffuse.

Lead author Jerome Karpiak, graduate student in the UCSD Biomedical Sciences Program, said, "We're excited about the relevance of this method to tissue engineering. Since it offers such straightforward spatial control over structure and composition of stratified tissue scaffolds, including cell type and density, this technology could help the field move much faster." Tissues cultured in vitro to mimic those in the body can potentially provide an alternative to transplantation for injured or degenerated tissue.

"We believe this approach will vastly broaden the number of labs capable of culturing complex tissue," said Adah Almutairi, PhD, assistant professor at the UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences, the Department of Nanoengineering and the Materials Science and Engineering Program at the UCSD Jacobs School of Engineering. "Because manipulation of structure and concentrations of signal molecules is much easier in this system than in intact organisms, it holds great potential to advance the study of development and disease." For example, this method may offer a novel approach to study how surrounding molecules affect the growth of axons in neurodevelopmental disorders.

Additional researchers included Yogesh Ner, PhD. Research was funded in part by the National Institutes of Health Director's New Innovator program and King Abdulaziz City of Science and Technology.

http://www.sciencedaily.com/releases/2012/02/120209101839.htm?

New Target for Alzheimer's Drugs

Biomedical scientists at the University of California, Riverside have identified a new link between a protein called beta-arrestin and short-term memory that could open new doors for the therapeutic treatment of neurological disorders, particularly Alzheimer's disease.

ScienceDaily - Beta-arrestin is expressed in various cells of the body, including cells of the hippocampus, the region of the brain that is involved in learning and the formation of short-term memories. Beta-arrestin, the

absence of which impairs normal learning in mice, is one of many "scaffolding proteins" -- proteins that support the connections between neurons in the brain.

As our brain develops, new connections called synapses are formed between neurons. In the hippocampus, the formation of synapses is a continuous process. As we learn something new, new connections are formed and some old ones become stronger through a process known as long-term potentiation (LTP). But because brains have only a limited capacity, other old connections must disassemble through a process known as long-term depression (LTD) in order for new synapses to form.

The researchers report online last week in the Proceedings of the National Academy of Sciences that beta-arrestin plays an important role in the plasticity of synaptic connections and LTD by regulating the "actin cytoskeleton," a dynamic filamentous network of proteins that forms the "backbone" of neurons and is involved in forming new and disassembling old synaptic connections.

"In some pathological conditions such as Alzheimer's disease, loss of the old synaptic connections far exceeds the formation of new ones, resulting in overall loss of synapses and short-term memory loss," said Iryna M. Ethell, an associate professor of biomedical sciences and the lead author of the research paper. "Our work, done on mice, shows that if beta-arrestin is removed from neurons, this loss of synapses is prevented. But we also know that beta-arrestin is required for normal learning and memory; so a fine balance needs to be established. This balance could be easily achieved by pharmaceutical drugs in the future."

This is the first time researchers anywhere have linked beta-arrestin to Alzheimer's and learning/memory.

Ethell explained that beta-arrestin can be visualized as energy supplied to a puppeteer (actin cytoskeleton) controlling the strings of the puppets (inter-neuronal connections). For normal learning to take place, the puppeteer needs to move the strings in a specific order. But in patients with Alzheimer's, this supply of energy over-activates and the strings are pulled in a disorderly fashion that results in the strings being broken (loss of synapses) and the puppets collapsing. While the removal of beta-arrestin would prevent this collapse, a complete loss of beta-arrestin would mean no movement of the puppets at all (that is, no learning in the brain), which is equally undesirable.

"A selective tuning of beta-arrestin activity is therefore necessary to partially reduce synapse disassembly," said Crystal G. Pontrello, the first author of the research paper and a postdoctoral researcher in Ethell's lab. "What you want, ideally, is the elimination of only some unused old synaptic connections so that there is room to make new connections."

Ethell and Pontrello were joined in the research by UC Riverside's Min-Yu Sun, Alice Lin, Todd A. Fiacco and Kathryn A. DeFea. The research was supported by a grant to Ethell by the National Institutes of Health.

http://nyti.ms/yphrOY

Radioisotope Recipe Lacks One Ingredient: Cash

For years, scientists and policy makers have been trying to address two improbably linked problems that hinge on a single radioactive isotope

By MATTHEW L. WALD

WASHINGTON - For years, scientists and policy makers have been trying to address two improbably linked problems that hinge on a single radioactive isotope: how to reduce the risk of nuclear weapons proliferation, and how to assure supplies of a material used in thousands of heart, kidney and breast procedures a year.

They seemed to be getting close to a solution. But now General Electric, the company that developed a technology for carrying it out, has quietly dropped work on the project, saying it is not commercially viable.

The isotope is technetium 99m, or tech 99 for short. It is useful in diagnostic tests because it throws off an easy-to-detect gamma ray; also, because it breaks down very quickly, it gives only a small dose of radiation to the patient. But the recipe for tech 99 requires another isotope, molybdenum 99, that is now made in nuclear reactors using weapon-grade uranium. In May 2009, a Canadian reactor that makes most of the North American supply of moly 99 was shut because of a safety problem. A second reactor, in the Netherlands, was simultaneously closed for repairs.

The 54-year-old Canadian reactor, Chalk River in Ontario, is running now, but its license expires in four years. Canada built two replacement reactors, but even though they turned out to be unusable, their construction discouraged potential competitors. So the United States Energy Department, which regulates nuclear weapons, has been trying to find a way to make the molybdenum isotope without relying on leaky reactors that use bomb fuel. And in 2010 General Electric, which designs power reactors, came up with an innovative solution.

The commercial reactors have a big flow of neutrons, and if an atom of natural molybdenum absorbs one, it becomes moly 99.

G.E.'s reactors have an opening at the bottom for an instrument that measures the neutron density. The company said it could replace that monitor with a "target" made of molybdenum and pull it back out after about seven days, so it could be sent to a chemical processing plant for recovery of the moly 99. The company even picked out a reactor, Exelon's Clinton plant in DeWitt County, Ill. And it lined up industrial partners for the parts of the process it would not do itself, and tested the concept in research reactors. There is a drawback, though. Only about 24 percent of natural molybdenum is moly 98, the kind that can be converted to moly 99. To produce a given volume of tech 99, the volume of molybdenum in the generator has to be far larger.

Enter another player: Perma-Fix, a company based in Atlanta that makes a resin for treating contaminants at polluted industrial sites. The company came up with a resin that will hold the atom when it is molybdenum but release it when it decomposes into technetium. Perma-Fix executives say this is a good complement to the G.E. system.

But G.E. has given up. When the Canadian reactor was restarted, it said, it decided that its technology was not financially competitive. In a statement, G.E. said that while it and Exelon were confident "that large quantities of molybdenum 99 could safely be produced" in one of their reactors, financial projections "do not support the remaining cost."

Kevin Walsh, a nuclear-fuel executive at General Electric, said that the company would finish developing the system if the economics improved but that for now, "we've put all the engineering aside."

Louis Centofanti, chairman and chief executive of Perma-Fix, said his company was trying to line up other reactors to process the molybdenum. Federal officials say Perma-Fix may have a time advantage, because it is not using government money and thus does not have to file an environmental impact statement.

But experts say it may be nearly impossible to develop an alternative supply while highly enriched uranium is still in use, even though the reactors that do that work have an uncertain lifetime. Chalk River's license expired last year, but it was given a single five-year extension; the Dutch reactor's lifetime is less certain but also limited. "The economics is key," said Parrish Staples, director of European and African threat reduction at the National Nuclear Security Administration, who has been meeting with European officials looking for ways to stop using highly enriched uranium. The old, unreliable reactors now in use are subsidized by government, he said.

His agency backed G.E. but also a number of other companies. One, NorthStar Medical Radioisotopes, uses an accelerator to create gamma rays that bombard yet another type of molybdenum, moly 100; the bombardment causes the substance to eject a neutron and become moly 99.

Another organization, the Morgridge Institute for Research in Wisconsin, uses an accelerator to bombard uranium in a liquid solution, but it uses uranium with a much lower content of uranium 235, the kind that is useful in bombs.

And the Energy Department is helping finance a research program at Babcock & Wilcox to develop a new kind of reactor, in which uranium will be circulated in a liquid, and split; fission products, including the desired type of molybdenum, will be filtered out of the liquid for medical use.

Dr. Andrew J. Einstein, an assistant professor of clinical medicine at the Columbia University College of Physicians and Surgeons, who testified before a Senate committee in 2008 about the isotope shortage, said supplies were adequate at the moment. But he drew a biblical analogy. "This is the seven years of plenty," he said. "It certainly is time to be preparing for supply beyond Chalk River."

Dr. Einstein said that when tech 99 was not available, doctors could use substitutes, but that these gave the patient larger radiation doses or provided poorer image quality to the doctor. And for some uses, doctors can substitute PET scans, he said. But the equipment is in high demand for other procedures, and many medical facilities do not have it.

http://medicalxpress.com/news/2012-02-metastatic-breast-cancer-hitches-free.html

Metastatic breast cancer hitches a free ride from the immune system

Inflammatory breast cancer (IBC) is the most lethal form of breast cancer . It spreads easily through the lymphatic and blood vessels, forming metastasis which can lead to multi-organ failure.

New research published in BioMed Central's open access journal Cell Communication and Signaling demonstrates how IBC cells use IL-8, secreted as part of the anti-inflammatory response by a specific set of white blood cells (monocytes), to increase fibronectin expression.

Fibronectin is a cell-adhesion molecule which is usually involved in wound healing and cell migration during embryogenesis. Over-expression of this molecule is thought to allow cancer to metastasize. Prof Mona Mohamed from Cairo University used a cytokine antibody array to identify which immune-regulating

molecules (cytokines, chemokines, and growth factors) were secreted by monocytes and found that, while monocytes secreted a small amount each of a wide range of molecules, there was up to 10 times more IL-8 and MCP-1.

The cocktail of immune-regulating molecules from the monocytes was able to increase the amount of fibronectin produced in IBC cells and in 3D culture produced branch-like structures typical of fibronectin over-expression. IL-8 on its own also turned up fibronectin expression in IBC cells. Prof Mohamed explained, "Adding IL-8 on its own to IBC cells caused an increase in the signaling proteins PI3K and AKT and it is this pathway which is responsible for fibronectin production."

The monocyte cocktail did not alter expression of another cell adhesion molecule, E-cadherin. Prof Mohamed continued, "From what we already knew about cell adhesion and these results, it seems that IBC cells are held together in clumps by E-cadherin, but fibronectin, and the IL-8 signaling pathway, are involved in branching and invasion necessary for metastasis of IBC."

More information: *Monocytes conditioned media stimulate fibronectin expression and spreading of inflammatory breast cancer cells in three-dimensional culture: A mechanism mediated by IL-8 signaling pathway, Mona M Mohamed, Cell Communication and Signaling (in press) Provided by BioMed Central*

http://www.physorg.com/news/2012-02-humans-decline-african-rainforests-years.html

Humans may have helped the decline of African rainforests 3000 years ago

Large areas of rainforests in Central Africa mysteriously disappeared over three thousand years ago, to be replaced by savannas.

PhysOrg.com - Large areas of rainforests in Central Africa mysteriously disappeared over three thousand years ago, to be replaced by savannas. The prevailing theory has been that the cause was a change in climate, and the deforestation then enabled humans to increase their agricultural activities. A new study suggests that climate change alone cannot fully explain the transition and that human activities might be implicated.

Geochemist Germain Bayon and colleagues from the French Research Institute for Exploration of the Sea in Plouzané, France, analyzed marine sediment cores representing the last 40,000 years, taken from the mouth of the Congo River. The team looked for geochemical markers such as hydrogen, which correspond to rainfall levels that affect natural levels of erosion, and they also looked at potassium, which erodes quickly, and aluminum, which is more immobile.

The core samples revealed evidence of severe chemical weathering starting around 1,500 BCE, a time that coincided with a period in which Bantu-speaking tribes arrived in the area, having migrated from regions near what is now the border between Nigeria and Cameroon. Chemical weathering in samples dating before this era was consistent with the changes in rainfall patterns, but by 1,000 BCE the weathering seen was decoupled from the rainfall evidence.

Chemical weathering can be caused naturally by rainfall and normal erosion, but it can be accelerated by deforestation and intensive agriculture. Since the climate was changing at the time and becoming drier, a reduction in chemical weathering would ordinarily be expected rather than the peak actually found.

The Bantu people were farmers and had developed iron-smelting techniques. Iron-Age Bantu archaeological sites have yielded ceramics, furnaces, tools, the remains of agricultural products, and a variety of iron artifacts.

Bayon and colleagues suggest, in their paper published in the journal Science, that the farmers' clearing of land for agriculture and their iron smelters, in addition to the changing climate, would explain the collapse of the rainforest and its replacement by grasslands and savannas in the region. The researchers were unable to estimate to what extent human activities were responsible, but they suggest the evidence from the sediment core shows human influence was "already significant."

The paper's authors say their results were unexpected, but reveal that humans can have an enormous effect on the environment. While their findings do not necessarily contradict the prevailing theories, because the changing climate enabled the farmers to practice agriculture in the region, the Buntu farming practices themselves then changed the patterns of soil erosion.

The study could have implications for the current situation in the world's largest rainforests in the Amazon, where large areas are being deforested, largely for cattle or soy bean farms, and for industrial purposes and road construction. This, together with the current changes in climate, could also result in a rapid disappearance of remaining rainforests and their replacement by grasslands, with a massive resultant loss in biodiversity, and feedback changes to the local climate. Rainfall in the Amazon is already reducing, and there have been major droughts, notably in 2005 and 2010.

More information: Intensifying Weathering and Land Use in Iron Age Central Africa, Science, DOI: 10.1126/science.1215400

ABSTRACT
About 3000 years ago, a major vegetation change occurred in Central Africa, when rainforest trees were abruptly replaced by savannas. The consensus is that the forest disturbance was caused by climate change. We show here that chemical weathering in Central Africa, reconstructed from geochemical analyses of a marine sediment core, intensified abruptly at the same period, departing significantly from the long-term weathering fluctuations related to the Late Quaternary climate. Evidence that this weathering event was also contemporaneous with the migration of Bantu-speaking farmers across Central Africa suggests that human land-use intensification at that time already had a significant impact on the rainforest.

http://bit.ly/zcfwd0

First Neanderthal cave paintings discovered in Spain

Cave paintings in Malaga, Spain, could be the oldest yet found – and the first to have been created by Neanderthals.

12:20 10 February 2012 by Fergal MacErlean

Looking oddly akin to the DNA double helix, the images in fact depict the seals that the locals would have eaten, says José Luis Sanchidrián at the University of Cordoba, Spain. They have "no parallel in Palaeolithic art", he adds. His team say that charcoal remains found beside six of the paintings – preserved in Spain's Nerja caves – have been radiocarbon dated to between 43,500 and 42,300 years old.

That suggests the paintings may be substantially older than the 30,000-year-old Chauvet cave paintings in south-east France, thought to be the earliest example of Palaeolithic cave art.

The next step is to date the paint pigments. If they are confirmed as being of similar age, this raises the real possibility that the paintings were the handiwork of Neanderthals – an "academic bombshell", says Sanchidrián, because all other cave paintings are thought to have been produced by modern humans.

Were these seals painted by Neanderthals? (Image: Nerja Cave Foundation)

Neanderthals are in the frame for the paintings since they are thought to have remained in the south and west of the Iberian peninsula until approximately 37,000 years ago – 5000 years after they had been replaced or assimilated by modern humans elsewhere in their European heartland.

Until recently, Neanderthals were thought to have been incapable of creating artistic works. That picture is changing thanks to the discovery of a number of decorated stone and shell objects – although no permanent cave art has previously been attributed to our extinct cousins.

Neanderthals' creativity

Now some researchers think that Neanderthals had the same capabilities for symbolism, imagination and creativity as modern humans. The finding "is potentially fascinating", says Paul Pettitt at the University of Sheffield, UK. He cautions that the dating of cave art is fraught with potential problems, though, and says that clarification of the paintings' age is vital. "Even some sites we think we understand very well such as the Grotte Chauvet in France are very problematic in terms of how old they are," says Pettitt. If the age is confirmed, Pettitt suggests that the cave paintings could still have been the work of modern humans.

"We can't be absolutely sure that Homo sapiens were not down there in the south of Spain at this time," he says.

Sanchidrián does not rule out the possibility that the paintings were made by early Homo sapiens but says that this theory is "much more hypothetical" than the idea that Neanderthals were behind them.

Dating of the Nerja seal paintings' pigments will not take place until after 2013. Further excavations in the extensive cave system – discovered by a group of boys hunting bats in 1959 – is ongoing.

http://www.sciencedaily.com/releases/2012/02/120209172627.htm

A Gentler Way of Doing Brain Surgery

Brain surgery is getting much easier for many patients. Neurosurgeons are using catheters rather than open surgery to repair aneurysms and other defects. Patients recover in a few days, with less chance of cognitive deficits.

ScienceDaily - Carolyn Davis checked into Loyola University Medical Center with a life-threatening brain aneurysm that caused the worst headache in her life. Traditional surgery to repair such a defect is highly invasive. It involves opening the skull, retracting the brain and placing a clip to seal off the ruptured aneurysm. Recovery takes months, and patients can suffer cognitive deficits.

But Loyola neurosurgeon William W. Ashley, Jr., MD, PhD, was able to repair Davis' aneurysm without cutting into her skull. He instead repaired the defect with a catheter that he threaded through her blood vessels up to her brain.

Davis went home with only a puncture wound where the catheter had been inserted. She has fully recovered from an aneurysm that, if left untreated, could have been fatal. "I'm very thankful for Dr. Ashley," she said.

An aneurysm is a bulge in a blood vessel. As the bulge expands, the artery wall thins. Eventually, it can leak or burst, causing damage similar to a stroke.

About 6 million Americans -- 1 in 50 people -- have brain aneurysms that potentially could rupture. Each year, aneurysms burst in about 25,000 people, and most die or suffer permanent disabilities, according to the Brain Aneurysm Foundation.

Davis' aneurysm leaked and later ruptured, causing an excruciating headache and subarachnoid hemorrhage (bleeding in the area between the brain and the thin tissues that cover the brain.) "I had never felt anything like that before," Davis, 55, said. "I knew something bad was going on in my head."

Left untreated, the aneurysm almost certainly would have ruptured again, and this time, it could have been fatal or caused severe brain damage.

Davis, who lives in Chicago, went to the emergency room of a community hospital, which transferred her to Loyola.

Ashley used a less invasive endovascular technique to repair her aneurysm. He inserted a catheter (thin tube) in an artery in the groin and guided it up past the heart and carotid artery into the brain. Ashley then passed tiny coils of platinum wire through the catheter and released them into the bulging aneurysm. The bulge filled with coils, causing the blood to clot. This effectively sealed off the aneurysm.

"It likely is permanently fixed," Ashley said.

Ashley is among a new generation of neurosurgeons who are using this less-invasive endovascular technique to repair aneurysms and other vascular problems in the brain. He also is trained in traditional open brain surgery. With his dual training, Ashley can offer patients the safest and most effective treatment options for complex neurovascular disease. Ashley is an assistant professor in the Departments of Neurological Surgery and Radiology of Loyola University Chicago Stritch School of Medicine.

http://www.eurekalert.org/pub_releases/2012-02/nioa-dho021012.php

Drug halts organ damage in inflammatory genetic disorder

NIH study shows benefits of long-term Kineret therapy in people with NOMID

A new study shows that Kineret (anakinra), a medication approved for the treatment of rheumatoid arthritis, is effective in stopping the progression of organ damage in people with neonatal-onset multisystem inflammatory disease (NOMID). This rare and debilitating genetic disorder causes persistent inflammation and ongoing tissue damage. The research was performed by scientists at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), part of the National Institutes of Health.

NOMID affects numerous organs and body systems, including the skin, joints, eyes, and central nervous system. The first sign of the disease is often a rash that develops within the first weeks of life. Other problems, including fever, meningitis, joint damage, vision and hearing loss, and mental retardation, can follow. Kineret, one of a relatively new class of drugs known as biologic response modifiers or biologics, blocks the activity of interleukin-1 (IL-1), a protein made by cells of the immune system. IL-1 is overproduced in NOMID and a number of other diseases, leading to damaging inflammation. Previous work by the same NIAMS group showed that blocking IL-1 was effective in relieving symptoms of NOMID. However, this is the first study to show that Kineret works over the long-term and, at higher doses, can also control damage that often results in vision and hearing loss, and brain lesions.

"Inflammation prolonged over many years will eventually cause irreversible damage and loss of function," said lead author Dr. Raphaela Goldbach-Mansky of the NIAMS Translational Autoinflammatory Disease Section. For example, inflammation of the cochlea — a tiny structure of the inner ear — was found to be responsible for hearing loss in people with NOMID. Thinning of the optic nerve caused by inflammation-related pressure in the brain has been identified as a cause of vision loss. "We knew we could effectively block inflammation in the inner ear and in the brain and eyes. The next step was to find out if we could sufficiently prevent the progression of hearing or vision loss," said Goldbach-Mansky.

The group sought the answers to their questions in the study published online in Arthritis & Rheumatism. Study participants, who ranged in age from 10 months to 42 years, were treated with daily doses of Kineret based on body weight — 1 to 5 milligrams of Kineret per kilogram of body weight (1 to 5 mg/kg/day) — for at least 36 months and as long as 60 months. Disease activity was monitored with blood tests to measure C-reactive protein, a marker for inflammation in the body, and by daily diaries kept by the patients or their parents. The researchers also used sensitive MRI imaging methods to assess inflammation in the inner ear and brain.

Researchers found the initial Kineret doses used were insufficient to control organ inflammation, but by increasing the dose, they were able to do so. By preventing organ inflammation, scientists were able to preserve organ function in most patients. In addition, the scientists found ways to predict who is at greatest risk of hearing and vision loss.

"The few patients in the study who had hearing loss were also the ones who continued to have inflammation in the inner ear," said the study's first author Dr. Cailin H. Sibley. "We also found that people who had thin optic nerves when we assessed their vision were more likely to lose vision than those who had thick optic nerves, simply because they had already lost fibers due to untreated disease and, therefore, started with a huge disadvantage."

These findings point to the importance of early diagnosis and treatment to keep organ damage from developing. "We are continuing the study with an emphasis on enrolling very young children to prospectively show that we can prevent any organ damage from developing if we start treatment early in life," Goldbach-Mansky said.

Because IL-1 is needed to fight infections, there has been concern that blocking it with high doses of Kineret might leave the body vulnerable to infections. But overall, the study drug was well tolerated. "While we have seen infections in the study, none were serious enough to discontinue the drug, and all healed well with appropriate treatment."

While Kineret is not a cure for NOMID — its effects last only as long as the drug is taken — the study offers hope for people with the disease. "Without Kineret, people with NOMID are at risk of progressive organ damage that results in hearing and vision loss, cognitive impairment and, in many cases, early death. As many as 20 percent of children with this genetic disorder do not live to adulthood," said Goldbach-Mansky. "This study shows that treatment over five years is safe and effective, and can prevent organ damage."

In addition to funding from the NIAMS, portions of this work were also supported by the Intramural Research Programs of the National Cancer Institute, the National Institute on Deafness and Other Communication Disorders, the National Eye Institute, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and the NIH Clinical Center. For more information on NOMID, visit http://www.niams.nih.gov/Health_Info/Autoinflammatory/default.asp.

http://www.eurekalert.org/pub_releases/2012-02/si-cwo021012.php

Complex wiring of the nervous system may rely on a just a handful of genes and proteins

Discovery provides clues to development of neurological diseases and cancer

LA JOLLA, CA - Researchers at the Salk Institute have discovered a startling feature of early brain development that helps to explain how complex neuron wiring patterns are programmed using just a handful of critical genes. The findings, published February 3 in Cell, may help scientists develop new therapies for neurological disorders, such as amyotrophic lateral sclerosis (ALS), and provide insight into certain cancers.

The Salk researchers discovered that only a few proteins on the leading edge of a motor neuron's axon - its outgoing electrical "wire" - and within the extracellular soup it travels through guide the nerve as it emerges from the spinal cord. These molecules can attract or repel the axon, depending on the long and winding path it must take to finally connect with its target muscle.

"The budding neuron has to detect the local environment it is growing through and decide where it is, and whether to grow straight, move to the left or right, or stop," says the study's senior investigator, Sam Pfaff, a professor in Salk's Gene Expression Laboratory and a Howard Hughes Medical Institute investigator.

"It does this by mixing and matching just a handful of protein products to create complexes that tell a growing neuron which way to go, in the same way that a car uses the GPS signals it receives to guide it through an unfamiliar city," he says.

The brain contains millions of times the number of neuron connections than the number of genes found in the DNA of brain cells. This is one of the first studies to try and understand how a growing neuron integrates many different pieces of information in order to navigate to its eventual target and make a functional connection.

"We focused on motor neurons that control muscle movements, but the same kind of thing is going on throughout embryonic development of the entire nervous system, during which millions of axons make trillions of decisions as they move to their targets," he says. "It is the exquisite specificity with which they grow that underlies the basic architecture and proper function of the nervous system."

These findings might eventually shed new light on a number of clinical disorders related to faulty nerve cell functioning, such as ALS, which is also known as Lou Gehrig's disease, says the first author on the paper, Dario Bonanomi, a post-doctoral researcher in Pfaff's laboratory.

"These are the motor neurons that die in diseases like Lou Gehrig's disease and that are linked to a genetic disorder in children known as spinal muscle atrophy," Bonanomi says.

"It is also a jumping off point to try and understand the basis for defects that might arise during fetal development of the nervous system," he added. "A better understanding of those signals might help to be able to regenerate and rewire circuits following diseases or injuries of the nervous system."

The researchers say the study also offers insights into cancer development, because a protein the researchers found to be crucial to the "push and pull" signaling system - Ret- is also linked to cancer. Mutations that activate Ret are linked to a number of different kinds of tumors. The other protein receptors described in the study, known as Ephs, have also been implicated in cancer, Pfaff says.

"This study suggests that the way cells detect signals in their environment is likely a universal strategy," he says, "and we know that genes and proteins known to function primarily during embryonic development have been linked to cancer."

"Controlling neuronal growth requires very potent signaling molecules, and it makes sense they would be linked to disease," Pfaff says. "We hope our findings help further unravel these connections."

The study was funded by the National Institute of Neurological Disorders and Stroke and by the Howard Hughes Medical Institute.

Co-authors include, from Salk, Onanong Chivatakar, Ge Bai, and Karen Lettieri; Houari Abdesselem and Brian A. Pierchala, from the University of Michigan School of Dentistry; and Till Marquardt, from the European Neuroscience Institute-Göttingen, in Germany.

http://www.scientificamerican.com/article.cfm?id=is-cadmium-as-dangerous-for-children-lead

Is Cadmium as Dangerous for Children as Lead?

Signs are emerging that children are suffering from exposure to cadmium, a widespread heavy metal

By Marla Cone and Environmental Health News | Friday, February 10, 2012 | 11

It's a heavy metal. It's linked to learning problems in school children. And every child is exposed.

Sounds like lead?

It's cadmium.

Signs are emerging that cadmium – a widespread contaminant that gets little attention from health experts and regulators – could be the new lead.

Children with higher cadmium levels are three times more likely to have learning disabilities and participate in special education, according to a new study led by Harvard University researchers.

Absorbed from the soil, cadmium is found in certain foods, particularly potatoes, grains, sunflower seeds and leafy greens, as well as tobacco. It also has been discovered in some inexpensive children's jewelry, prompting new voluntary industry standards last fall.

Dr. Robert Wright, the study's senior author, emphasized that the links to learning disabilities and special education were found at commonplace levels previously thought to be benign. "One of the important points of the study is that we didn't study a population of kids who had very high exposures. We studied a population representative of the U.S. That we found any [effect] suggests this is occurring at relatively low levels," said Wright, an associate professor of pediatrics and environmental health at Harvard.

Scientists said the new findings are a sign that cadmium could have dangerous properties similar to lead that alter the way children's brains develop. More research is necessary, though, to confirm and refine the potential effects on kids. "It does certainly point to the fact that we need more attention paid to the neurotoxic effects of cadmium in children," Wright said.

Until now, the nervous system has not received much attention as a target for cadmium. Some studies of adult workers, however, have shown that high exposures can trigger neurological problems, and small, earlier studies of children found links to mental retardation and decreased IQs.

The new study is the largest to look at connections between cadmium in urine and neurological effects, and the only one that has used a national group of children.

"Collectively, the studies are very consistent. They provide fairly substantial support that cadmium is a neurotoxin," said Dr. Bruce Lanphear, a pediatrician and epidemiologist at Simon Fraser University who was a co-author of the study. Lanphear, one of the world's leading experts on the effects of lead in children, added that "the pattern we're seeing here with cadmium is very consistent with what we see with other toxicants," including lead and mercury.

The two scientists recommended that government re-examine its standards and guidelines for cadmium in food, soil, workplaces and consumer products to consider the effects on children's brains.

Current regulations for cadmium are based on threats to adults, and the kidneys have been considered the most sensitive organ to its toxic effects. Classified as a known human carcinogen, it is linked to lung, kidney and prostate cancer in workers.

"We've got a large new national study showing a threefold increase [in children's learning disabilities and special education]. But I wouldn't go so far to say we definitely need to lower regulatory levels. It deserves to be re-evaluated, though," said Lanphear.

Of the 2,199 children between the ages of 6 and 15 included in the new study, 12.6 percent had a learning disability and 10.5 percent were enrolled in special education classes, according to the study, published online in Environmental Health Perspectives last month. The children were not tested for disabilities; instead it was reported by their parents on a questionnaire that is part of the National Health and Nutrition Examination Study.

For those with the highest cadmium levels, the odds of having a learning disability were 3.21 times higher than for the children with the lowest exposures. For special education, the odds were 3 times higher. No association was found with attention deficit hyperactivity disorders.

"The three times higher risk is high for such low cadmium levels," said Aimin Chen, an assistant professor of environmental health at University of Cincinnati's College of Medicine. He was not associated with the study.

But Chen said the link at this point is preliminary because researchers have not yet looked for any specific, more definitive neurological effects, such as reduced IQs, memories or vocabularies -- outcomes already linked to two other toxic metals, lead and mercury.

The connection to both learning disabilities and special education could indicate cadmium has an array of effects on a child's brain just like lead does. Those two outcomes "are actually a mixture of different brain function problems," Chen said.

Lead has been studied and regulated for many decades, leading to a large amount of evidence that it reduces children's IQs at low concentrations and contributes to attention disorders and even violent behaviors. It interferes with the development of synopses, or connections between neurons, that allow a child to learn.

Since cadmium is also a heavy metal, it might have similar effects on the brain, Lanphear and Wright said. But unlike lead, cadmium "is relatively understudied as respect to brain toxicity," Wright said.

One big difference turned up in the new study: No link was found between cadmium and attention deficit disorders. "It stands out because one thing we've found fairly consistently with lead, tobacco and others is that it seems that some of these contaminants might increase the risk for ADHD," Lanphear said. That could be a sign that cadmium is working on a different part of the brain, not the prefrontal cortex.

Another big mystery is the source of the cadmium in the kids. Cadmium stays in the body for long periods, so the tests measured amounts the children were exposed to over years.

Cadmium is in tobacco smoke, but surprisingly, concentrations in the kids were similar whether they lived with smokers or not. That "might mean for most kids [secondhand] smoking was not a major source," Wright said.

An abundant element in the Earth's crust, cadmium is found naturally in soil in some parts of the country. But it also is released by battery manufacturers, smelters, electroplating plants and other industries. It is one of the top chemicals reported in Superfund sites, found in virtually all of them, according to a Centers for Disease Control and Prevention document.

Renee Gardner, a postdoctoral fellow at Sweden's Karolinska Institutet who studies heavy metals, said "the most important source of exposure is food. Green leafy vegetables and grains are the biggest sources, though most plant foods have some cadmium in them." Since these foods are important nutritionally, they shouldn't be avoided. But Gardner said that iron helps prevent absorption of cadmium, so parents worried about exposure should ensure their kids have adequate iron in their foods.

Some children may have been exposed through inexpensive jewelry. In 2010, the Associated Press tested children's jewelry manufactured in China and found cadmium, prompting recalls by stores. Cadmium was being used to replace lead. Last fall, the Consumer Product Safety Commission considered standards, but backed off when the industry set its own voluntary testing procedures and limits for cadmium in children's jewelry. California set its own standards.

Lanphear said for most children, jewelry probably isn't responsible for the cadmium in their bodies. "But for some kids, those kids that swallow it, it's an extraordinarily important source," he said. It also can enter the body by mouthing the jewelry.

Saying the voluntary standards don't go far enough, Wright recommended that cadmium be removed from all jewelry and other children's products. "It's very concerning to me that cadmium can be found in a children's product," Wright said. "Even if one child in a million is exposed that's one child too many."

The jewelry is an example of how one dangerous substance often replaces another, Lanphear said.

"Perhaps the biggest failure is to fail to learn the lesson of the lead pandemic, that environmental chemicals and metals have the potential to be toxic, so in the end they shouldn't be treated any differently than drugs. They shouldn't be used unless proven safe," he said.

This article originally ran at Environmental Health News, a news source published by Environmental Health Sciences, a nonprofit media company.

http://news.discovery.com/animals/snakes-pheromones-estrogen-120211.html

Estrogen Turns Male Snakes into Same-Sex Charmers

The finding has implications for understanding the environmental impact of compounds that mimic the effect of estrogen.

Sat Feb 11, 2012 09:31 AM ET | content provided by Jeanna Bryner, LiveScience Managing Editor

Give a male garter snake a taste of estrogen and watch out, as the hormone turns these lads into the sexiest thing on the block, attracting dozens of other males eager to mate.

The finding, published in the Journal of Experimental Biology, has implications for understanding the environmental impact of compounds that mimic the effect of estrogen, found in some chemicals and pesticides.

Estrogen, the researchers found, is key to a female's release of pheromones and thus, reproduction.

Here's how it works: For the red-sided garter snake, picking up a mate takes but a second and a flick of the tongue. When a male detects a possible mate nearby, he licks the female with a quick flick of his tongue. The chemical cues, called pheromones, exuded by the females are so strong it takes but an instant, the researchers say, for the male to determine the other snake's species, sex, population, reproduction condition, size and age. In fact, the males are totally dependent on these pheromones for snake reproduction.

Every spring, tens of thousands of these garter snakes emerge from their limestone caves north of Manitoba, Canada, for mating. Intense competition ensues, as males swarm (and tongue) female snakes in an effort to be the first to mate with her. The frenzy appears as twisting balls of snakes called mating balls.

The males tend to choose the larger, more mature gals, because these females can produce more babies; they also have a slightly different chemical signature in their pheromones. While young, small females do get action, they aren't the preferred mates. Once they mate, the females emit a different pheromone, confirming "no more sex," causing other males to lose interest and leave the area.

In the new study, the researchers implanted male garter snakes in their natural environment, each with a capsule that raised their estrogen levels to approximately match those of female snakes. After one year of these estrogen supplements, the male snakes started secreting a pheromone that seemed to cause other males to swarm to them, forming clumps of writhing snakes tangled together. Apparently, the estrogen caused the males to secrete "female" pheromones.

"We thought this might work, but we were surprised the results were so compelling," study researcher Robert Mason, a professor of zoology at Oregon State University, said in a statement. "The amount of estrogen the male snakes received was nothing unusual, just about what a normal female would produce." The other males, in fact, preferred the male snakes with boosted estrogen levels to the small female snakes, the researchers found. When the researchers stopped giving the males estrogen, they reverted back to their normal behaviors.

This work was supported by the National Science Foundation and the U.S. Environmental Protection Agency.

http://www.eurekalert.org/pub_releases/2012-02/aaon-omd020712.php

Overeating may double risk of memory loss

New research suggests that consuming between 2,100 and 6,000 calories per day may double the risk of memory loss, or mild cognitive impairment (MCI), among people age 70 and older.

NEW ORLEANS - The study was released today and will be presented at the American Academy of Neurology's 64th Annual Meeting in New Orleans April 21 to April 28, 2012. MCI is the stage between normal memory loss that comes with aging and early Alzheimer's disease.

"We observed a dose-response pattern which simply means; the higher the amount of calories consumed each day, the higher the risk of MCI," said study author Yonas E. Geda, MD, MSc, with the Mayo Clinic in Scottsdale, Arizona and a member of the American Academy of Neurology.

The study involved 1,233 people between the ages of 70 and 89 and free of dementia residing in Olmsted County, Minn. Of those, 163 had MCI. Participants reported the amount of calories they ate or drank in a food questionnaire and were divided into three equal groups based on their daily caloric consumption. One-third of the participants consumed between 600 and 1,526 calories per day, one-third between 1,526 and 2,143 and one-third consumed between 2,143 and 6,000 calories per day.

The odds of having MCI more than doubled for those in the highest calorie-consuming group compared to those in the lowest calorie-consuming group. The results were the same after adjusting for history of stroke, diabetes, amount of education, and other factors that can affect risk of memory loss. There was no significant difference in risk for the middle group.

"Cutting calories and eating foods that make up a healthy diet may be a simpler way to prevent memory loss as we age," said Geda.

The co-authors of the study include Ronald C. Petersen, MD, Fellow of the American Academy of Neurology, and other investigators of the Mayo Clinic Study of Aging in Rochester, Minn.

The study was supported by the National Institutes of Health, the Robert Wood Johnson Foundation and the Robert H. and Clarice Smith and Abigail van Buren Alzheimer's Disease Research Program.

http://www.eurekalert.org/pub_releases/2012-02/hms-rdm020812.php

Researchers discover molecular secrets of ancient Chinese herbal remedy

2,000-year-old herb regulates autoimmunity and inflammation

Cathryn Delude

BOSTON, Mass. - For roughly two thousand years, Chinese herbalists have treated Malaria using a root extract, commonly known as Chang Shan, from a type of hydrangea that grows in Tibet and Nepal. More recent studies suggest that halofuginone, a compound derived from this extract's bioactive ingredient, could be used to treat many autoimmune disorders as well. Now, researchers from the Harvard School of Dental Medicine have discovered the molecular secrets behind this herbal extract's power.

It turns out that halofuginone (HF) triggers a stress-response pathway that blocks the development of a harmful class of immune cells, called Th17 cells, which have been implicated in many autoimmune disorders.

"HF prevents the autoimmune response without dampening immunity altogether," said Malcolm Whitman, a professor of developmental biology at Harvard School of Dental Medicine and senior author on the new study. "This compound could inspire novel therapeutic approaches to a variety of autoimmune disorders."

"This study is an exciting example of how solving the molecular mechanism of traditional herbal medicine can lead both to new insights into physiological regulation and to novel approaches to the treatment of disease," said Tracy Keller, an instructor in Whitman's lab and the first author on the paper.

This study, which involved an interdisciplinary team of researchers at Massachusetts General Hospital and elsewhere, will be published online February 12 in Nature Chemical Biology.

Prior research had shown that HF reduced scarring in tissue, scleroderma (a tightening of the skin), multiple sclerosis, scar formation and even cancer progression. "We thought HF must work on a signaling pathway that had many downstream effects," said Keller.

In 2009, Keller and colleagues reported that HF protects against harmful Th17 immune cells without affecting other beneficial immune cells. Recognized only since 2006, Th17 cells are "bad actors," implicated in many autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis and psoriasis. The researchers found that minute doses of HF reduced multiple sclerosis in a mouse model. As such, it was one of a new arsenal of drugs that selectively inhibits autoimmune pathology without suppressing the immune system globally. Further analysis showed that HF was somehow turning on genes involved in a newly discovered pathway called the amino acid response pathway, or AAR.

Scientists have only recently appreciated the role of the nutrient sensing-AAR pathway in immune regulation and metabolic signaling. There is also evidence that it extends lifespan and delays age-related inflammatory diseases in animal studies on caloric restriction. A conservationist of sorts, AAR lets cells know when they need to preserve resources. For example, when a cell senses a limited supply of amino acids for building proteins, AAR will block signals that promote inflammation because inflamed tissues require lots of protein. "Think about how during a power outage we conserve what little juice we have left on our devices, foregoing chats in favor of emergency calls," said Whitman. "Cells use similar logic."

For the current study, the researchers investigated how HF activates the AAR pathway, looking at the most basic process that cells use to translate a gene's DNA code into the amino acid chain that makes up a protein.

The researchers were able to home in on a single amino acid, called proline, and discovered that HF targeted and inhibited a particular enzyme (tRNA synthetase EPRS) responsible for incorporating proline into proteins that normally contain it. When this occurred, the AAR response kicked in and produced the therapeutic effects of HF-treatment.

Providing supplemental proline reversed the effects of HF on Th17 cell differentiation, while adding back other amino acids did not, establishing the specificity of HF for proline incorporation. Added proline also reversed other therapeutic effects of HF, inhibiting its effectiveness against the malaria parasite as well as

certain cellular processes linked to tissue scarring. Again, supplementation with other amino acids had no such effect. Such mounting evidence clearly demonstrated that HF acts specifically to restrict proline.

The researchers think that HF treatment mimics cellular proline deprivation, which activates the AAR response and subsequently impacts immune regulation. Researchers do not yet fully understand the role that amino acid limitation plays in disease response or why restricting proline inhibits Th17 cell production.

Nevertheless, "AAR pathway is clearly an interesting drug target, and halofuginone, in addition to its potential therapeutic uses, is a powerful tool for studying the AAR pathway," said Whitman.

"Halofuginone and other febrifugine derivatives inhibit prolyl-tRNA synthetase" by Keller et al. Nature Chemical Biology, online publication, February 12

This research was funded by the National Institutes of Health and a Harvard Technology Accelerator Award.

http://www.eurekalert.org/pub_releases/2012-02/uorm-sav020912.php

Starve a virus, feed a cure?

New findings show how some cells protect themselves against HIV

A protein that protects some of our immune cells from the most common and virulent form of HIV works by starving the virus of the molecular building blocks that it needs to replicate, according to research published online in Nature Immunology. The finding comes from an international team of researchers including scientists from the University of Rochester Medical Center, NYU Langone Medical Center, several institutions in France – and a graduate student who is a political refugee from Africa and is now at work in a Rochester laboratory, intent on helping his people who have been devastated by the HIV epidemic.

While researchers hope the work will one day lead to a way to make anti-HIV drugs more effective by increasing their potency against the virus, they're also excited about its implications for our knowledge of other pathogens, such as herpes viruses, which use the same machinery within our cells that HIV does to replicate.

"The findings may explain why certain anti-HIV drugs used today are more effective under some circumstances and not others," said Baek Kim, Ph.D., professor of Microbiology and Immunology at the University of Rochester Medical Center and one of three corresponding authors of the paper. "It also provides new insights on how many other viruses that afflict people operate in the body."

The work centers on a protein known as SAMHD1, which is found in white blood cells known as macrophages and related cells known as dendritic cells. Last year scientists discovered that the molecule makes it difficult for HIV-1 to infect macrophages – cells that specialize in gobbling up and destroying invaders like viruses.

Now researchers have discovered that the molecule cuts off the supply line of the raw material that HIV needs to create DNA and replicate. That raw material, dNTP, comprises the building blocks of DNA, and without it, HIV can't recreate its DNA in our cells.

The team found that SAMHD1 destroys most of these building blocks, making it nearly impossible for HIV-1 to replicate itself where SAMHD1 resides – the macrophages. Instead, HIV-1 uses the macrophage as a safe haven, surviving in patients for years as it dodges the immune system as well as the drugs designed to kill it. It's thanks largely to its ability to hide out in the body that HIV is able to survive for decades and ultimately win out against the body's relentless immune assault.

The team also discovered how a protein in the other common type of HIV – HIV-2, which is found mainly in Africa – knocks out SAMHD1. They found that the protein Vpx destroys SAMHD1, clearing the way for HIV-2 to infect macrophages. While scientists have known that HIV-2 needs Vpx to infect macrophages, they hadn't known precisely why.

Interestingly, while one might think that a virus that is able to replicate itself in crucial cells like macrophages might be more dangerous than one that cannot, that's not the case with HIV. HIV-2 is actually less virulent than HIV-1. "We don't know precisely how SAMHD1 and Vpx affect the virulence of HIV-1 and HIV-2, but it's something we're actively exploring," said Kim. "In this case, the ability of HIV-2 to replicate more quickly in macrophages does not help it become more virulent."

One possibility is that, like a starving man who becomes more and more desperate for food, the virus – when faced with a shortage of raw materials – puts its mutation gear into overdrive, creating more mutations in an effort to circumvent the pathway blocked by SAMHD1. Such constant mutations are one feature of HIV that makes it so challenging to treat patients.

"It makes sense that a mechanism like this is active in macrophages," said Kim. "Macrophages literally eat up dangerous organisms, and you don't want those organisms to have available the cellular machinery needed to replicate. And macrophages themselves don't need it, because they don't replicate. So macrophages have SAMHD1 to get rid of the raw material those organisms need to copy themselves. It's a great host defense.

"The work suggests new ways to target virus replication in macrophages, a critically important cell population that serves as a key reservoir of virus infection and a contributor to HIV-induced disease," added Kim.

At Rochester, Kim was joined in the research by graduate student Waaqo Daddacha, one of two first authors of the paper. A native of the Oromia region of Ethiopia, Daddacha came as a political refugee to the United States. He started out as a computer programmer, then decided to pursue HIV research as a way to help his homeland, where the rate of HIV is one of the highest in the world. As an undergraduate in Minnesota, he visited several laboratories around the nation that focus on HIV, eventually settling on the Kim lab, which he joined four years ago.

"Back home, many people are infected with HIV, and many people are dying because of it. I wanted to contribute to help solve the problem, and that's why I decided to pursue HIV research," said Daddacha, who still has family in Oromia. In Kim's lab he is focusing on understanding drug resistance among HIV patients and on finding ways to limit resistance to make the drugs more effective in patients.

Like Daddacha, Hichem Lahouassa of the National Health and Medical Research Institute is also co-first author of the paper. The other corresponding authors, in addition to Kim, are Nathaniel Landau, Ph.D., of NYU Langone Medical Center, and Florence Margottin-Goguet, Ph.D., of the National Health and Medical Research Institute in France.

The research was supported by the National Institutes of Health, the American Foundation for AIDS Research, the European Research Council, and several organizations in France.