## Higher folates, not antioxidants, can reduce hearing loss risk in men

***New research released at world's largest ENT meeting***

San Diego, CA – Increased intakes of antioxidant vitamins have no bearing on whether or not a man will develop hearing loss, but higher folate intake can decrease his risk by 20 percent, according to new research presented at the 2009 American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) Annual Meeting & OTO EXPO, in San Diego, CA.

The study, which identified 3,559 cases of men with hearing loss, found that there was no beneficial association with increased intakes of antioxidant vitamins such as C, E, and beta carotene. However, the authors found that men over the age of 60 who have a high intake of foods and supplement high in folates have a 20 percent decrease in risk of developing hearing loss.

Hearing loss is the most common sensory disorder in the United States, affecting more than 36 million people. High folate foods include leafy vegetables such as spinach, asparagus, turnip greens, lettuces, dried or fresh beans and peas, fortified cereal products, sunflower seeds and certain other fruits and vegetables are rich sources of folate. Baker's yeast, liver and liver products also contain high amounts of folate.

The authors believe this is the largest study to delve prospectively into the relation between dietary intake and hearing loss. They used the most recent figures from the Health Professionals Follow-up Study cohort from years 1986 to 2004, a group consisting of 51,529 male health professionals. They were first enrolled into this study in 1986 and filled out detailed health and diet questionnaires every other year. The authors believe their findings can allow greater education, prevention, and screening efforts.

***Title:*** *Vitamin Intake and Risk of Hearing Loss in Men*

***Author:*** *Josef Shargorodsky, MD; Gary Curhan, MD; Sharon Curhan, MD; Ronald Eavey, MD*

## Air pollution may trigger appendicitis

A new study http://www.cmaj.ca/press/cmaj082068.pdf in CMAJ (Canadian Medical Association Journal) www.cmaj.ca suggests that air pollution may trigger appendicitis in adults.

The study, conducted by researchers at the University of Calgary, University of Toronto and Health Canada, looked at 5191 adults admitted to hospital in Calgary, Alberta, Canada. Fifty-two per cent of admissions occurred between April and September, the warmest months of the year in Canada during which people are more likely to be outside.

The dominant theory of the cause of appendicitis has been obstruction of the appendix opening, but this theory does not explain the trends of appendicitis in developed and developing countries. Appendicitis cases increased dramatically in industrialized countries in the 19th and early 20th centuries, then decreased in the middle and late 20th century, coinciding with legislation to improve air quality. The incidence of appendicitis has been growing in developing countries as they become more industrialized.

Using Environment Canada's air pollution data for Calgary, the researchers determined the levels of ozone, nitrogen dioxide and other air-borne pollutants along with temperature. They found correlations between high levels of ozone and nitrogen dioxide and the incidence of appendicitis between age groups and genders. More men than women were found to have the condition.

"For unexplained reasons, men are more likely than women to have appendicitis," write Dr. Gilaad Kaplan of the University of Calgary and coauthors. "Men may be more susceptible to the effects of outdoor air pollution because they are more likely to be employed in outdoor occupations," although they note that misclassifications of data could explain some of the difference.

While it is not known how air pollution may increase the risk of appendicitis, the authors suggest pollutants may trigger inflammatory responses. They recommend further studies to determine the link.

## Prostate cancer gives a new outlook on life

Men who have prostate cancer often feel quite healthy, but the diagnosis still gives them a whole new outlook on life. Once they have learned to live with their cancer, they choose to focus on valuable relationships and appreciate the little things in life, shows a dissertation thesis from the Sahlgrenska Academy.

"We need a better understanding of how men with prostate cancer experience their illness and how they choose to adapt their new circumstances," says district nurse Annikki Jonsson, who interviewed 37 men with prostate cancer for her thesis. "We can then support them better and tailor their treatment to the phase they are in."

The results show that the men go through different phases of adjustment in succession after getting their diagnosis, and that their everyday lives are affected differently according to which phase they are in. Those with less serious prostate cancer find themselves in an emotional vacuum immediately after receiving their diagnosis. During this phase, which normally lasts around a week, it is pointless for medical personnel to try to give men information about their illness.

"But they do appreciate positive reception without pity during this initial phase. And, of course, if they do choose to get in touch and ask some questions, it's important to answer and tell where you can turn to with different thoughts." Once these men have negotiated this initial phase, they regain control over their lives and find their driving force for life. They begin actively seek out information about their illness.

Men who learn that they have an aggressive form of prostate cancer find that the disease is always at present and they feel often a sense of emptiness during the initial period following the diagnosis. For these men, the disease is an existential threat. They think a lot about how the future will be and how they will die.

"The men I interviewed said that they lived life more intense, but that they had their ups and downs," says Jonsson. "Sometimes they felt more alive, and in the next minute got a feeling that they risked losing control or being reminded of their changed masculinity."

The men were interviewed again two years after receiving their diagnosis. They told that they had realised that life is fragile, and they were aware that they did not know how long the life will be. They got more faith and trust in life and had discovered that they could preserve their autonomy and integrity despite their illness.

"Life changes, and it's important to achieve some kind of balance," says Jonsson. "The men focused their energy on the relationships which were valuable for them. They appreciated the little things in life in a different way nowadays and developed an inner strength to be true to themselves."

## Research points to potential chink in cancer's armour

Scientists at the University of York have identified and successfully silenced a gene that appears essential to cancer cell survival.

Professor Jo Milner and Dr Shafiq Ahmed, from the YCR P53 Research Unit in the Department of Biology, used a process called RNA interference to target the JNK2 gene in both cancer and healthy cells. The cancer cells died but the healthy cells were unaffected.

This discovery suggests that the survival of cancer cells depends upon certain genes which healthy cells can survive without, an important step towards the development of the next generation of cancer treatments.

Dr Ahmed said: "Our results indicate that one day it may be possible to treat cancer without the harmful side-effects so often associated with today's treatments. Our study has identified a cancer-specific target which could be selectively inhibited using small-molecules, or other means, without the use of radiotherapy and chemotherapy."

This laboratory-based work is still at a very early stage and the next step is to test a larger range of different cancer cell types and also to test normal healthy cells from different tissues.

The research, which examined colorectal cancer and breast cancer cell lines among others, was funded by Yorkshire Cancer Research and is published in the journal PLoS One.

A major aim of Professor Milner's research team is to identify cancer-specific survival genes and to ask if such genes offer a new route for cancer treatment. This field of research has been made possible through the development of RNA interference which allows the silencing of a single gene amongst thousands of genes.

Professor Milner said: "Our approach is now revealing unexpected properties for certain genes including JNK2. We have also studied JNK2's close relative, JNK1, and found that these two genes seem to oppose each other. JNK1 and JNK2 resemble the 'Jekyll and Hyde' for cancer cell survival."

"A further surprise is that the mechanism by which these two genes function under normal every-day conditions appears distinct from the mechanism which is activated by current anti-cancer therapies."

Dr Kathryn Scott, from Yorkshire Cancer Research, said: "The work of Professor Milner and Dr Ahmed represents another example of the world-class research that Yorkshire Cancer Research funds throughout the region."

## Toronto researchers discover novel circulation in human eye, new glaucoma treatment target

Researchers at the University of Toronto, St. Michael's Hospital and Sunnybrook Health Sciences Centre have discovered a previously unidentified form of circulation within the human eye which may provide important new insights into glaucoma, a leading cause of blindness.

For over a century, the eye has been considered to lack lymphatics, a circulation responsible for pumping fluid and waste out of tissues. The inability to clear that fluid from the eye is linked to glaucoma, a leading cause of irreversible blindness affecting over 66 million people worldwide.

"We challenged this assumption about a lack of lymphatics and discovered specialized lymphatic channels in the human eye," said Prof. Yeni Yücel, a pathologist-scientist in U of T's Faculty of Medicine and St. Michael's Hospital, and lead author of the study which appears in the current issue of Experimental Eye Research.

Glaucoma is a degenerative disease believed to be caused by the death of nerve cells at the back of the eye and in vision centers of the brain. It is often associated with elevated pressure in the eye. Current treatments for glaucoma rely on eye drops or surgery to lower eye pressure either by reducing fluid formation or improving fluid drainage from the eye.

"Good vision depends on the stable flow of fluid into and out of the eye. Any disturbance of this delicate fluid balance can lead to high eye pressure and irreversible glaucoma damage," said study co-author Dr. Neeru Gupta, Director of the Glaucoma Unit and Nerve Protection Unit at St. Michael's Hospital and Professor of Ophthalmology at U of T.

The lymphatic circulation, distinct from blood circulation, carries a colorless fluid called, lymph containing extra water, proteins and antigens through lymphatic vessels to lymph nodes and then to the blood stream. This circulation is critical for the drainage of the fluid from tissues, clearance of proteins and immune monitoring of the tissue. sing molecular tools and three-dimensional reconstruction, the team of researchers identified a rich network of lymphatic channels in the ciliary body of the human eye. These studies were confirmed by electron microscopy.

The discovery of a lymphatic circulation in the eye overthrows the idea that the eye is an immune privileged site due to the lack of lymphatics and has major implications for understanding eye inflammations and eye tumor spread, among other eye disorders.

"This 'uveolymphatic' circulation plays a role in the clearance of fluid from the eye, making it highly relevant to glaucoma. This discovery is exciting because it means we can focus on innovative treatment strategies for patients with glaucoma by specifically targeting this new circulation to lower eye pressure," said Dr. Gupta.

According to the researchers, future studies will be directed at better understanding how to manipulate the lymphatic circulation in the eye. "It's clear that if we want to develop new strategies to prevent blindness, we need to challenge existing beliefs, and hopefully open the door to new treatments for eye disease," said Prof. Yücel, who also serves as Director of the Ophthalmic Pathology Laboratory in U of T's Department of Ophthalmology and research Scientist at the Keenan Research Center at Li Ka Shing Knowledge Institute, SMH.

Glaucoma is expected to affect 80 million people worldwide by 2020. Although the disease can affect anybody, those with elevated eye pressure, the elderly, blacks and persons with a family member with glaucoma are at greatest risk. Other risk factors that may be associated with glaucoma include diabetes, high blood pressure and near-sightedness.

*This study was a collaboration between the University of Toronto and two fully-affiliated hospitals: St. Michael's Hospital and Sunnybrook Health Sciences Centre. Other co-authors include Miles G. Johnston, Professor Laboratory Medicine and Pathobiology and scientist at Neuroscience Program, Sunnybrook Hospital, Tina Ly, Manoj Patel, Ersin Gümüş, Stephan A. Fraenkl and Eva Horvath from SMH, and Brian Drake, Sara Moore, Dalia Tobbia, Dianne Armstrong from Sunnybrook Hospital Research Institute. This research was supported by this work was supported by the Canadian Institutes of Health Research (85053), Nicky And Thor Eaton Fund, The Dorothy Pitts Fund, and Henry Farrugia Fund.*

## High mortality rates may explain small body size

A new study suggests that high mortality rates in small-bodied people, commonly known as pygmies, may be part of the reason for their small stature. The study, by Jay Stock and Andrea Migliano, both of the University of Cambridge, helps unravel the mystery of how small-bodied people got that way.

The article appears in the October issue of Current Anthropology.

Adult males in small-bodied populations found in Africa, Asia and Australia are less than four feet, 11 inches (150 centimeters) tall, which is about one foot shorter than the average adult male in the U.S. Why people in these populations are so small remains a mystery, but several hypotheses have been proposed.

Some scientists think that small bodies provide an evolutionary advantage under certain circumstances. For example, a smaller body needs less food - a good thing in places where food supplies are inconsistent. Small bodies also may provide an advantage in getting around in thickly forested environments.

Recently, however, a new hypothesis has come to the fore suggesting that reproductive consequences of high mortality rates explain small body size.

If death comes at an early age, then natural selection would favor those who are able to reproduce at an early age. But early sexual maturity comes with a cost. When the body matures early, it diverts resources to reproduction that otherwise would have gone to growth. So small body size could be essentially a side effect of early sexual maturity.

Stock's and Migliano's study provides the first long-term evidence for the mortality hypothesis.

The two researchers looked at over 100 years of data on three small-bodied populations from the Andaman Islands in the Bay of Bengal, south of Burma. When the British established colonies on the islands in the 1850s,

these indigenous tribes had very different reactions to their new neighbors. Those reactions would have vast implications for the tribes' mortality rates.

Two tribes, the Onge and the Jarawa, resisted relations with the British, and retreated deep into the forest to avoid them. But the largest group of tribes, the Great Andamanese, befriended the British, some even living in homes built and supervised by colonists. In doing so, the tribesmen were unwittingly exposed to infectious diseases for which they had no defenses. As a result, the Great Andamanese experienced a sharp increase in mortality due to influenza, tuberculosis, measles and syphilis. By 1900 their numbers had dwindled to 600, from 6000 just 50 years before. By the 1960s, only 19 individuals remained.

Using historical records compiled by British researchers at the time, Stock and Migliano found that during the peak period of increased mortality, the Great Andamanese got smaller in stature. From 1879 to 1927, the height of the adult males who were measured decreased at a rate of 4.7 centimeters per 100 years.

Meanwhile, the Onge and the Jarawa, who for the most part isolated themselves from colonists and did not have dramatic increases in mortality, saw no drop in stature. The Jarawa, which have had the most stable mortality rate, remain the tallest of the three tribes today.

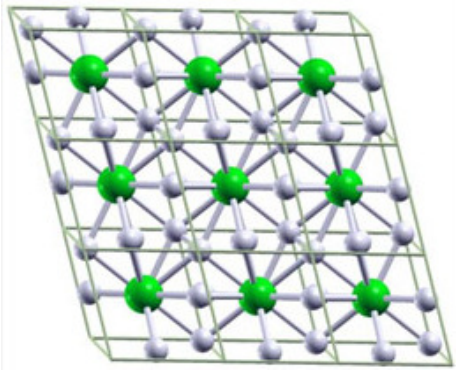
The relationships of the tribes with colonists "led to differences in mortality among these tribes, which appears to have been a fundamental determinant of variation in body size," the authors conclude.

This is first time that a link between mortality and body size has been shown using long-term data, the authors say. And it bolsters the idea that the reproductive trade-off associated with a short life could play a role in the evolution of human body size.

## For Future Superconductors, a Little Bit of Lithium May Do Hydrogen a Lot of Good

Study suggests strategies for converting hydrogen to metal at significantly lower pressures

Image of hypothetical metallic crystal cells composed of one lithium atom and six hydrogen atoms.



Scientists have a long and unsuccessful history of attempting to convert hydrogen to a metal by squeezing it under incredibly high and steady pressures.

Metallic hydrogen is predicted to be a high-temperature superconductor. A superconductor is a state of matter where electrons, and thus electricity, can flow indefinitely and without resistance.

In a paper published this week in the online edition of the Proceedings of the National Academy of Sciences, a team of scientists from Cornell University and the State University of New York at Stony Brook announce a theoretical study that predicts the metallization of hydrogen-rich mixtures at significantly lower pressures.

*Ball-and-stick image of hypothetical metallic crystal cells composed of one lithium, or Li, atom and six hydrogen, or H, atoms. The lithium-hydrogen compound is predicted to form under approximately 1 million atmospheres, which is one-fourth the amount of pressure required to metalize pure hydrogen. The pressure at sea level is one atmosphere and the pressure at the center of the Earth is around 3.5 million atmospheres. Li atoms are green and H atoms are white. Eva Zurek, Department of Chemistry, State University of New York at Buffalo*

By adding small amounts of lithium to hydrogen, the study calculates that the resulting system may be metalized at around one-fourth the pressure required to metalize pure hydrogen. Funding for the project was provided by the National Science Foundation (NSF).

Hydrogen and lithium are the first and third lightest elements in the universe, respectively. Under the temperature and pressures found on Earth, hydrogen is a gas and lithium is a metal. In hydrogen gas, the atoms are robustly bonded together in pairs and each hydrogen atom contributes one electron to the bonding. In chemistry shorthand, hydrogen is called H2.

Hydrogen and lithium normally react with each other to form a stable compound. This lithium-hydrogen compound, or LiH, is not metallic. Metallic hydrogen is thought to be present in the interiors of planets like Jupiter and Saturn because of the intense gravitational forces and pressures that are found there.

On Earth, researchers have tried to pry loose hydrogen's electron by squeezing it between the facets of a diamond anvil cell under pressures up to 3.4 million atmospheres. The pressure at sea level is one atmosphere. The pressure at the center of the Earth is around 3.5 million atmospheres. Scientists have not been successful with this method of steady pressures. They have been, however, with shock-wave methods.

To get around hydrogen's decidedly fixed stance of not becoming a metal under currently accessible laboratory pressures, the research team used sophisticated computer programs. The programs theoretically calculate if hydrogen can be metalized by combining a lithium atom with varying numbers of hydrogen atoms. The programs also compute if metallic hydrogen can be made under pressures achievable in a laboratory.

The lithium and hydrogen combinations predicted by the study currently do not exist on Earth.

One of the combinations predicted by the team contains one lithium atom for every six hydrogen atoms or LiH6 (see top right image). The complex calculations predict that in the hypothetical compound the Li atom is triggered to release its lone outer electron, which is then distributed over the three H2 molecules.

Under pressure, the hypothetical reaction forms a stable and metallic hydrogen compound.

The calculations also predict that LiH6 could be a metal at normal pressures. However, under these conditions it is not stable and would decompose to form LiH and H2.

"The stable and metallic LiH6 compound is predicted to form around 1 million atmospheres, which is around 25 percent of the pressure required to metalize hydrogen by itself," said Eva Zurek, lead author of the paper and an assistant professor of chemistry at The State University of New York, Buffalo.

"Interestingly, between approximately 1 and 1.6 million atmospheres, all the LiH combinations studied were stable or metastable and all were metallic," said Roald Hoffmann, co-author, recipient of the 1981 Nobel Prize in chemistry and Cornell's Frank H.T. Rhodes Professor of Humane Letters, Emeritus.

Another one of the hypothetical compounds studied by the team was composed of one lithium atom and two hydrogen atoms or LiH2 (see bottom right image).

"The theoretical study opens the exciting possibility that non-traditional combinations of light elements under high pressure can produce metallic hydrogen under experimentally accessible pressures and lead to the discovery of new materials and new states of matter," said Daryl Hess, a program director in the NSF Division of Materials Research.

"Once again, these researchers have taken chemistry to a new frontier," said Carol Bessel, a program director in the NSF Division of Chemistry. "They have described, through their theories and calculations, molecules that test our fundamental assumptions about atoms, molecules and structures. In doing so, they challenge the experimentalists to make what they have imagined in their minds a reality to be held in the hand."

The team members believe the information gleaned from the study suggests that one may combine large amounts of hydrogen with other elements. The information may also some day assist with the design of a metallic hydrogen-based superconductor.

"We have already been in touch with laboratory experimentalists about how LiH6 might be fabricated, starting perhaps with very finely divided forms of the common LiH compound along with extra hydrogen," said Neil W. Ashcroft, co-author, and Cornell's Horace White Professor of Physics, Emeritus.

*Additional authors include Artem R. Oganov, an associate professor, and Andriy O. Lyakhov, a post doctoral research associate, of the State University of New York at Stony Brook, Department of GeoSciences. Zurek was a postdoctoral associate in Hoffmann's research group when the studies were completed.*

*Funding for the study was provided by the NSF Divisions of Chemistry and Materials Research. The research was also supported in part by NSF through TeraGrid resources provided by the National Center for Supercomputing Applications. NSF-*

## Could antioxidants make us more, not less, prone to diabetes? Study says yes

We've all heard about the damage that reactive oxygen species (ROS) – aka free radicals – can do to our bodies and the sales pitches for antioxidant vitamins, skin creams or "superfoods" that can stop them. In fact, there is considerable scientific evidence that chronic ROS production within cells can contribute to human diseases, including insulin resistance and type 2 diabetes.

But a new report in the October 7th Cell Metabolism, a Cell Press publication, adds to evidence that it might not be as simple as all that. The researchers show that low levels of ROS – and hydrogen peroxide in particular - might actually protect us from diabetes, by improving our ability to respond to insulin signals.

"Our studies indicate that 'physiological' low levels of ROS may promote the insulin response and attenuate insulin resistance early in the progression of type 2 diabetes, prior to overt obesity and hyperglycemia," said Tony Tiganis of Monash University in Australia. "In a way, we think there is a delicate balance and that too much of a good thing - surprise, surprise - might be bad."

Tiganis' team found that mice with a deficiency that prevented them from eliminating physiological ROS didn't become insulin resistant on a high-fat diet as they otherwise would have. They showed that those health benefits could be attributed to insulin-induced signals and the uptake of glucose into their muscles. When those animals were given an antioxidant, those benefits were lost, leaving the mice with more signs of diabetes.

Tiganis said whether antioxidants are ultimately good for people will probably depend on their state of health or disease. "In the case of early type 2 diabetes and the development of insulin resistance, our studies suggest that antioxidants would be bad for you." Under some conditions, treatments designed to selectively increase ROS in muscle – if they can be devised – might even help, he says.

It's not the first time studies have suggested that antioxidants can be a negative, Tiganis adds. Studies in worms have suggested that antioxidants can shorten lifespan, as have some epidemiological studies in humans.

Other recent reports indicate that antioxidants may negate the longer-term benefits of exercise training by lowering the activity of certain genes involved in ROS defense.

Tiganis said it will ultimately be important to work out at what stage ROS go from being good to bad. He suspects it probably depends on the levels and/or the source of their generation. (ROS are generated both on the surfaces of cells and within cells by mitochondria, which convert nutrients such as glucose into energy, he explained.)

Although any health implications of the new findings would require further study, the findings lead Tiganis to suspect it is best not to take daily antioxidant vitamins, especially if you are otherwise healthy. "Do exercise," he says, as this is a natural source of ROS that may promote insulin action.

*The researchers include Kim Loh, Monash University, Victoria, Australia; Haiyang Deng, Monash University, Victoria, Australia; Atsushi Fukushima, Monash University, Victoria, Australia; Xiaochu Cai, Monash University, Victoria, Australia; Benoit Boivin, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; Sandra Galic, Monash University, Victoria, Australia; Clinton Bruce, Baker IDI Heart and Diabetes Institute, Victoria, Australia; Benjamin J. Shields, Monash University, Victoria, Australia; Beata Skiba, Baker IDI Heart and Diabetes Institute, Victoria, Australia; Lisa M. Ooms, Monash University, Victoria, Australia; Nigel Stepto, Monash University, Victoria, Australia; Ben Wu, Monash University, Victoria, Australia; Christina A. Mitchell, Monash University, Victoria, Australia; Nicholas K. Tonks, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; Matthew J. Watt, Monash University, Victoria, Australia; Mark A. Febbraio, Baker IDI Heart and Diabetes Institute, Victoria, Australia; Peter J. Crack, The University of Melbourne, Victoria, Australia; Sofianos Andrikopoulos, The University of Melbourne, Victoria, Australia; and Tony Tiganis, Monash University, Victoria, Australia.*

## MicroRNA drives cells' adaptation to low-oxygen living

Researchers have fresh insight into an evolutionarily ancient way that cells cope when oxygen levels decline, according to a new study in the October 7th issue of Cell Metabolism, a Cell Press publication. In studies of cells taken from the lining of human pulmonary arteries, they show that a microRNA – a tiny bit of RNA that regulates the activity of particular genes and thus the availability of certain proteins – allows cells to shift their metabolic gears, in a process known as the Pasteur effect.

While the discovery is a fundamental one, the researchers say it could point to new ways to tackle diseases, including cancer and cardiovascular disease.

"The Pasteur effect is really best defined as the way by which cells adapt to low oxygen concentrations," said Joseph Loscalzo of Brigham and Women's Hospital and Harvard Medical School. Cells do that by switching from mitochondrial metabolism to glycolysis.

Normally, cells produce high-energy molecules such as ATP through components known as mitochondria, he explained. Loscalzo likens mitochondria to little factories that churn out ATP under normal oxygen conditions. If mitochondria continue to operate when oxygen becomes limited, they do so inefficiently, he said, spewing out toxic derivatives of oxygen (including superoxide and hydrogen peroxide) in the process.

"When cells encounter that situation, they need to direct their energy program from one with mitochondria to one that uses less oxygen," Loscalzo continued. That secondary program, called glycolysis, doesn't produce as much cellular fuel, but it does so without toxic byproducts.

In the new study, the researchers first went in search of microRNA that rise when cells become hypoxic, meaning that they are deprived of sufficient oxygen. That screen done in many types of cells landed them miR-210 as a key player. Using several methods, they were able to predict that miR-210 would influence activity of iron-sulfur cluster assembly proteins (ISCU1/2). Those proteins act as scaffolds that assist in the assembly of iron-sulfur clusters, important ingredients for mitochondria to function.

The team shows that miR-210 does in fact directly target ISCU1/2, which disrupts the integrity of iron-sulfur clusters. As a result, mitochondrial respiration and associated functions get shut down.

The basic findings may have clinical implications, Loscalzo said, noting that scientists have devised increasingly interesting ways to selectively inhibit microRNAs. For instance, cancer cells typically operate under Pasteur effect conditions (a phenomenon known as the Warburg effect.) The ability allows tumors to grow even when they outstrip their blood supplies and prevents the generation of toxic oxygen derivatives within them.

You could imagine that treatments designed to block miR-210 might hobble tumors by manipulating their usual metabolic profile, Loscalzo said. In other settings, you may want to increase miR-210, he added. Such a therapy may have potential in patients with blocked coronary arteries, for instance.

"The transition of heart muscle to miR-210-dependent glycolysis might be enhanced by administering [the miRNA]," he said. By helping that transition along, physicians might be able to help minimize the production of toxic byproducts by mitochondria in their patients, and ultimately preserve more heart tissue, Loscalzo adds.

*The researchers include Stephen Y. Chan, Massachusetts General Hospital, Boston, MA, Harvard Medical School, Boston, MA; Ying-Yi Zhang, Brigham and Women's Hospital, Boston, MA, Harvard Medical School, Boston, MA; Craig Hemann, Ohio*

*State University, Columbus, OH; Christopher E. Mahoney, Brigham and Women's Hospital, Boston, MA, Harvard Medical School, Boston, MA; Jay L. Zweier, Ohio State University, Columbus, OH; and Joseph Loscalzo, Brigham and Women's Hospital, Boston, MA, Harvard Medical School, Boston, MA.*

## Heart disease: B vitamin pills have no effect

B-vitamin supplements should not be recommended for prevention of heart disease, say scientists. A Cochrane Systematic Review has shown these supplements do not reduce the risk of developing or dying from the disease.

"There is no evidence to support the use of B-vitamins as supplements for reducing the risk of heart attack, stroke or death associated with cardiovascular disease," says lead researcher, Arturo Martí-Carvajal of the Iberoamerican Cochrane Network in Valencia, Venezuela. "And it is important to point out that although we may have not found a positive effect, these kinds of studies are vitally important for determining the factors that influence the risk of developing and dying from this disease, which is the number one cause of death in the world today."

Certain B-vitamins, specifically B12, B9 (folic acid) and B6, influence levels of an amino acid in the blood called homocysteine. High levels of this molecule are associated with an increased risk of heart disease. It has been suggested that giving B-vitamin supplements could help regulate levels of homocysteine, thereby reducing the risk of cardiovascular disease and death. But according to the researchers, there is no scientific basis for this claim.

The review included eight trials involving a total of 24,210 people. None of the eight trials individually supported the idea that giving B-vitamin supplements could prevent cardiovascular disease. Together the data show that B-vitamin supplements, whether compared with placebos or standard care, have no effect on the incidence of heart attack, stroke or death associated with heart disease.

"Prescription of these supplements cannot be justified, unless new evidence from large high quality trials alters our conclusions. There are currently three ongoing trials that will help to consolidate or challenge these findings," says Martí-Carvajal.

## Eating liquorice in pregnancy may affect a child's IQ and behavior

***Expectant mothers who eat excessive quantities of liquorice during pregnancy could adversely affect their child's intelligence and behavior, a study has shown***

Expectant mothers who eat excessive quantities of liquorice during pregnancy could adversely affect their child's intelligence and behaviour, a study has shown.

A study of eight year old children whose mothers ate large amounts of liquorice when pregnant found they did not perform as well as other youngsters in cognitive tests. They were also more likely to have poor attention spans and show disruptive behaviour such as ADHD (attention deficit hyperactivity disorder).

It is thought that a component in liquorice called glycyrrhizin may impair the placenta, allowing stress hormones to cross from the mother to the baby. High levels of such hormones, known as glucocorticoids, are thought to affect fetal brain development and have been linked to behavioural disorders in children.

The results of the study are published in the American Journal of Epidemiology. Eight year olds whose mothers had been monitored for liquorice consumption during pregnancy were tested on a range of cognitive functions including vocabulary, memory and spatial awareness.

Behaviour was assessed using an in-depth questionnaire completed by the mother, which is also used by clinicians to evaluate children's behaviour.

The study, carried out by the University of Helsinki and the University of Edinburgh, looked at children born in Finland, where consumption of liquorice among young women is common.

Professor Jonathan Seckl, from the University of Edinburgh's Centre for Cardiovascular Science, said: "This shows that eating liquorice during pregnancy may affect a child's behaviour or IQ and suggests the importance of the placenta in preventing stress hormones that may affect cognitive development getting through to the baby."

Women who ate more than 500mg of glycyrrhizin per week – found in the equivalent of 100g of pure liquorice – were more likely to have children with lower intelligence levels and more behavioural problems.

"Expectant mothers should avoid eating excessive amounts of liquorice", said Professor Katri Räikkönen, from the University of Helsinki's Department of Psychology.

Of the children who took part in the study, 64 were exposed to high levels of glycyrrhizin in liquorice, 46 to moderate levels and 211 to low levels.

The research followed on from a study which showed that liquorice consumption was also linked to shorter pregnancies. Laboratory studies have also shown a link between the placenta not working to prevent stress hormones from passing through to the fetus, as well as a link to cardiac and metabolic disorders and behavioural problems in later life.

## Preventing allergies

Vaccination can lower children's risk of allergy. Cathleen Muche-Borowski and her coauthors present a clinical practice guideline for allergy prevention in the current issue of Deutsches Ärzteblatt International (Dtsch Arztebl Int 2009; 106[39]: 625-31).

Allergic diseases are becoming increasingly common in Western industrialized countries. As there is still no etiologically based treatment of allergic asthma, hay fever, or atopic eczema, the prevention of these diseases is a matter of special importance.

The majority of the 217 studies that the authors analyzed documented a protective effect of fish consumption in the diet of both the mother and the child. Soy-based baby food, in contrast, has no protective effect. In fact, because preparations of this type contain phytoestrogens, the authors even express concern about a potential harmful effect on health. Furthermore, delaying the introduction of solid food in the child's diet was not shown to have any beneficial effect on the development of allergy in the German cohort studies that the authors reviewed.

The reduction of dust mite allergens in the home as a single primary preventive measure has been removed from the guideline. A further change is that the updated version by Dr. Muche-Borowski et al. no longer contains any statement about specific immune therapy.

Vaccination, however, can lower the risk of allergy, in the authors' expert opinion. Recent studies indicate, too, that overweight in childhood is associated with asthma, although dietary measures for either mothers or children cannot be considered indicated at present, because relevant data are lacking. The updated clinical guideline enables physicians to give recommendations about allergy prevention based on the current state of the evidence. *http://www.aerzteblatt.de/v4/archiv/pdf.asp?id=66129*

## New findings about brain proteins suggest possible way to fight Alzheimer's

DALLAS - The action of a small protein that is a major villain in Alzheimer’s disease can be counterbalanced with another brain protein, researchers at UT Southwestern Medical Center have found in an animal study.

The findings, available online in the journal Proceedings of the National Academy of Sciences, suggest a promising new tactic against the devastating illness, the researchers said.

The harmful protein, called beta-amyloid, is found in the brain and, when functioning properly, suppresses nerve activity involved with memory and learning. Its normal function can be likened to a red traffic light, restraining nerve cells from getting overexcited when they receive stimulating signals from neighboring cells. People with Alzheimer’s disease, however, accumulate too much beta-amyloid — the traffic light gets stuck on “red” and nerve cells become less responsive.

Another brain protein, called Reelin, acts as a “green light,” stimulating nerve cells to respond more strongly to their neighbors’ signals.

The new study shows that applying Reelin directly to brain slices from mice prevents excess beta-amyloid from completely silencing nerves.

“If we can identify a mechanism to keep the nerve cells functioning strongly, that might provide a way to fight Alzheimer’s disease,” said Dr. Joachim Herz, professor of molecular genetics and neuroscience at UT Southwestern and the study’s senior author.

In the study, the researchers recorded electrical currents in the mouse hippocampus, an area of the brain associated with learning and memory. From their experiments they determined that Reelin and beta-amyloid interact with the same protein complex, called an NMDA receptor, which plays an important role in coordinating chemical signals between adjacent nerve cells.

They found that Reelin activates and strengthens the response of the NMDA receptor. In the presence of too much beta-amyloid, the receptor migrates into the cell, reducing the cell’s sensitivity to incoming signals. By contrast, in strong concentrations of Reelin, the receptor remains active and the cell has the green light to continue receiving normally.

Dr. Herz said the study is especially important because this mechanism involves another protein involved in Alzheimer’s called ApoE4, which is the primary risk factor for the most frequent late-onset form of the disease. The receptor that binds to ApeE molecules also binds to Reelin, and is part of the red-light/green-light complex that controls the sensitivity of the NMDA receptors.

“These results imply that Reelin, ApoE and beta-amyloid converge on the same molecular mechanism, which is critical in the Alzheimer’s disease process, and Reelin may be a common factor to fight both beta-amyloid and mutated ApoE,” Dr. Herz said. “This study establishes a rationale that ApoE receptors have an action that can keep the Alzheimer’s disease process at bay by preventing damage in the first place.”
The researchers are currently studying the role of ApoE4 in this mechanism. Mimicking or preserving normal Reelin function to stimulate the ApoE receptors might provide a path to stave off the disease, Dr. Herz said.

*Other UT Southwestern authors included lead author Dr. Murat Durakoglugil, assistant instructor of molecular genetics; graduate student Ying Chen; Dr. Charles White, professor of pathology; and Dr. Ege Kavalali, associate professor of neuroscience. The study was funded by the National Institutes of Health, the American Health Assistance Foundation, the Perot Family Foundation and the Humboldt Foundation.*

## New Chemo Cocktail Blocks Breast Cancer Like a Fence

### *Drug aimed at preventing spread of breast cancer to organs*

**By Marla Paul**

CHICAGO --- Think of a protective fence that blocks the neighbor's dog from charging into your backyard. The body, too, has fences - physical and biochemical barriers that keep cells in their place.

When breast cancer spreads or metastasizes, it crashes through the body's protective fences. The disease becomes fatal when it travels outside the mammary ducts, enters the bloodstream and spreads to the bones, liver or brain. Currently, there are only drugs that try to stem the uncontrolled division of cancer cells within the ducts. Until now, no drugs specifically targeted the invasion and spread of breast cancer to the organs.

A researcher from Northwestern University Feinberg School of Medicine has found a way to strengthen the breast's "fence" to prevent cancer from metastasizing. Researcher Seth Corey, M.D., has discovered that when a drug normally used to treat leukemia is added to a commonly used breast cancer drug, the potent new chemotherapy cocktail helps prevent breast cancer cells from invading.

"This is an entirely new way of targeting a cancer cell," said Corey, the Sharon B. Murphy-Steven T. Rosen Research Professor of Cancer Biology and Chemotherapy at the Feinberg School and director of the pediatric oncology program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Working in the lab with women's breast cancer cells, Corey found that when the leukemia drug dasatinib is combined with the breast cancer drug doxorubicin, the potent mix inhibits breast cancer cell invasion by half. Corey is the principal investigator of the study, which recently was reported in the British Journal of Cancer. Dasatinib targets an enzyme called the Src kinase, which is believed to play a key role in breast cancer invasion and metastases. "Perhaps this drug could be given to prevent invasion from happening in the first place," said Corey, who also is a pediatric oncologist at Children's Memorial Hospital. "This might keep the disease in check and prevent it from progressing."

## New treatment more than doubles survival for high risk childhood leukemia

### *Phase 2 study results of targeted therapy added to chemo*

Results of a phase two clinical trial published October 5th in the Journal of Clinical Oncology show that adding continuous daily doses of a targeted drug called imatinib mesylate to regular chemotherapy more than doubled three-year survival rates for children with a high risk type of blood cancer called Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

The Children's Oncology Group performed the study at nearly 20 North American centres under the leadership of Dr. Kirk Schultz, head of childhood cancer research at the Child & Family Research Institute (CFRI) and a pediatric oncologist at BC Children's Hospital, an agency of the Provincial Health Services Authority.

"With conventional chemotherapy, the three-year survival rate for children with this high-risk type of leukemia is between 30-35 per cent," says Dr. Kirk Schultz, professor of pediatrics at the University of British Columbia.

“Adding continuous exposure to imatinib for two-and-a-half years made a big difference and increased the survival rates to 87 per cent. The drug was well tolerated and it didn't have any significant side effects," he says. Survival rate refers to the length of time that a patient survived without a relapse and without developing a new cancer.

There are multiple types of acute lymphoblastic leukemia and each responds differently to treatment. Ph+ ALL involves genetic abnormalities on two specific chromosomes.

Because traditional chemotherapy doesn't work well for many children with Ph+ ALL, the standard treatment is blood and marrow transplantation, a life-saving procedure that's associated with a risk of complications.

"By using the targeted drug imatinib in combination with traditional chemotherapy, these results suggest that we've been able to improve survival enough that we may no longer have to do blood and marrow transplants for this disease," says Dr. Schultz. "Understanding more about the genetics of cancers allows us to determine the best way to treat each child and be more selective in the appropriate use of expensive medications."

Known commercially as Gleevec®, imatinib is a pill that's used to treat some adult leukemias and gastrointestinal cancers. It binds to a specific protein in cancer cells and prevents the cells from proliferating.

Collaborative networks such as the Children's Oncology Group are crucial for recruiting sufficient numbers of patients to trial new treatments for rare diseases such as Ph+ ALL, which is diagnosed in approximately six children and 90 adults each year in Canada.

For this study, there were 92 children and adolescents between one and 21 years of age with Ph+ ALL. Each received an initial four weeks of standard chemotherapy. They were assigned to five different groups that received imatinib for different lengths of time: either 42, 63, 84, 126, or 280 days. All patients received an additional 336 days of imatinib.

The group that received imatinib for more than 280 continuous days had survival rates of 87 per cent, a dramatic improvement over traditional chemotherapy and blood and marrow transplantation. Groups that received imatinib for 84 and 126 days showed moderate improvement in survival rates, while groups receiving the drug for 42 and 63 days had the same survival rates as current standard treatments. There were also 21 patients with Ph+ ALL who were treated with blood and marrow transplantation followed by six months of imatinib. This approach didn't affect survival rates.

"Using imatinib plus chemotherapy had a synergistic type of interaction," says Dr. Schultz. "I never expected these results. Although it's very promising, we need to do more follow up to get the five-year survival data and determine the long-term survival. We submitted our study for publication earlier instead of waiting because the data was so exciting and this type of leukemia is such high risk."

The researchers are now looking at setting up a phase three study to validate whether adding imatinib to chemotherapy could replace blood and marrow transplantation as the standard treatment for Ph+ ALL.

"Using other targeted drugs with regular chemotherapy might give results for other types of cancer in children and adults," says Dr. Schultz.

*The study was funded by the National Cancer Institute of the U.S. National Institutes of Health. During the course of the study, Dr. Schultz held the Wyeth/ Canadian Institutes of Health Research Clinical Research Chair in Transplantation.*

## Unnatural selection: Birth control pills may alter choice of partners

There is no doubt that modern contraception has enabled women to have unprecedented control over their own fertility. However, is it possible that the use of oral contraceptives is interfering with a woman's ability to choose, compete for and retain her preferred mate? A new paper published by Cell Press in the October issue of the journal Trends in Ecology and Evolution reviews emerging evidence suggesting that contraceptive methods which alter a woman's natural hormonal cycles may have an underappreciated impact on choice of partners for both women and men and, possibly, reproductive success.

Human females are only fertile for a brief period during their menstrual cycle, just prior to ovulation. Many scientific studies have established that partner preferences of both women and men vary significantly according to predictable hormonal fluctuations associated with the natural menstrual cycle. Ovulation is associated with a profound shift in some female physical characteristics, behaviors and perceptions related to mate attraction.

Ovulating women exhibit a preference for more masculine male features, are particularly attracted to men showing dominance and male-male competitiveness and prefer partners that are genetically dissimilar to themselves. This is significant because there is evidence suggesting that genetic similarity between couples might be linked with infertility. Further, some studies have suggested that men detect women's fertility status, preferring ovulating women in situations where they can compare the attractiveness of different women.

The oral contraceptive pill alters the hormonal fluctuations associated with the menstrual cycle and essentially mimics the more steady hormonal conditions associated with pregnancy. "Although mate choice studies in humans have routinely recorded pill use during the last decade to control for its confounding effects, little effort has been invested in understanding the consequences of such effects of the pill," offers study author Dr. Alexandra Alvergne from the Department of Animal and Plant Sciences at the University of Sheffield.

Dr. Alverne and colleague Dr. Virpi Lumma reviewed and discussed new research supporting the conclusion that use of the pill by women disrupted their variation in mate preferences across their menstrual cycle. The authors also speculate that the use of oral contraceptives may influence a woman's ability to attract a mate by reducing attractiveness to men, thereby disrupting her ability to compete with normally cycling women for access to mate.

Of particular interest is the fact that women taking the pill do not exhibit the ovulation-specific attraction to genetically dissimilar partners. "The ultimate outstanding evolutionary question concerns whether the use of oral contraceptives when making mating decisions can have long-term consequences on the ability of couples to reproduce," suggests Dr. Lummaa.

Taken together, an increasing number of studies suggest that the pill is likely to have an impact on human mating decisions and subsequent reproduction. "If this is the case, pill use will have implications for both current and future generations, and we hope that our review will stimulate further research on this question," concludes Dr. Lummaa. Alvergne et al.: "***Does the contraceptive pill alter mate choice in humans***?'"

## Italian scientist reproduces Shroud of Turin

**By Philip Pullella** – Mon Oct 5, 11:30 am ET

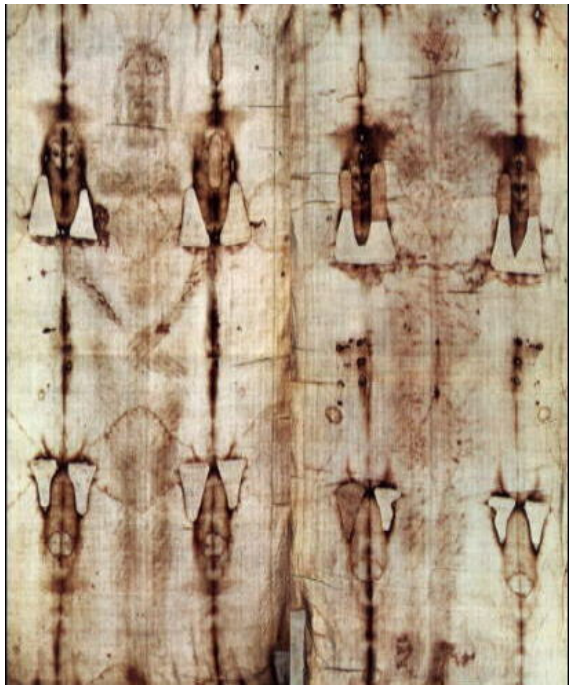
ROME (Reuters) – An Italian scientist says he has reproduced the Shroud of Turin, a feat that he says proves definitively that the linen some Christians revere as Jesus Christ's burial cloth is a medieval fake.

The shroud, measuring 14 feet, 4 inches by 3 feet, 7 inches bears the image, eerily reversed like a photographic negative, of a crucified man some believers say is Christ.

"We have shown that is possible to reproduce something which has the same characteristics as the Shroud," Luigi Garlaschelli, who is due to illustrate the results at a conference on the para-normal this weekend in northern Italy, said on Monday.

A professor of organic chemistry at the University of Pavia, Garlaschelli made available to Reuters the paper he will deliver and the accompanying comparative photographs.

The Shroud of Turin shows the back and front of a bearded man with long hair, his arms crossed on his chest, while the entire cloth is marked by what appears to be rivulets of blood from wounds in the wrists, feet and side.



***The Turin Shroud Reuters – The Turin Shroud is shown in this August 1978 file photo in negative version. An Italian scientist says …***

Carbon dating tests by laboratories in Oxford, Zurich and Tucson, Arizona in 1988 caused a sensation by dating it from between 1260 and 1390. Sceptics said it was a hoax, possibly made to attract the profitable medieval pilgrimage business.

But scientists have thus far been at a loss to explain how the image was left on the cloth.

Garlaschelli reproduced the full-sized shroud using materials and techniques that were available in the middle ages. They placed a linen sheet flat over a volunteer and then rubbed it with a pigment containing traces of acid. A mask was used for the face.

**PIGMENT, BLOODSTAINS AND SCORCHES**

The pigment was then artificially aged by heating the cloth in an oven and washing it, a process which removed it from the surface but left a fuzzy, half-tone image similar to that on the Shroud. He believes the pigment on the original Shroud faded naturally over the centuries. They then added blood stains, burn holes, scorches and water stains to achieve the final effect.

The Catholic Church does not claim the Shroud is authentic nor that it is a matter of faith, but says it should be a powerful reminder of Christ's passion.

One of Christianity's most disputed relics, it is locked away at Turin Cathedral in Italy and rarely exhibited. It was last on display in 2000 and is due to be shown again next year.

Garlaschelli expects people to contest his findings. "If they don't want to believe carbon dating done by some of the world's best laboratories they certainly won't believe me," he said.

The accuracy of the 1988 tests was challenged by some hard-core believers who said restorations of the Shroud in past centuries had contaminated the results.

The history of the Shroud is long and controversial. After surfacing in the Middle East and France, it was brought by Italy's former royal family, the Savoys, to their seat in Turin in 1578. In 1983 ex-King Umberto II bequeathed it to the late Pope John Paul.

The Shroud narrowly escaped destruction in 1997 when a fire ravaged the Guarini Chapel of the Turin cathedral where it is held. The cloth was saved by a fireman who risked his life.

Garlaschelli received funding for his work by an Italian association of atheists and agnostics but said it had no effect on his results. "Money has no odor," he said. "This was done scientifically. If the Church wants to fund me in the future, here I am." **Reuters**

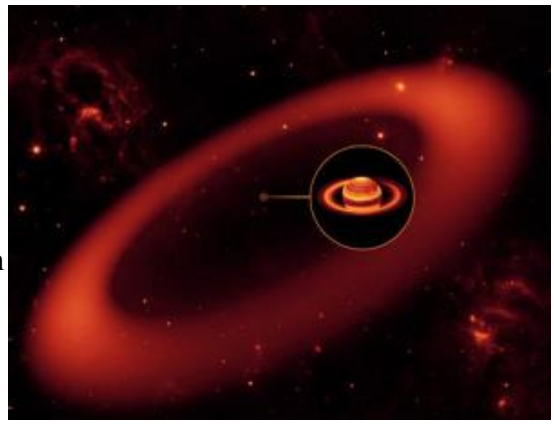
## Largest ring in solar system found around Saturn

* Updated 20:13 09 October 2009 **by Rachel Courtland**, Fajardo, Puerto Rico

A colossal ring of debris found around Saturn is the largest in the solar system. The new ring could be the 'smoking gun' that explains the curious two-faced appearance of Saturn's moon Iapetus, whose leading hemisphere is much darker than its trailing side.

Until now, the biggest known planetary rings in the solar system were Saturn's E ring and faint, gossamer sheets of dust orbiting Jupiter. Saturn's E ring, a diffuse disc of icy material fed by the moon Enceladus, extends from 3 to perhaps 20 times the radius of Saturn.

The newly discovered ring spans from 128 to 207 times the radius of Saturn – or farther – and is 2.4 million kilometres thick. It was found using NASA's Spitzer Space Telescope, which revealed an infrared glow thought to come from sun-warmed dust in a tenuous ring.



The discovery was announced on Tuesday at a meeting of the American Astronomical Society's Division for Planetary Sciences in Fajardo, Puerto Rico. "This is a unique planetary ring system, because it's the largest planetary ring in the solar system," team leader Anne Verbiscer of the University of Virginia in Charlottesville told the meeting.

***This illustration shows the size of a large, nearly invisible ring around Saturn (enlarged in this representation) that was detected by its infrared glow by the Spitzer Space Telescope*** **(Image: NASA/JPL-Caltech/Keck)**

Although the ring is large, it is quite diffuse, making it difficult to detect using visible light. "It's so faint you could look right through it," team member Douglas Hamilton of the University of Maryland in College Park told New Scientist.

The source of the ring's material seems to be Saturn's far-flung moon Phoebe, which orbits the planet at an average distance of 215 times the radius of Saturn. When Phoebe is hit by wayward space rocks, the impacts could generate debris that fills the rings.

**Moon to moon**

The new ring is so far away from Saturn that it is not strongly affected by the gravity of the giant planet's bulge, which pulls Saturn's other, closer-in rings into a plane around the planet's equator. As a result, the new ring shares the plane of Phoebe's orbit, which is tilted by 27° with respect to the other rings.

Because the ring feels lower gravitational forces from Saturn, relatively weak pressure from sunlight can push its particles into new orbits. Computer simulations show that many of the ring particles should spread inwards to collide with Saturn's two-toned moon Iapetus, Hamilton told meeting attendees.

Phoebe and its ring are orbiting in the opposite direction to Iapetus and Saturn's other rings, so inward-moving material should hit Iapetus head-on. "It's going to strike Iapetus's windshield like little bugs splattering on the windshield of a car," he said.

***When Saturn's moon Phoebe (shown) is hit by wayward interplanetary bodies or rocky debris in orbit around Saturn, the impacts generate detritus that likely fills the newly found dust ring*** **(Image: Cassini Imaging Team/SSI/JPL/ESA/NASA)**

The team reported that over the course of the solar system's history, enough material might have been created by collisions with Phoebe to coat Iapetus's leading hemisphere with a metres-thick layer of ring material.

That may bolster previous suggestions that material from Phoebe is responsible for Iapetus's dark side, although it may require some more work to account for colour differences between the two objects. The dark material on Iapetus is reddish in visible light, while Phoebe's surface appears gray.

Still, early reaction to the discovery is optimistic. "The Phoebe ring here is the smoking gun for what has caused the colouration of Iapetus," planetary scientist Joe Burns of Cornell University, who was not part of the team, commented after the presentation. *Journal reference: Nature (DOI: 10.1038/nature08515)*

**Really?**

## The Claim: With a Runny Nose, Green Calls for an Antibiotic

**By ANAHAD O'CONNOR**


**THE FACTS** Old prescription habits apparently die hard.

Studies have suggested that most doctors say they would prescribe an antibiotic if a child with sinus symptoms also had green nasal discharge. The habit stems from the notion that green indicates a bacterial infection.

But other studies show that green is no more common in a bacterial infection than a viral one, for which antibiotics are ineffective.

**Leif Parsons**

In a definitive study from 1984, scientists put 142 children with green nasal discharge into groups, including one that was treated with antibiotics and another that received a placebo. They found that the drugs had no effect on "potentially pathogenic organisms" or on symptoms. About 35 percent of subjects treated with antibiotics showed improvement, compared with 31 percent in the placebo group. More recent studies have bolstered that conclusion.

According to the Centers for Disease Control and Prevention, when cold viruses infect the respiratory tract, the body makes clear mucus that helps wash away germs from the nose and sinuses. After about three days, the body's immune cells fight back, changing the discharge to a white or yellow color. "As the bacteria that live in the nose grow back, they may also be found in the mucus, which changes to a greenish color," the agency says. "This is normal."

The only time antibiotics are needed for a runny nose, experts say, is when the diagnosis is bacterial sinusitis.

**THE BOTTOM LINE** The color of nasal discharge should not dictate the medicine.

**Vital Signs**

## Childhood: Autism Diagnoses Rising, U.S. Reports

**By BENEDICT CAREY**

More than 1 in 100 American children and teenagers may have autism, Asperger's syndrome or a related developmental problem, although such diagnoses often do not hold up, according to a government report released on Monday.

The estimate, based on a telephone survey of some 78,000 households and published in the journal Pediatrics, is the highest yet of the prevalence of so-called autism spectrum disorders, which include everything from severe autism to milder social difficulties to "pervasive developmental disorder," a description given to many troubled children.

Nearly 40 percent of the children in the study who were given such a diagnosis grew out of it or no longer qualified for it, the study found. The estimate is based on those whose parents said they were currently struggling with one of the disorders.

Prevalence estimates for autism-related disorders have increased so quickly over the past decade - to 1 in 150 in 2007, from 1 in 300 in the early 2000s - that researchers have debated whether the disorder is in fact becoming more common or is simply diagnosed more often.

The new survey is not likely to settle the question. "This is an excellent study, but what it looks at is the prevalence of the diagnosis, not the disorder," said Dr. Susan L. Hyman, a pediatrician at Golisano Children's Hospital in Rochester. "The next step scientifically is to see whether those diagnoses are being made accurately."

**Mind**

## How Nonsense Sharpens the Intellect

**By BENEDICT CAREY**

In addition to assorted bad breaks and pleasant surprises, opportunities and insults, life serves up the occasional pink unicorn. The three-dollar bill; the nun with a beard; the sentence, to borrow from the Lewis Carroll poem, that gyres and gimbles in the wabe.

An experience, in short, that violates all logic and expectation. The philosopher Soren Kierkegaard wrote that such anomalies produced a profound "sensation of the absurd," and he wasn't the only one who took them seriously. Freud, in an essay called "The Uncanny," traced the sensation to a fear of death, of castration or of "something that ought to have remained hidden but has come to light."

At best, the feeling is disorienting. At worst, it's creepy.

Now a study suggests that, paradoxically, this same sensation may prime the brain to sense patterns it would otherwise miss - in mathematical equations, in language, in the world at large.

"We're so motivated to get rid of that feeling that we look for meaning and coherence elsewhere," said Travis Proulx, a postdoctoral researcher at the University of California, Santa Barbara, and lead author of the paper appearing in the journal Psychological Science. "We channel the feeling into some other project, and it appears to improve some kinds of learning."

Researchers have long known that people cling to their personal biases more tightly when feeling threatened. After thinking about their own inevitable death, they become more patriotic, more religious and less tolerant of outsiders, studies find. When insulted, they profess more loyalty to friends - and when told they've done poorly on a trivia test, they even identify more strongly with their school's winning teams.

In a series of new papers, Dr. Proulx and Steven J. Heine, a professor of psychology at the University of British Columbia, argue that these findings are variations on the same process: maintaining meaning, or coherence. The brain evolved to predict, and it does so by identifying patterns.

When those patterns break down - as when a hiker stumbles across an easy chair sitting deep in the woods, as if dropped from the sky - the brain gropes for something, anything that makes sense. It may retreat to a familiar ritual, like checking equipment. But it may also turn its attention outward, the researchers argue, and notice, say, a pattern in animal tracks that was previously hidden. The urge to find a coherent pattern makes it more likely that the brain will find one.

"There's more research to be done on the theory," said Michael Inzlicht, an assistant professor of psychology at the University of Toronto, because it may be that nervousness, not a search for meaning, leads to heightened vigilance. But he added that the new theory was "plausible, and it certainly affirms my own meaning system; I think they're onto something."

In the most recent paper, published last month, Dr. Proulx and Dr. Heine described having 20 college students read an absurd short story based on "The Country Doctor," by Franz Kafka. The doctor of the title has to make a house call on a boy with a terrible toothache. He makes the journey and finds that the boy has no teeth at all. The horses who have pulled his carriage begin to act up; the boy's family becomes annoyed; then the doctor discovers the boy has teeth after all. And so on. The story is urgent, vivid and nonsensical - Kafkaesque.

After the story, the students studied a series of 45 strings of 6 to 9 letters, like "X, M, X, R, T, V." They later took a test on the letter strings, choosing those they thought they had seen before from a list of 60 such strings. In fact the letters were related, in a very subtle way, with some more likely to appear before or after others.

The test is a standard measure of what researchers call implicit learning: knowledge gained without awareness. The students had no idea what patterns their brain was sensing or how well they were performing.

But perform they did. They chose about 30 percent more of the letter strings, and were almost twice as accurate in their choices, than a comparison group of 20 students who had read a different short story, a coherent one.

"The fact that the group who read the absurd story identified more letter strings suggests that they were more motivated to look for patterns than the others," Dr. Heine said. "And the fact that they were more accurate means, we think, that they're forming new patterns they wouldn't be able to form otherwise."

**B**rain-imaging studies of people evaluating anomalies, or working out unsettling dilemmas, show that activity in an area called the anterior cingulate cortex spikes significantly. The more activation is recorded, the greater the motivation or ability to seek and correct errors in the real world, a recent study suggests. "The idea that we may be able to increase that motivation," said Dr. Inzlicht, a co-author, "is very much worth investigating."

**R**esearchers familiar with the new work say it would be premature to incorporate film shorts by David Lynch, say, or compositions by John Cage into school curriculums. For one thing, no one knows whether exposure to the absurd can help people with explicit learning, like memorizing French. For another, studies have found that people in the grip of the uncanny tend to see patterns where none exist - becoming more prone to conspiracy theories, for example. The urge for order satisfies itself, it seems, regardless of the quality of the evidence.

Still, the new research supports what many experimental artists, habitual travelers and other novel seekers have always insisted: at least some of the time, disorientation begets creative thinking.

**Secrets of the Cell**

## Self-Destructive Behavior in Cells May Hold Key to a Longer Life

**By CARL ZIMMER**

Deep down, we are all cannibals. Our cells are perpetually devouring themselves, shredding their own complex molecules to pieces and recycling them for new parts. Many of the details of our endless self-destruction have come to light only in the past few years. And to the surprise of many scientists, links are now emerging between this inner cannibalism and diseases like Alzheimer's disease and cancer.

"There's been an explosion," said Daniel Klionsky of the University of Michigan. "All of a sudden, researchers in different fields are seeing a connection."

In fact, as Dr. Klionsky wrote in a paper published online in Trends in Cell Biology, this cannibalism may extend our lifespan. Increasing our body's ability to self-destruct may, paradoxically, let us live longer.

Our cells build two kinds of recycling factories. One kind, known as the proteasome, is a tiny cluster of proteins. It slurps up individual proteins like a child sucking a piece of spaghetti. Once inside the proteasome, the protein is chopped up into its building blocks.

For bigger demolition jobs, our cells rely on a bigger factory: a giant bubble packed with toxic enzymes, known as a lysosome. Lysosomes can destroy big structures, like mitochondria, the sausage-shaped sacs in cells that generate fuel. To devour a mitochondrion, a cell first swaddles it in a shroudlike membrane, which is then transported to a lysosome. The shroud merges seamlessly into the lysosome, which then rips the mitochondrion apart. Its remains are spit back out through channels on the lysosome's surface.

Lysosomes are versatile garbage disposals. In addition to taking in shrouded material, they can also pull in individual proteins through special portals on their surface. Lysosomes can even extend a mouthlike projection from their membrane and chew off pieces of a cell.

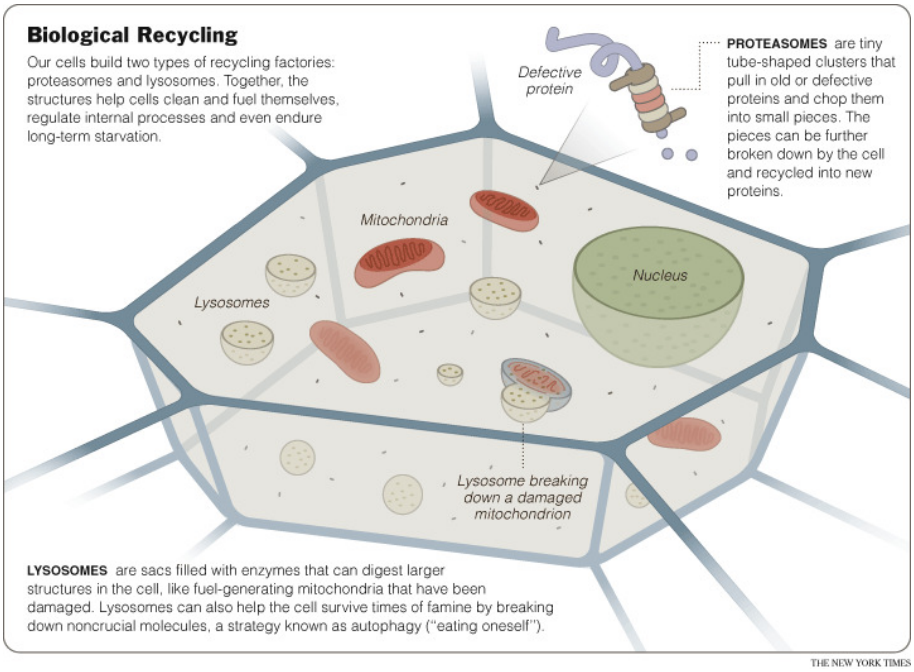
The shredded debris that streams out of the lysosomes is not useless waste. A cell uses the material to build new molecules, gradually recreating itself from old parts. “Every three days, you basically have a new heart,” said Dr. Ana Maria Cuervo, a molecular biologist at Albert Einstein College of Medicine.

This self-destruction may seem like a reckless waste of time and energy. Yet it is essential for our survival, and in many different ways. Proteasomes destroy certain proteins quickly, allowing them to survive for only about half an hour. That speed allows cells to keep tight control over the concentrations of the proteins. By tweaking the rate of destruction, it can swiftly raise or lower the number of any kind of protein.

Lysosomes, which eat more slowly than proteasomes, serve different roles that are no less essential. They allow cells to continue to build new molecules even when they are not getting a steady supply of raw ingredients from the food we eat. Lysosomes also devour oily droplets and stores of starch, releasing energy that cells can use to power the construction of new molecules.

“If you don’t have a snack between lunch and dinner,” Dr. Cuervo said, “you’re going to have to activate your lysosomes to get nutrients.”

Lysosomes become even more active if dinner never comes, and a short-term hunger turns to long-term starvation. Cells respond to famine by making only a small number of crucial molecules and using lysosomes to destroy the rest. “When times are good, make everything,” Dr. Klionsky said. “When times are lean, focus on what you need. You can get rid of everything else.”




This strategy for survival, known as autophagy (“eating oneself”), evolved in our ancestors over two billion years ago. Today, all animals rely on it to endure famines, as do plants, fungi and single-cell protozoa.

Autophagy’s great antiquity has helped scientists discover the genes that make it possible in humans. Rather than study starving people, they introduced mutations into yeast and then observed which strains could no longer survive without food. In many cases, the scientists discovered, the mutations that made yeast vulnerable struck genes that are involved in autophagy. They were then able to find nearly identical versions of those genes in the human genome.

The protection humans get from lysosomes is essential not just during famines. It is also vital just after birth. When babies emerge from their mothers, they need huge amounts of energy so that they can start to run their bodies on their own. But this demand comes at precisely the moment that babies stop getting food through their umbilical cord. Japanese scientists have found that lysosomes in mice kick into high gear as soon as they are born. After a day or two, as they start to nurse, the rate of autophagy drops back to normal.

When the scientists engineered mice so they could not use their lysosomes at birth, the newborn mice almost immediately died of starvation.

Even if you enjoy a steady supply of food your entire life, you still rely on autophagy for another reason: to keep the molecules in your cells in good working order. Cells make a lot of defective molecules. They misread genes, for example, and misfold proteins. Even a perfectly crafted molecule does not stay perfect for long. “Proteins go bad with time,” Dr. Klionsky said. “They age, and they wear out.”

When proteins and other molecules go bad, they can start to gum up the intricate chemical reactions on which a cell’s survival depends. The cell recognizes defective parts and tags them for destruction. Experiments on flies show the harm that can occur when cells cannot clear away the old and bring in the new. Flies that are genetically engineered with defective lysosomes start to accumulate abnormal clumps of proteins in their cells. The clumps build up especially in their neurons, which start to die as a result.

The Belgian biochemist Christian de Duve discovered lysosomes in 1955, for which he later won the Nobel Prize. In 1963, scientists discovered that a genetic defect in lysosomes was responsible for a disorder known as Pompe disease, which weakens the heart and muscles. Those who have the disease are missing a protein that lysosomes need to break down stores of energy. Today over 50 disorders are recognized as the result of one defect or another in lysosomes. Doctors can now treat some of these diseases by supplying people with the proteins they lack.

In recent years, scientists have also found evidence of autophagy in preventing a much wider range of diseases. Many disorders, like Alzheimer's disease, are the result of certain kinds of proteins forming clumps. Lysosomes can devour these clumps before they cause damage, slowing the onset of diseases.

Lysosomes may also protect against cancer. As mitochondria get old, they cast off charged molecules that can wreak havoc in a cell and lead to potentially cancerous mutations. By gobbling up defective mitochondria, lysosomes may make cells less likely to damage their DNA. Many scientists suspect it is no coincidence that breast cancer cells are often missing autophagy-related genes. The genes may have been deleted by mistake as a breast cell divided. Unable to clear away defective mitochondria, the cell's descendants become more vulnerable to mutations.

Unfortunately, as we get older, our cells lose their cannibalistic prowess. The decline of autophagy may be an important factor in the rise of cancer, Alzheimer's disease and other disorders that become common in old age. Unable to clear away the cellular garbage, our bodies start to fail.

If this hypothesis turns out to be right, then it may be possible to slow the aging process by raising autophagy. It has long been known, for example, that animals that are put on a strict low-calorie diet can live much longer than animals that eat all they can. Recent research has shown that caloric restriction raises autophagy in animals and keeps it high. The animals seem to be responding to their low-calorie diet by feeding on their own cells, as they do during famines. In the process, their cells may also be clearing away more defective molecules, so that the animals age more slowly.

Some scientists are investigating how to manipulate autophagy directly. Dr. Cuervo and her colleagues, for example, have observed that in the livers of old mice, lysosomes produce fewer portals on their surface for taking in defective proteins. So they engineered mice to produce lysosomes with more portals. They found that the altered lysosomes of the old experimental mice could clear away more defective proteins. This change allowed the livers to work better.

"These mice were like 80-year-old people, but their livers were functioning as if they were 20," Dr. Cuervo said. "We were very happy about that."

Andrea Ballabio, the scientific director of Telethon Institute of Genetics and Medicine in Naples, Italy, and his colleagues have found another way to raise autophagy. By studying the activity of genes that build lysosomes, they discovered that at least 68 of the genes are switched on by a single master protein, known as TFEB.

When Dr. Ballabio and his colleagues engineered cells to make extra TFEB, the cells made more lysosomes. And each of those lysosomes became more efficient. The scientists injected the cells with huntingtin, a protein that clumps to cause the fatal brain disorder Huntington's disease. The cells did a much better job of destroying the huntingtin than normal cells.

"This is a very good sign," Dr. Ballabio said. "We're very excited because this network of genes may apply to a number of diseases."

Dr. Ballabio and other researchers are now investigating ways in which they can increase autophagy with drugs or diets - raising the number of portals on lysosomes, for example, or causing cells to make extra TFEB. But developing such treatments will require a sophisticated understanding of autophagy. After all, autophagy is a potent force for destruction, and if lysosomes are accidentally ripped open, their toxic enzymes can kill a cell.

As Dr. Klionsky, of the University of Michigan, said, "You can't just turn this on and let it go."

## 'Leopard Behind You!'

I'd like to continue Predator Appreciation Month with reflections on one of the more intriguing effects that predators can have on their prey: the development of a vocabulary of alarm. (Or should that be "an alarming vocabulary"?)

This isn't a complicated vocabulary, with thousands of words. Nonetheless, it's clear that for many animals, alarm calls are more than simple squawks of fear. Vervet monkeys, for instance, use different sounds to warn of different types of predator. "Leopard!" is not the same as "snake!" or "eagle!" If you hide a loudspeaker in the bushes, and startle unsuspecting monkeys by playing recordings of "snake!" at them, they will look around at the ground. "Eagle!" makes them look up. "Leopard!" sends them scampering to the trees.

Vervets aren't unique. Other primates - including Diana monkeys and Campbell's monkeys - also distinguish between eagles and leopards. (Diana monkeys are elegant animals, with fur of several colors. Also, like male vervets and Campbell's monkeys, male Dianas have a scrotum that's a tasteful shade of blue.)

Some animals make rather subtle distinctions. Gunnison's prairie dogs have a different sound for each of coyotes, dogs, hawks and humans. More impressive, they describe what a particular dangerous animal looks like: a human in a blue shirt is announced differently from a human in a yellow shirt. Similarly, meerkats - those charismatic mongooses that stand on their hind legs to scan for predators - give calls that announce both the general type of predator (coming from the sky, coming from the ground) and how close it is - in other words, how urgently everyone should react. Black-capped chickadees - small songbirds that live in North America - have calls that say whether a predator is flying or resting, and if it is resting, how dangerous it is. For example, pygmy owls eat lots of songbirds; horned owls don't. Sure enough, chickadees kick up more of a fuss about perched pygmy owls than they do about perched horned owls.

In and of itself, it's not surprising that the sounds animals make are not just noise, or a reflection of the state an animal's in (scared, happy and so on). But the subtlety of the calls - the full amount of meaning they contain - is only now being appreciated. Decoding animal sounds isn't straightforward; indeed, alarm calls are among the easiest sounds to study, because the animals hearing the alarms tend to respond in ways that are easy for us to understand and describe - for instance, they stop eating and look about, or run away.

But here's what I particularly like about all this: animals of one species often respond to the alarms of another. In a small way, it's like those childrens' stories that have rats talking to toads, or elephants arguing with ostriches.

Diana monkeys, for example, don't use the same sounds for "eagle!" or "leopard!" as Campbell's monkeys do. But they respond to recordings of a Campbell's monkey shouting "eagle!" or "leopard!" just as they would to a shout from one of their own, or a sighting of the predator itself. Yellow-casqued hornbills - forest birds that have problems with eagles but not leopards - react to Diana monkey shouts of "eagle!" but ignore their cries of "leopard!" (Yellow-casqued hornbills remind me of aging rock stars: their head feathers have that kind of wild look.)

Predators sometimes respond too. After all, alarm calls don't just let other animals know there's danger in the area. They can also let a predator know that it's been seen. Ambush predators, like leopards, often give up and go away once an alarm has been sounded.

Paying attention to the cries and hoots of others can be particularly important for animals that have a bad view of the neighborhood, or that spend a lot of time alone and thus don't get warnings from their own kind. An example: Gunther's dik-dik, a species of miniature antelope. These creatures live in pairs, in large territories. They have many enemies - leopards, lions, eagles, hyenas, vultures and the like - and spend much of their time hiding in thickets of undergrowth, where they don't have a good view. So perhaps it's not surprising that they tune into the alarm calls of go-away birds - which sit high in the tree-tops, announcing passing predators.

All of this makes sense: you'd expect animals to evolve to pay attention to all the information available to them, especially in matters of life and death. The more important question is, how do they come to know what the different calls mean?

The short answer is, we don't really know yet. However, there are three basic possibilities. One: they are born with the knowledge - it's innate. Two: they learn by personal experience, or by watching the fates of others. Three: it's some combination.

Young vervet monkeys, for example, appear to have an innate tendency to shout "eagle!" - but they do it at anything that's in the air, be it an eagle, a vulture or a falling leaf. They shout "snake!" at long, thin things on the ground - like twigs. As they get older they learn to refine their calls. This seems to be through positive reinforcement - when they make the right call, adults join in and do it too. (It's tempting to think there may be negative reinforcement as well. One researcher reported seeing a mother run up a tree after her infant gave a "leopard!" alarm. But there was no leopard - only a harmless mongoose - and when the mother caught up with the infant, she gave it a smack.)

Moreover, many animals are quick to make associations between sounds and danger. In areas where wolves have been absent and then reintroduced, female moose that have lost a calf to wolves are much more attentive than other females to the sounds of wolf howls. Perhaps dik-dik fawns see their parents reacting to the cries of the go-away bird, and learn to do it too.

This subject is not merely of academic interest. Many programs in animal conservation depend on reintroducing captive animals to the wild. But if an animal doesn't know what to be afraid of, it probably won't last long Out There. Understanding how animals acquire fear of predators - and then teaching them what to be afraid of, and what to listen out for - may be essential if newly freed animals are to survive.

## Strategy for mismatched stem cell transplants triggers protection against graft-vs.-host disease

BOSTON--A new technique being tested in stem-cell transplants from imperfectly matched donors has revealed a striking, unforeseen response that can suppress graft-versus-host disease, a common and dangerous complication of mismatched transplants, report scientists from Dana-Farber Cancer Institute.

Analysis of blood samples from a small number of clinical trial patients showed that the novel method - which inactivates specific immune cells from the donor that would attack the recipient's body - also unleashes a surge of T-cells that further dampen the immune reaction.

The previously unrecognized specificity of these regulatory T-cells (also called Tregs) helps explain why the patients treated with the new strategy - known as "co-stimulatory blockade" - have shown a gratifyingly low level of graft-vs-host disease, according to the report published online by the new journal Science Translational Medicine.

The findings also suggest that optimizing the activity of Tregs in this manner might prove valuable in transplants of kidneys and other solid organs, as well as in treating autoimmune disease, say the scientists, led by Eva Guinan, MD, senior author, of Dana-Farber and Children's Hospital Boston, and Jeff Davies, MD, PhD, first author, of Dana-Farber. Both are also on the Harvard Medical School faculty.

The innovative method for improving mismatched bone-marrow and stem-cell transplants was first described clinically 10 years ago in the New England Journal of Medicine by Guinan, Lee Nadler, MD, also at Dana-Farber and a co-author on the new publication, and others. They employed a technique called "co-stimulatory blockade" to prevent certain T-cells in the donor material from recognizing and attacking cells in the patient's body, causing graft-vs-host inflammatory reactions that can affect the gastrointestinal system, skin, and other organs. The need for techniques that can reduce complications in mismatched transplants is great; the odds of a patient having a perfectly matched sibling for a donor are only about 25 percent.

"Originally we thought that using this method to specifically block the harmful response by donor T-cells explained the decrease in graft-vs-host disease and the rapid recovery of immune function we have seen in the clinical trials," said Guinan. "Now we learn that there is another powerful mechanism that is induced - the generation and rapid expansion of Treg cells in the three months following the transplant."

Regulatory T-cells are a special population of T-cells that suppress immunity. They have two important functions: Turning off immune reactions following a successful defense against infectious organisms, and preventing immune cells from attacking the body's own tissues, which are identified by distinctive "self-antigen" markers.

In the past five years or so, scientists have used new tools to study Tregs and consider ways they could be harnessed for therapy in transplantation and autoimmune disease. In 2008, Davies and Guinan reported low levels of graft-vs-host disease in a small number of mismatched transplants using co-stimulatory blockade, which not only neutralized the T-cells that cause the harmful graft-vs-host response but also led to rapid reconstitution of the patients' bone marrow.

The researchers then designed experiments to learn more molecular details about how the blockade strategy had reduced graft-vs-host complications. Based on few reports in the literature, "We wondered whether Tregs were playing an additional role," said Davies.

Davies analyzed frozen blood samples taken from five patients and donors at various intervals after the transplants. The analysis showed that during the first three months, the level of Tregs in the patients rapidly rose to very high levels, which helped explain why the recipients experienced only mild graft-vs-host symptoms. The Tregs, they confirmed, were generated from the donated T-cells – not remnants of the recipient's immune system.

"We found there was something about co-stimulatory blockade that caused this rapid expansion of Tregs," said Davies, adding that further studies are exploring this question.

Importantly, the researchers noted, the Tregs acted in a highly specific fashion: They turned off only the donor T-cells that would have triggered the immune attack on the recipient's tissues - other T-cells that help the patients fight off infections were spared. This specificity appears to have developed in the recipient's body, where the Tregs were "educated" to respond only to a harmful T-cell reaction.

As a result, said Guinan, this technique "creates a good balance of effects - inactivating the T-cells that cause graft-vs-host disease (GVHD), revving up the Tregs to turn off any incipient GVHD, while bringing about a rapid reconstitution of the recipient's immune system."

The scientists expect the new findings to influence the design of further clinical tests of the co-stimulatory blockade technique. And, they said, it opens a window on other potential applications of co-stimulatory

blockade, which is already being used clinically to treat rheumatoid arthritis (an autoimmune disease) and is being tested in mismatched kidney transplants.

*Guinan is the associate director of the Center for Clinical and Translational Research at Dana-Farber and an associate professor of pediatrics at Harvard Medical School.*

*The research was funded by grants from the National Institutes of Health, the Leukemia & Lymphoma Society, and the American Society of Blood and Marrow Transplantation.*

## Genome-wide study of autism published in Nature

### *Combining family- and population-based approaches sheds new light on the potential roles of both common and rare forms of human genetic variation*

In one of the first studies of its kind, an international team of researchers has uncovered a single-letter change in the genetic code that is associated with autism. The finding, published in the October 8 issue of the journal Nature, implicates a neuronal gene not previously tied to the disorder and more broadly, underscores a role for common DNA variation. In addition, the new research highlights two other regions of the genome, which are likely to contain rare genetic differences that may also influence autism risk.

"These discoveries are an important step forward, but just one of many that are needed to fully dissect the complex genetics of this disorder, " said Mark Daly, one of the study's senior authors, a senior associate member at the Broad Institute of Harvard and MIT and an associate professor at the Center for Human Genetic Research at Massachusetts General Hospital (MGH). "The genomic regions we've identified help shed additional light on the biology of autism and point to areas that should be prioritized for further study."

"The biggest challenge to finding the genes that contribute to autism is having a large and well studied group of patients and their family members, both for primary discovery of genes and to test and verify the discovery candidates," said Aravinda Chakravarti, professor of medicine, pediatrics and molecular biology and genetics at the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins, and one of the study's senior authors. "This latest finding would not have been possible without these many research groups and consortia pooling together their patient resources. Of course, they would not have been possible without the genomic scanning technologies either."

Autism is a common neurodevelopmental disorder characterized by impaired social, behavioral and communication abilities. Compared to other complex diseases, which are caused by a complicated mix of genetic, environmental and other factors, autism is highly heritable - roughly 90% of the disorder is thought to be genetic in origin. Yet the majority of autism cases cannot be attributed to known inherited causes.

Modern approaches that harness genome-scale technologies have begun to yield some insights into autism and its genetic underpinnings. However, the relative importance of common genetic variants, which are generally present in the human population at a frequency of about 5%, as well as other forms of genetic variation, remains an unresolved question.

To more deeply probe autism's complex genetic architecture, a large multinational collaboration led by researchers at the Broad Institute of Harvard and MIT, Massachusetts General Hospital, Johns Hopkins University and elsewhere devised a two-pronged, genome-scale approach. The first component makes use of a family-based method (called "linkage") that analyzes DNA from autism patients and their family members to detect portions of the genome that harbor rare but high-impact DNA variants. The second harnesses a population-based method (known as "association") that examines DNA from unrelated individuals and can expose common genetic variants associated with autism and which tend to exert more modest effects.

"Given the genetic complexity of autism, it's unlikely that a single method or type of genomic variation is going to provide us with a complete picture," said Daly. "Our approach of combining multiple complementary methods aims to meet this critical challenge."

For their initial studies, the researchers examined roughly half a million genetic markers in more than 1,000 families from the Autism Genetic Resource Exchange (AGRE) and the US National Institute of Mental Health (NIMH) repositories. Follow-up analyses were conducted in collaboration with the Autism Genome Project as well as other international groups. "We are deeply grateful to all of the patients and their families who made this work possible," said Daly.

The researchers' results highlight three regions of the human genome. These include parts of chromosomes 6 and 20, the top-scoring regions to emerge from the family-based linkage studies. Although further research is needed localize the exact causal changes and genes within these regions that contribute to autism, these findings can help guide future work.

The other major result, this one flowing from the population-based analyses, is a single-letter change in the genetic code known as a single nucleotide polymorphism, or SNP (pronounced "snip"). This common variant lies on chromosome 5 near a gene known as semaphorin 5A, which is thought to help guide the growth of

neurons and their long projections called axons. Notably, the activity or "expression" of this gene appears to be reduced in the brains of autism patients compared to those without the disorder.

"These genetic findings give us important new leads to understand what's different in the developing autistic brain compared with typical neurodevelopment. We can now begin to explore the pathways in which this novel gene acts, expanding our knowledge of autism's biology," said co-lead author Lauren Weiss, a former postdoctoral fellow who collaborated with Daly and his colleagues at MGH and the Broad Institute. Weiss is now an assistant professor of psychiatry and human genetics at University of California, San Francisco (UCSF).

Although the Nature paper identifies a handful of new genes and genomic regions, the researchers emphasize that the findings are just one piece of a very large - and mostly unfinished - puzzle. Future studies involving larger patient cohorts and higher resolution genomic technologies, such as next-generation DNA sequencing, promise to yield a deeper understanding of autism and its complex genetic roots.

*This work was supported by the Autism Consortium, the Nancy Lurie Marks Family Foundation, NARSAD, the National Center for Research Resources, the National Institute of Mental Health, the Simons Foundation as well as other funding agencies.*

***Paper cited:*** *Weiss LA, Arking DE, The Gene Discovery Project of Johns Hopkins & the Autism Consortium. A genome-wide linkage and association scan reveals novel loci for autism. Nature DOI:10.1038/nature08490.*

## Heartburn drugs deemed safe for fetuses according to Ben-Gurion University researchers

BEER-SHEVA, Israel - H2 Blocker drugs, such as Famotidine, Cimetidine and Ranitidine, approved in the U.S. for acid reflux (heartburn), pose no significant risks for the fetus according to a large collaborative cohort study by researchers at Ben-Gurion University of the Negev.

The study published in the Journal of Clinical Pharmacology provides significant reassurance for the safety of the fetus when H2 blocker drugs are given to women to relieve acid reflux during pregnancy.

H2 blockers are among the most frequently recommended drugs for acid reflux symptoms of heartburn, regurgitation and trouble swallowing, which are common in pregnant women. The findings of a large cohort study examining infants born to mothers who were exposed to H2 blockers, particularly Famotidine, during pregnancy. Usually symptoms of acid reflux are more frequent and more severe in the latter months of gestation. It has been estimated that between 30 percent to 80 percent of pregnant women are affected.

The study was a collaboration between Ben-Gurion University of the Negev, Soroka University Medical Center and Clalit Health Services - all in Beer-Sheva, Israel - along with the Division of Pharmacology, Hospital for Sick Children in Toronto, Canada. It was part of the doctoral thesis of Ilan Matok under the supervision of principal investigators epidemiologist Dr. Amalia Levy and pediatrician and clinical pharmacologist professor emeritus Rafael Gorodischer. The study was conducted by the three Israeli entities as part of the BeMORE collaboration (Ben-Gurion MotheRisk Obstetric Registry of Exposure). The investigation of the safety of other medications commonly used off-label in pregnancy is an ongoing project of BeMORE investigators in large cohorts of women in Southern Israel.

"Of the vast majority of medications approved for use, there is insufficient data from human studies to determine whether the benefits of therapy exceed the risk to the fetus," according to the pediatrician and clinical pharmacologist, principal investigator Dr. Rafael Gorodischer, professor emeritus at Ben-Gurion University of the Negev. "Medicines are approved for use only after there is sufficient scientific evidence demonstrating the drug safety and effectiveness for its intended uses."

The safety of H2 blockers used during the first trimester of pregnancy was investigated by linking a database of medications dispensed over 10 years to all women registered in Clalit Health Services in the Southern District of Israel, with databases containing maternal and infant hospital records, and with therapeutic abortion records of Soroka University Medical Center, during the same period. In the study, 1,148 (or 1.4 percent) were exposed to H2 blockers during the first trimester of pregnancy of the 84,823 infants born to mothers during the study period.

The rate of major congenital malformations identified in the group that was exposed to H2 blockers during the first trimester was 5.7 percent (65 of 1,148 infants), as compared with a rate of 5.3 percent (4,400 of 83,675 infants) in the unexposed group.

According to principal investigator epidemiologist Dr. Amalia Levy of the BGU Faculty of Health Sciences, and chairwoman of the BeMORE collaboration, "Exposure to H2 blockers among this group was not associated with significantly increased risks of major congenital malformations. The results were unchanged when therapeutic abortions of exposed fetuses were included in the analysis. Also, infants exposed in utero had no increased risk of perinatal mortality, low birth weight or premature birth".

*Journal of Clinical Pharmacology: "The Safety of H2Blockers Use During Pregnancy" (J Clin Pharm OnlineFirst, doi:10.1177/0091270009350483).*

## Rare head and neck cancer linked to HPV, study finds

ANN ARBOR, Mich. - An increase in cases of a rare type of head and neck cancer appears to be linked to HPV, or human papillomavirus, according to a new study from researchers at the University of Michigan Comprehensive Cancer Center.

The study looked at patients with nasopharyngeal cancer, a tumor that grows behind the nose and at the top of the throat, above the tonsils. This rare cancer occurs in less than 1 of every 100,000 Americans.

"Though rare, this is the first report of nasopharyngeal cancer being caused by the HPV epidemic. We are in the middle of a tonsil cancer epidemic, seeing many patients with tonsil cancer linked to HPV. It turns out that HPV may also be a new cause of this rare form of cancer that occurs in this hidden location," says study author Carol Bradford, M.D., professor and chair of otolaryngology at the U-M Medical School.

In the study, which appears online in the journal Head & Neck, the researchers looked at tissue samples taken before treatment for either nasopharyngeal cancer or tonsil cancer. Of the 89 patients in the study, five had nasopharyngeal cancer, and four of those were positive for HPV.

At the same time, the four HPV-positive tumors were also all negative for Epstein-Barr virus, which has previously been one of the biggest infectious causes of nasopharyngeal cancer.

"Since I began studying head and neck cancer, I have wondered what the cause of Epstein-Barr virus-negative nasopharyngeal tumors might be. This research suggests that there is a changing etiology for nasopharyngeal cancer in the North American population that may mirror the HPV-positive epidemic of tonsil cancer," says study author Thomas Carey, Ph.D., professor of otolaryngology and pharmacology and co-director of the head and neck oncology program at the U-M Comprehensive Cancer Center.

Overall, about 60 percent of nasopharyngeal cancer patients are alive five years after treatment. In fact, death rates for this type of cancer have declined 4 percent per year. The researchers suspect one potential reason is that HPV-related tumors are more responsive to chemotherapy or radiation than tumors linked to the Epstein-Barr virus.

Because nasopharyngeal cancer is so rare, the authors propose a multi-center trial to recruit more patients to verify the role of HPV in nasopharyngeal cancer.

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*Reference: Head & Neck, published online Sept. 15, 2009, DOI:10.1002/hed.21216*

## Has the pill changed the rules of sexual attraction?

* 17:23 07 October 2009 **by Linda Geddes**

The contraceptive pill alters monthly fluctuations in hormones associated with the menstrual cycle, mimicking the more stable hormonal conditions associated with pregnancy. This might not only disrupt the natural processes which influence women's choice of partner, but it could also make them less able to compete with women who have a natural menstrual cycle, a paper published this week in Trends in Ecology and Evolution suggests. How worried should we be, and what other strategies can men and women use to tip the odds in their favour? New Scientist investigates.

**What do we know about how women choose a mate?**

Recent studies have confirmed that women tend to prefer taut bodies, broad shoulders, clear skin and defined, masculine facial features – all of which may indicate sexual potency and good genes. Women also tend to be attracted to men who look as if they have wealth, or the ability to acquire it.

Smell may also be a factor: women seem to prefer the scent of men who have immune systems dissimilar to their own, as measured by genes for the major histocompatibility complex (MHC). A number of companies have sprung up recently that even claim to be able to match couples on the basis of their genes.

**How might the contraceptive pill interfere with this?**

Levels of the sex hormones oestrogen and progesterone fluctuate throughout a woman's monthly menstrual cycle. At the start of the cycle – when the egg is maturing – the body releases oestrogen. During the second half of the cycle, after the egg has been released and might implant, progesterone is secreted. A woman's most fertile period comes in between these two phases, shortly before and immediately after the egg is released.

Women's preferences for certain male scents and features are thought to change during their cycle. For example, as they approach ovulation, women prefer men with more masculine features, possibly because these

reflect high sexual potency and better genes. During non-fertile periods they prefer more feminine facial features and attributes, perhaps because such men may be more nurturing and therefore better at helping to raise children, even if they are not their own.

The pill may throw a spanner in the works. It stops this cyclical release of oestrogen and progesterone, and so may interfere with women's natural choice of partner. Some studies have suggested that while women usually prefer the scent of men with immune profiles dissimilar to their own, those on the pill preferred men with similar immune profiles.

**Should women on the contraceptive pill be worried?**

Although studies have hinted that women's choice of partner may be affected by the pill, such basic mechanisms of mate choice likely evolved in very different conditions to today's society. Our ancestors lived in far smaller communities and rarely had the chance to meet outsiders. This means the chances of inbreeding would have been much higher, and subtle cues like smell might well have reduced the chances of this happening.

Today, our communities are far more diverse, so the chances of inbreeding are more remote. Many would argue that personality is a far better way to choose a life partner than what they smell like. One recent study involving speed-dating experiments suggested that although women might say they prefer the scent of men with dissimilar immune systems, this doesn't correspond with the men they actually chose to go out with.

As the authors of the new Trends in Ecology and Evolution paper point out, more studies are needed to establish whether mate preferences in lab experiments actually correlate with how men and women behave in the real world.

**Don't men have any say in the matter?**

As a general rule, men tend to desire women with features that suggest youth and fertility, including a low waist-to-hip ratio, full lips and soft facial features.

Some studies have looked at men's preferences for women at different stages of the menstrual cycle. For example, women's voices are thought to be more attractive during the most fertile period of their cycle. During this part of their cycle, lap dancers also reportedly earn more that at other times.

The contraceptive pill might in theory iron out some of these differences. The problem is that many of these studies have relied on artificial conditions – by asking men to rate women's walks in video clips, for example.

It's unlikely that we pay such close attention to these cues in the real world. Even if we do, it's obvious that the majority of women who are on the pill have no problem attracting or retaining a partner. In the case of the lap dancers, those on the pill earned similar tips to those with normal cycles during the non-fertile periods of their menstrual cycle, suggesting that men found them equally attractive.

**Is there anything men can do to make themselves more attractive to women?**

If you're not tall, toned and masculine-looking, don't despair. Whether they are looking for a one-night stand or a long-term relationship, women tend to go for intelligence as well as good looks. Showing your creative side also helps: both artists and poets seem to attract a lot of sexual partners.

There is also empirical evidence that women find wealthy men attractive, and one recent study concluded that richer men father more children.

If all else fails, try surrounding yourself with beautiful female friends or slipping a wedding ring on your finger. Both men and women find members of the opposite sex more attractive, if others seem attracted to them too. *Journal reference: Trends in Ecology and Evolution, DOI: 10.1016/j.tree.2009.08.003*

## Specialty hospitals cherry-pick patients, exaggerate success, says INFORMS meeting paper

### *California cardiac care hospitals studied in INFORMS annual meeting paper*

Although many specialized hospitals deliver better and faster services in cardiac care and other specialties, a paper being presented at the annual meeting of the Institute for Operations Research and the Management Sciences (INFORMS®) maintains that these hospitals cherry-pick patients to achieve these results, and that average patients actually receive worse care.

"The Effect of Focus on Performance: Evidence from California Hospitals" is by Diwas KC, Asst Prof at Goizueta Business School at Emory University and Christian Terwiesch, Professor at The Wharton School at the University of Pennsylvania.

The annual meeting (http://www.informs.org/article.php?id=1615&p=1|) of the Institute for Operations Research and the Management Sciences (INFORMS®) takes place at the San Diego Convention Center and the Hilton San Diego from Sunday, October 11 - Wednesday, October 14. Some 4,000 experts in analytics, operations research, and applied math are expected to attend.

The authors acknowledge that focused hospitals deliver faster services at higher levels of quality, as indicated by lower lengths of stay and reduced mortality rates.

They investigated the extent to which the superior operational outcome is driven by focused hospitals truly excelling in their operations or by focused hospitals simply selectively admitting patients who are easier to treat.

Their analysis shows that for randomly assigned patients, focused hospitals deliver a lower quality of care, as measured by a higher mortality rate. They also find that the average length of stay for a randomly assigned patient is longer at focused hospitals.

In other words, patient selectivity is an important driver of the superior outcomes at focused hospitals.

In addition, the authors show that the market entry of a focused hospital has a negative effect on the performance of other hospitals operating in the same region. Their results show that the average operational performance of existing hospitals deteriorates following the entry of a focused competitor, who attracts the easy-to-treat patients.

Overall, they conclude that this business focus can indeed be the source of a competitive advantage in hospital operations. However, this advantage is substantially driven by focused hospitals cherry-picking easy-to-treat patients at the expense of other, full-service hospitals in the region.

*Operations research, also known as analytics, is the application of advanced analytical methods to help make better decisions. Information about the field, often referred to as analytics, is at www.scienceofbetter.org.*
*Additional information about the conference is at www.informs.org.*

## MU Researchers Create Smaller and More Efficient Nuclear Battery

### *Mizzou scientist develops a powerful nuclear battery that uses a liquid semiconductor*

COLUMBIA, Mo. – Batteries can power anything from small sensors to large systems. While scientists are finding ways to make them smaller but even more powerful, problems can arise when these batteries are much larger and heavier than the devices themselves. University of Missouri researchers are developing a nuclear energy source that is smaller, lighter and more efficient.

"To provide enough power, we need certain methods with high energy density," said Jae Kwon, assistant professor of electrical and computer engineering at MU. "The radioisotope battery can provide power density that is six orders of magnitude higher than chemical batteries."

Kwon and his research team have been working on building a small nuclear battery, currently the size and thickness of a penny, intended to power various micro/nanoelectromechanical systems (M/NEMS). Although nuclear batteries can pose concerns, Kwon said they are safe. "People hear the word 'nuclear' and think of something very dangerous," he said. "However, nuclear power sources have already been safely powering a variety of devices, such as pace-makers, space satellites and underwater systems."

His innovation is not only in the battery's size, but also in its semiconductor. Kwon's battery uses a liquid semiconductor rather than a solid semiconductor.

"The critical part of using a radioactive battery is that when you harvest the energy, part of the radiation energy can damage the lattice structure of the solid semiconductor," Kwon said. "By using a liquid semiconductor, we believe we can minimize that problem."

Kwon has been collaborating with J. David Robertson, chemistry professor and associate director of the MU Research Reactor, and is working to build and test the battery at the facility. In the future, they hope to increase the battery's power, shrink its size and try with various other materials. Kwon said that the battery could be thinner than the thickness of human hair. They've also applied for a provisional patent.

Kwon's research has been published in the Journal of Applied Physics Letters and Journal of Radioanalytical and Nuclear Chemistry. In addition, last June, he received an "outstanding paper" award for his research on nuclear batteries at the IEEE International Conference on Solid-State Sensors, Actuators and Microsystems in Denver (Transducers 2009).

## New aluminum-water rocket propellant promising for future space missions

WEST LAFAYETTE, Ind. - Researchers are developing a new type of rocket propellant made of a frozen mixture of water and "nanoscale aluminum" powder that is more environmentally friendly than conventional propellants and could be manufactured on the moon, Mars and other water-bearing bodies.

The aluminum-ice, or ALICE, propellant might be used to launch rockets into orbit and for long-distance space missions and also to generate hydrogen for fuel cells, said Steven Son, an associate professor of mechanical engineering at Purdue University.

Purdue is working with NASA, the Air Force Office of Scientific Research and Pennsylvania State University to develop ALICE, which was used earlier this year to launch a 9-foot-tall rocket. The vehicle reached an altitude of 1,300 feet over Purdue's Scholer farms, about 10 miles from campus.

"It's a proof of concept," Son said. "It could be improved and turned into a practical propellant. Theoretically, it also could be manufactured in distant places like the moon or Mars instead of being transported at high cost."

Findings from spacecraft indicate the presence of water on Mars and the moon, and water also may exist on asteroids, other moons and bodies in space, said Son, who also has a courtesy appointment as an associate professor of aeronautics and astronautics.

The tiny size of the aluminum particles, which have a diameter of about 80 nanometers, or billionths of a meter, is key to the propellant's performance. The nanoparticles combust more rapidly than larger particles and enable better control over the reaction and the rocket's thrust, said Timothée Pourpoint, a research assistant professor in the School of Aeronautics and Astronautics.

"It is considered a green propellant, producing essentially hydrogen gas and aluminum oxide," Pourpoint said. "In contrast, each space shuttle flight consumes about 773 tons of the oxidizer ammonium perchlorate in the solid booster rockets. About 230 tons of hydrochloric acid immediately appears in the exhaust from such flights."

ALICE provides thrust through a chemical reaction between water and aluminum. As the aluminum ignites, water molecules provide oxygen and hydrogen to fuel the combustion until all of the powder is burned.

"ALICE might one day replace some liquid or solid propellants, and, when perfected, might have a higher performance than conventional propellants," Pourpoint said. "It's also extremely safe while frozen because it is difficult to accidentally ignite."

The research is helping to train a new generation of engineers to work in academia, industry, for NASA and the military, Son said. More than a dozen undergraduate and graduate students have worked on the project. "It's unusual for students to get this kind of advanced and thorough training - to go from a basic-science concept all the way to a flying vehicle that is ground tested and launched," he said. "This is the whole spectrum."

Research findings were detailed in technical papers presented this summer during a conference of the American Institute of Aeronautics and Astronautics. The papers will be published next year in the conference proceedings.

Leading work at Penn State are mechanical engineering professor Richard Yetter and assistant professor Grant Risha. The Purdue portion of the research is based at the university's Maurice J. Zucrow Laboratories, where researchers created a special test cell and control room to test the rocket. The rocket's launching site was located on a facility maintained by Purdue's School of Veterinary Medicine.

"Having a launching site near campus greatly facilitated this project," Pourpoint said.

Other researchers previously have used aluminum particles in propellants, but those propellants usually also contained larger, micron-size particles, whereas the new fuel contained pure nanoparticles.

Manufacturers over the past decade have learned how to make higher-quality nano-aluminum particles than was possible in the past. The fuel needs to be frozen for two reasons: It must be solid to remain intact while subjected to the forces of the launch and also to ensure that it does not slowly react before it is used. Initially a paste, the fuel is packed into a cylindrical mold with a metal rod running through the center. After it's frozen, the rod is removed, leaving a cavity running the length of the solid fuel cylinder. A small rocket engine above the fuel is ignited, sending hot gasses into the center hole, causing the ALICE fuel to ignite uniformly.

"This is essentially the same basic procedure used in the space shuttle's two solid-fuel rocket boosters," Son said. "An electric match ignites a small motor, which then ignites a bigger motor."

Future work will focus on perfecting the fuel and also may explore the possibility of creating a gelled fuel using the nanoparticles. Such a gel would behave like a liquid fuel, making it possible to vary the rate at which the fuel is pumped into the combustion chamber to throttle the motor up and down and increase the vehicle's distance. A gelled fuel also could be mixed with materials containing larger amounts of hydrogen and then used to run hydrogen fuel cells in addition to rocket motors, Son said.

## Targeted therapies exploit tiny chinks in cancer's armour

* 07 October 2009 **by Linda Geddes**, Birmingham

THE weakness in Achilles' heel didn't pose much of a problem until it came into contact with Paris's arrow - at which point it killed him. Now a range of tumours are meeting a similar fate thanks to drugs that turn otherwise insignificant gaps in their defences into fatal flaws.

A pioneering therapy that exploits such weaknesses is allowing women with late-stage, drug-resistant breast and ovarian tumours to survive for longer. More recent discoveries of similar genetic weaknesses in a range of other cancers are opening up the promise of new treatments for hard-to-treat tumours.

These "Achilles' heel" therapies have another advantage over existing ones. Because they exploit weaknesses that are unique to cancer cells, they are less likely to cause the devastating side effects characteristic of many chemotherapy agents, which attack healthy cells as well. "It has the potential to be a

landscape-shifting change in the way we approach cancer," says oncologist Gary Gilliland of Merck Research Laboratories in Boston.

Until recently, most anti-cancer drugs have followed a more obvious line of attack. They work by interfering with the activities tumours are specially good at - and which are responsible for the damage they do - such as proliferating in an uncontrolled way or overriding signals that should tell abnormal cells to die.

Most drugs target the activities tumour cells are specially good at - and which do us damage

But what if we could target tumours' weaknesses, as well as their strengths? "Cancer cells have all kinds of changes that could be paired with another change - or a drug - to be lethal," says Stephen Elledge of Harvard Medical School in Boston.

The idea, known as "synthetic lethality", is not new. It was shown to work in fruit flies as long ago as the 1940s, when it was noticed that the insects could survive the mutation of a single gene unscathed, but were killed if two such genes were knocked out at the same time. But it is only recently that Alan Ashworth at the Institute of Cancer Research in London and his colleagues have found a way to apply the same method to selectively kill cancer cells.

Ashworth's team focuses on genes called BRCA1 and BRCA2, which, when mutated, interfere with an enzyme that cells use to repair DNA and increase the chances that breast and ovarian cells will accumulate cancer-causing mutations. Several years ago, the team gave molecules called PARP inhibitors, which inhibit a different DNA repair enzyme, to women with breast or ovarian cancer caused by the mutated versions of the BRCA genes. They reasoned that because the cancer cells have no other means of repairing their DNA they would die, while normal cells would not be badly affected.

The idea seems to work. This week Ashworth reported at a conference in Birmingham, UK, organised by the National Cancer Research Institute (NCRI) that in 11 out of 27 women with recurrent breast cancer given the PARP inhibitor olaparib, the tumour shrank significantly; in one of the women it disappeared completely. In 33 women with recurrent ovarian cancer, nine partially responded to the drug while in two the tumours disappeared.

"Essentially, women are living for much longer than expected with very heavy tumour burdens," says Ashworth. The women also experience very few side effects compared with existing chemotherapies.

The same principles are also being applied to a variety of other common cancers. A separate study by Esther Hammond at the University of Oxford and her colleagues suggests that PARP inhibitors might work on cancer cells that are deprived of oxygen - which is common in aggressive tumours - as hypoxia suppresses the same DNA repair process as mutant BRCA genes.

Meanwhile, a study published last month suggests that PARP inhibitors could treat cancers carrying common mutations in a gene called PTEN, which also impairs a cell's ability to repair DNA (EMBO Molecular Medicine, DOI: 10.1002/emmm.200900041).

Ashworth also recently showed that an existing cancer drug called methotrexate could kill colorectal and endometrial cancer cells with a defect in MSH2, a DNA repair gene (EMBO Molecular Biology, DOI: 10.1002/emmm.200900040). He believes this is due to synthetic lethality.

But DNA repair mechanisms are not the only chink in tumour cells' armour. Genes that drive the tumour growth may also provide an opening for a similar approach. One is Ras, a genetic switch that enables cells to divide. In many cancers, a mutation in the gene, called KRAS keeps it permanently switched on, so the cells keep dividing. An obvious line of attack on such cancers would be to create drugs that bind to KRAS and block its actions, but this has always failed. "Even though we know it's a driver for a broad spectrum of human cancers, we've never been able to drug it," says Gilliland.

Now separate teams led by Elledge and Gilliland have tried the synthetic lethality approach. Taking cancer cells with KRAS, one of the commonest mutations in human cancer cells, they knocked out other genes one by one. This allowed them to pinpoint a bunch of genes involved in a different aspect of cell division called mitosis, without which cells with a KRAS mutation could not survive (Cell, DOI: 10.1016/j.cell.2009.05.006). Cells with normal Ras were relatively unscathed. Gilliland identified a gene in a different process which also seems to work. Unlike normal cells, those with a mutation could not survive without certain genes involved in mitosis

"The implications of these findings are both important and immediate," says Charles Sawyers of the Memorial Sloan-Kettering Cancer Center in New York. The next step is to develop drugs that block the expression of these genes and test them in patients with KRAS mutant tumours.

Elledge estimates that screening for other synthetic lethal combinations could identify hundreds of new drug targets. Some of them will be a gene that healthy cells need. "The question is what level do they need it at," says Elledge. "If the cancer cells need it more than normal cells, you might be able to get away with messing with it."

The tendency of cancer cells to mutate as the disease progresses means that they may develop resistance to PARP inhibitors and other synthetic lethal drugs. But it may also be possible to use synthetic lethality to combat drug resistance, by searching for a drug that overcomes the resistance and using it in conjunction with the original chemotherapy.

Merck is already using this approach to overcome resistance to at least one common chemotherapeutic agent. "We're very hopeful that this is going to make a difference in outcomes for patients," says Gilliland.

Stand-alone trees or a bed of weeds?

A controversial idea that challenges established notions of how cancer grows and spreads in the body got a fresh airing at the NCRI cancer conference in Birmingham, UK, this week. If verified, it could explain how cancers quickly grow so big, and also suggest ways in which cancer drugs could be used more effectively.

The conventional picture is that a tumour grows from a single clump of cells that divide uncontrollably. Like a tree, the tumour only acquires the ability to send out "seeds", or metastases, once it becomes mature. Following this thinking, therapy of early stages of cancer tends to target cell division, not metastasis.

But in 2006, Larry Norton and Joan Massagué at the Memorial Sloan-Kettering Cancer Center in New York suggested an alternative scenario: rather than growing solely by cell division, young tumours grow by metastasis too (Nature Medicine, vol 12, p 875). These seeds are released into the bloodstream, circulate around the body, and then return to the original tumour site - or occasionally lodge elsewhere. The result looks like one big tumour but is really lots of little ones growing next to each other, like a bed of weeds.

The model would explain how aggressive cancers grow quickly, which ordinary cell division does not, says Norton. It also suggests that it might pay to target metastatic processes in cancer's early stages.

The idea remains preliminary, but one especially contentious part - that cancer cells circulate around the body and then return to where they formed - now seems more plausible.

In Birmingham, Norton described how he and Massagué implanted mice with two fluorescently labelled early-stage tumours on opposite sides of their bodies. The tumours constantly released and exchanged cells, demonstrating that even young tumours can send out seeds. Meanwhile, other researchers have reported that women with early, "stage-zero" breast cancer already have large numbers of tumour cells circulating in their bodies (Cancer Cell, DOI: 10.1016/j.ccr.2007.12.003).

As tumours manipulate their local environment to make it easier for them to grow there, Norton reasons that if a cancer is releasing seed cells, these are most likely to take root back at the primary site, rather than elsewhere in the body. This might also explain why metastases often don't manifest themselves until a primary tumour is removed, he says.

## Cheap naked chips snap a perfect picture

* 07 October 2009 **by Paul Marks**

HOW can image sensors - the most complicated and expensive part of a digital camera - be made cheaper and less complex? Easy: take the lid off a memory chip and use that instead.

As simple as it sounds, that pretty much sums up a device being developed by a team led by Edoardo Charbon, of the Technical University of Delft, in the Netherlands. In a paper presented at an imaging conference in Kyoto, Japan, this week, the team say that their so-called "gigavision" sensor will pave the way for cellphones and other inexpensive gadgets that take richer, more pleasing pictures than today's devices. Crucially, Charbon says the device performs better in both very bright light and dim light - conditions which regular digital cameras struggle to cope with.

While Charbon's idea is new and has a patent pending, the principle behind it is not. It has long been known that memory chips are extremely sensitive to light: remove their black plastic packages to let in light, and the onrush of photons energises electrons, creating a current in each memory cell that overwhelms the tiny stored charge that might have represented digital information. "Light simply destroys the information," says Martin Vetterli, a member of the EPFL team.

A similar effect occurs aboard spacecraft: when energetic cosmic rays hit a cell in an unprotected memory chip they can "flip" the state of the cell, corrupting the data stored in the chip.

What Charbon and his team have found is that when they carefully focus light arriving on an exposed memory chip, the charge stored in every cell corresponds to whether that cell is in a light or dark area. The chip is in effect storing a digital image.

All very clever, you might say, but why would anyone want to do that? The answer is that the two types of sensor chips used in today's digital cameras store the brightness of each pixel as an analogue signal. To translate this into a form that can be stored digitally, they need complex, bulky, noise-inducing circuitry.

The charge-coupled device (CCD) sensors used on early cameras and camcorders, and the cheaper and more modern complementary metal oxide semiconductor (CMOS) type both operate on a similar principle. On each,

the area that forms an individual pixel can be thought of as a small charge-containing "bucket". The size of the charge contained in one of these buckets depends only on the amount of light falling on it.

In a CCD, the contents of each bucket of charge are "poured" into the bucket next door, and then the next until the signal reaches the edge of the chip. There, an analogue-to-digital converter (ADC) typically assigns it an 8-bit greyscale value, ranging from 0 to 255. In a CMOS sensor, the charge is converted to a voltage local to each pixel before being shunted off to an ADC at the edge of the chip - where it too is assigned a greyscale value between 0 and 255 (see diagram).

A memory chip needs none of this conversion circuitry, as it creates digital data directly. As a result, says Vetterli, the memory cell will always be 100 times smaller than CMOS sensor cells; it is bound to be that way because of the sheer number of signal-conditioning transistors the CMOS sensor needs around each pixel. "Our technology will always be two orders of magnitude smaller," he says.

So for every pixel on one of today's sensors, the memory-based sensor could have 100 pixels. A chip the size of a 10-megapixel camera sensor will have 100 times as many sensing cells if implemented in memory technology - hence the choice of the gigavision name.

But don't expect a gigapixel camera any time soon. Unlike the pixels in a conventional sensor, which record a greyscale, the cells in Charbon's memory-chip sensor are simple on-off devices: they can only store a digital 0 or 1, for which read either light or dark. To build a sensor that can record shades of grey, EPFL engineer Feng Yang, who presented the Kyoto paper, is developing a software algorithm that looks across an array of 100 pixels to estimate their overall greyscale value.

It's a technique called spatial oversampling - and while it's early days, he's getting somewhere. "It's turning out to be a lot more accurate than the greyscale values you get from regular CMOS sensors," says Vetterli. "Analogue to digital conversion gives only poor estimates of the actual analogue light value."

It's turning out to be a lot more accurate than the greyscale values you get from CMOS sensors

The EPFL team have found that the more binary pixels they have, the better their chips perform in rendering deep shadow and bright highlights. "Gigavision cameras do not saturate anywhere near so easily, so we'll be able to use it for high dynamic range applications like medical imaging," says Yang.

"This is not pure academic interest," says Vetterli. "We're hoping to have a big version of a gigavision memory chip fabricated late this year and working early next."

They'll have their work cut out, observers say. A major problem they will have to overcome is that of the poor sensitivity of their pint-sized pixels. Their size means the number of photons that can be scooped up by each of them will be small - and that can make for a very noisy signal.

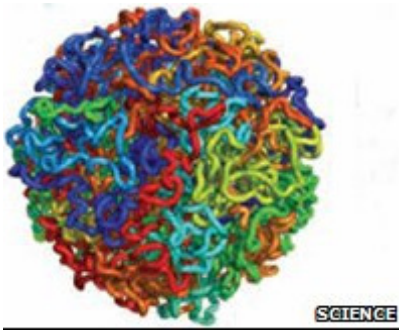
The prospect of producing image sensors as cheaply and easily as memory chips is bound to attract attention, says Alexis Gerard, an analyst and chief executive of the consultancy Future Image in San Mateo, California. "It will be pretty interesting if they can make these sensors using regular memory-chip-making technology."

## Revealed: The human genome in 3D

***Scientists have worked out the 3D structure of the human genome.***

Their findings, published in Science magazine, reveal how long strands of DNA code are folded and tightly packed into the nucleus of a human cell. Unfolded, the cell's genome - those strands of DNA code - would be approximately 2m in length. The team showed how this is organised into a tight ball to fit inside a nucleus, which is about one hundredth of a millimetre in diameter.

The US-based research team developed improved DNA sequencing and computational methods to build a model of the genome.




Job Dekker, from the University of Massachusetts Medical School, led the research. He explained to BBC News that, with its new approach, his team had discovered important patterns in the shape of the genome.

"For a given part of the genome, we can determine its neighbours," he said. “And if you can do that for every gene - if you know which other genes surround it - you can work your way back computationally to calculate the structure. "This is the first glimpse we're getting of a whole genome in 3D."

DNA is bundled into chromosomes. The combination of DNA and protein that makes up these chromosomes is called chromatin. Dr Dekker explained how a 3D view showed how chromatin's complicated folding pattern was important in the regulation of genes.

"We now see that things that are far apart along the linear sequence of the genome are actually next to each other in the folded structure," he said. "They're close together in the structure, and they're talking to each other."

This constant communication is the basis of the regulation that keeps a cell healthy and functional.

This means that a detailed view of the genome's structure could provide a new window into diseases such as cancer, which is caused by errors in the genetic code.

"Maybe we will be able to predict these [disease-causing] changes better now," said Dr Dekker.

The team also discovered that the human genome is organised into two separate compartments, keeping active genes accessible while keeping inactive DNA in a sort of storage compartment.

The chromosomes snake in and out of the two compartments - separating their active and inactive sections.

## Why the 'peak oil' debate is irrelevant

* 17:20 08 October 2009 **by Shanta Barley**

The debate over exactly when we will reach "peak oil" is irrelevant. No matter what new oil fields we discover, global oil production will start declining in 2030 at the very latest.

That's the conclusion of the most comprehensive report to date on global oil production, published on 7 October by the UK Energy Research Centre. The report, which reviewed over 500 research studies, suggests that global oil production could peak any time from right now to as late as 2030.

"Either way, our research shows that the difference between even the most pessimistic and optimistic claims is just 15 to 20 years," says Steve Sorrell, the report's lead author, who is based at Sussex University in the UK.

This is a problem, says Sorrell, because 20 years isn't long enough for governments to prepare well-thought-out policies that would tackle the economic chaos likely to occur when oil production begins to decline. Research in 2005 by the US Department of Energy suggests that policies to reduce the demand for oil while developing large-scale alternatives will take at least two decades to bear fruit, he says.

**New for old**

Global production of oil is declining at a rate of 4 per cent per year in existing oil fields and we have very little to replace it with, says Sorrell: "If we want to maintain global oil production at today's level we would need to discover the equivalent of a new Saudi Arabia every 3 years."

Yet discoveries of new oil fields are in decline. Even the "giant" Tiber field recently found by BP in the Gulf of Mexico "will only serve to delay peak oil by a matter of days", he says.

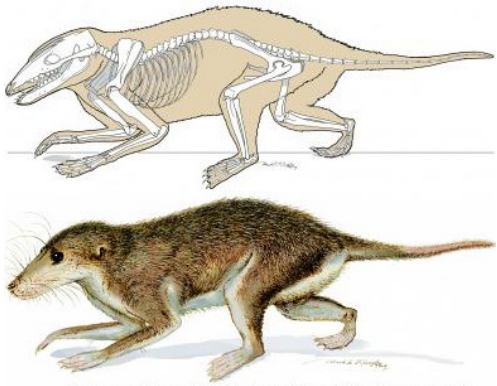
"Of the 70,000 oil fields on Earth, just 100 giant fields account for 50 per cent of the oil we use," says Sorrell. "Most of these giant fields are quite old and past their peak of production, and we're not going to find many new ones."

The International Energy Agency's latest estimate is that that oil production will not peak until after 2030, but that "is conservative to say the least", Sorrell warns.

## Chinese and American paleontologists discover a new Mesozoic mammal

***Ear structure shows how mammalian ear evolution occurred while dinosaurs dominated the world***

Pittsburgh, Pennsylvania, USA…An international team of paleontologists has discovered a new species of mammal that lived 123 million years ago in what is now the Liaoning Province in northeastern China. The newly discovered animal, Maotherium asiaticus, comes from famous fossil-rich beds of the Yixian Formation. This new remarkably well preserved fossil, as reported in the October 9 issue of the prestigious journal Science, offers an important insight into how the mammalian middle ear evolved. The discoveries of such exquisite dinosaur-age mammals from China provide developmental biologists and paleontologists with evidence of how developmental mechanisms have impacted the morphological (body-structure) evolution of the earliest mammals and sheds light on how complex structures can arise in evolution because of changes in developmental pathways.



Cretaceous Mammal *Maotherium asiaticus* (123 million years old)

Top: Skeletal Restoration of *Maotherium* as a terrestrial mammal
(Skeleton Reconstruction Illustration: Mark A. Klingler / Carnegie Museum of Natural History)
Bottom: Restoration of *Maotherium asiaticus*
(Life Reconstruction Illustration: Mark A. Klingler / Carnegie Museum of Natural History)

***The new Cretaceous mammal Maotherium is a chipmunk-sized nocturnal mammal. Because it is related to the common ancestor of marsupials and placentals, its tooth and skeletal structures show the ancestral condition from which marsupials and placentals could have evolved.*** **Mark A. Klingler/Carnegie Museum of Natural History**

"What is most surprising, and thus scientifically interesting, is this animal's ear," says Dr. Zhe-Xi Luo, curator of vertebrate paleontology and associate director of science and research at Carnegie Museum of Natural History. "Mammals have highly sensitive hearing, far better than the hearing capacity of all other vertebrates, and hearing is fundamental to the mammalian way of life. The mammalian ear evolution is important for understanding the origins of key mammalian adaptations."

Thanks to their intricate middle ear structure, mammals (including humans) have more sensitive hearing, discerning a wider range of sounds than other vertebrates. This sensitive hearing was a crucial adaptation, allowing mammals to be active in the darkness of the night and to survive in the dinosaur-dominated Mesozoic.

Mammalian hearing adaptation is made possible by a sophisticated middle ear of three tiny bones, known as the hammer (malleus), the anvil (incus), and the stirrup (stapes) plus a bony ring for the eardrum (tympanic membrane). These mammal middle ear bones evolved from the bones of the jaw hinge in their reptilian relatives. Paleontologists have long attempted to understand the evolutionary pathway via which these precursor jawbones became separated from the jaw and moved into the middle ear of modern mammals.

To evolutionary biologists, an understanding of how the sophisticated and highly sensitive mammalian ear evolved may illuminate how a new and complex structure transforms through evolution. According to the Chinese and American scientists who studied this new mammal, the middle ear bones of Maotherium are partly similar to those of modern mammals; but Maotherium's middle ear has an unusual connection to the lower jaw that is unlike that of adult modern mammals. This middle ear connection, also known as the ossified Meckel's cartilage, resembles the embryonic condition of living mammals and the primitive middle ear of pre-mammalian ancestors.

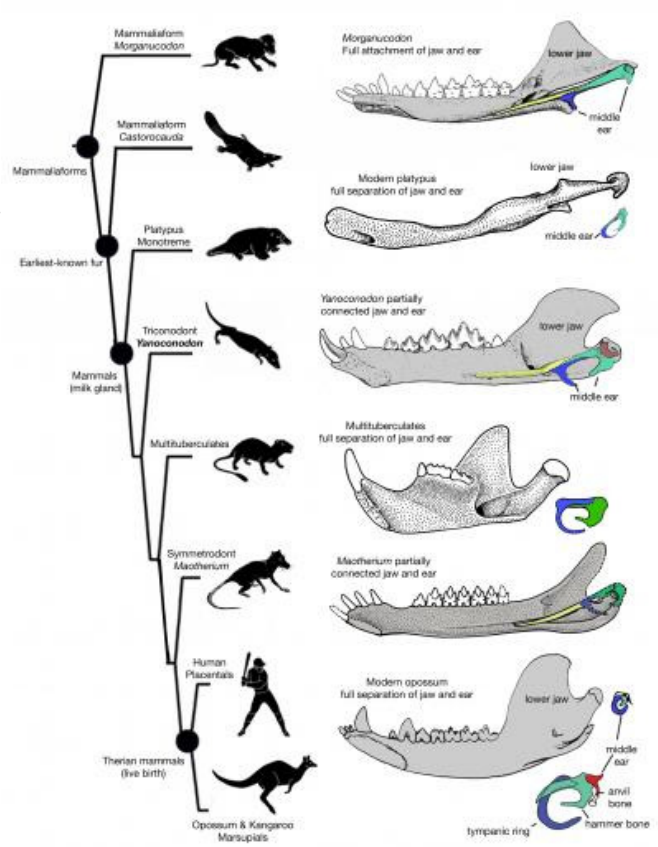


Image 4: Evolution of Mammalian Middle Ear
(Graphics: Zhe-Xi Luo)

***All modern mammals (platypus, opossum and human) have a middle ear separated from the lower jaw (see example from living opossum). This jaw-ear separation is an important evolutionary innovation. It becomes possible for mammals to have a delicate and highly sensitive ear structure for better hearing, and to have a more robust lower jaw and jaw hinge for better feeding. Also, the jaw and ear are not interfering with each other. The analysis of the new fossil suggests that the evolutionary pattern of the mammalian ear is directly related to timing changes in growth, as well as in changes in genes for mammalian development.*** **Zhe-Xi Luo/Carnegie Museum of Natural History**

Because Maotherium asiaticus is preserved three-dimensionally, paleontologists were able to reconstruct how the middle ear attached to the jaw. This can be a new evolutionary feature. Or, it can be interpreted as having a "secondarily reversal to the ancestral condition," meaning that the adaptation is the caused by changes in development. (See graphics of mammalian ear evolution, as represented by Maotherium).

Modern developmental biology has shown that developmental genes and their gene network can trigger the development of unusual middle ear structures, such as "re-appearance" of the Meckel's cartilage in modern mice. The middle ear morphology in fossil mammal Maotherium of the Cretaceous (145-65 million years ago) is very similar to the mutant morphology in the middle ear of the mice with mutant genes. The scientific team studying the fossil suggests that the unusual middle ear structure, such as the ossified Meckel's cartilage, is actually the manifestation of developmental gene mutations in the deep times of Mesozoic mammal evolution.

Maotherium asiaticus is a symmetrodont, meaning that it has teeth with symmetrically arranged cusps specialized for feeding on insects and worms. It lived on the ground and had a body 15 cm (5 inches) long and weighing approximately 70 to 80 grams (.15 to .17 lbs). By studying all features in this exquisitely preserved fossil, researchers believe Maotherium to be more closely related to marsupials and placentals than to monotremes - primitive egg-laying mammals of Australia and New Guinea such as the platypus.

*The article in Science is authored by Dr. Qiang Ji of Chinese Academy of Geological Sciences (Beijing), Dr. Zhe-Xi Luo (Carnegie Museum of Natural History) and Mr. Xinliang Zhang (Henan Provincial Geological Museum), along with other collaborators.*

*The researchers received support from National Science Foundation (USA), National Natural Science Foundation (China), Ministry of Science and Technology (China), and National Geographic Society.*

## Women with breast cancer have low vitamin D levels

### *High-dose supplements needed to boost levels, decrease fracture risk*

Women with breast cancer should be given high doses of vitamin D because a majority of them are likely to have low levels of vitamin D, which could contribute to decreased bone mass and greater risk of fractures, according to scientists at the University of Rochester Medical Center.

In a study of 166 women undergoing treatment for breast cancer, nearly 70 percent had low levels of vitamin D in their blood, according to a study being presented Thursday, Oct. 8, at the American Society of Clinical Oncology's Breast Cancer Symposium in San Francisco. The analysis showed women with late-stage disease and non-Caucasian women had even lower levels.

"Vitamin D is essential to maintaining bone health, and women with breast cancer have accelerated bone loss due to the nature of hormone therapy and chemotherapy. It's important for women and their doctors to work together to boost their vitamin D intake," said Luke Peppone, Ph.D., research assistant professor of Radiation Oncology, at Rochester's James P. Wilmot Cancer Center. He is a member of the National Cancer Institute's Community Clinical Oncology Program research base in Rochester.

Scientists funded by the NCI analyzed vitamin D levels in each woman, and the average level was 27 nanograms per milliliter; more than two-thirds of the women had vitamin deficiency. Weekly supplementation with high doses of vitamin D - 50,000 international units or more -- improved the levels, according to Peppone's study.

The U.S. Institute of Medicine suggests that blood levels nearing 32 nanograms per milliliter are adequate.

This problem is not unexpected, Peppone said, because previous studies have shown that nearly half of all men and women are deficient in the nutrient, with vitamin D levels below 32 nanograms per milliliter. Vitamin D, obtained from milk, fortified cereals and exposure to sunlight, is well known to play an essential role in cell growth, in boosting the body's immune system and in strengthening bones.

## PMH clinicians map group at high risk for aggressive, 'hidden' prostate cancer

Clinical researchers at Princess Margaret Hospital (PMH) can now answer the question that baffles many clinicians – why do some men with elevated prostate specific antigen (PSA) levels who are carefully monitored and undergo repeated negative biopsies still develop aggressive prostate cancer?

The answer is hidden tumours located on the top of the prostate that evade traditional diagnostic procedures, including ultrasound-guided needle biopsy. The PMH research, published online today in the British Journal of Urology International (BJU 8938), demonstrates that magnetic resonance imaging (MRI) is the best tool to reveal such tumours.

"Our findings identify a specific high-risk group whose tumours are difficult to diagnose because of location. These men benefit from MRI, which guides the biopsy procedure with a high degree of accuracy," says author Dr. Nathan Lawrentschuk, Urologic Oncology Fellow, PMH Cancer Program, University Health Network. "The research team calls the clinical presentation of elevated PSA and repeated negative biopsy results in 'prostate evasive anterior tumour syndrome' (PEATS)."

"Knowing about PEATS may also be important for men already on 'active surveillance' – patients with slow-growing prostate cancer who are being regularly monitored through PSA testing and biopsy. Every man does not need an MRI, but knowing about PEATS will help us identify those who do," says principal investigator Dr. Neil Fleshner, Head of the Division of Urology, Princess Margaret Hospital, Professor of Surgery at University of Toronto, and Love Chair in Prostate Cancer Prevention Research.

A team of urologists, surgeons, radiologists and pathologists studied 31 PMH patients who had positive biopsy results and tumours on top of their prostate as shown on MRI. They found that MRI was able to help diagnose hidden prostate tumours 87% of the time.

Dr. Lawrentschuk says clinicians need to be aware of PEATS because these hidden tumours can be aggressive.

## Paper Challenges Ideas About 'Early Bird' Dinosaur

**By JOHN NOBLE WILFORD**

The "early bird" Archaeopteryx may not be a bird, after all.

The first fossil of the raven-size species was an immediate sensation when it was excavated in 1860, in southern Germany. It had feathers and a wishbone, like birds, but teeth and a long, bony tail, like reptiles. Coming the year after publication of "The Origin of Species," the discovery swayed many scientists into accepting Darwin's theory of evolution by natural selection.

Thomas Henry Huxley, Darwin's staunch ally, recognized the fossil in a limestone slab as a transitional species between dinosaurs and birds. Over time, the 10 known specimens of Archaeopteryx became widely regarded as examples of the earliest bird, which lived about 150 million years ago.

Now scientists examining tiny pieces of a specimen's long bone under powerful microscopes for the first time said they found unexpected patterns indicating that the species grew at a rate faster than living reptiles but only one-third as fast as that of modern birds. The evidence, they reported Thursday, challenges the hypothesis that Archaeopteryx had already developed characteristics of a physiologically modern bird.

***This is the slab and counter slab of the Munich Archaeopteryx.*** **Mick Ellison/AMNH**

In a research paper being published in the online journal PLoS One, the science team led by Gregory M. Erickson, a paleontologist at Florida State University, concluded that Archaeopteryx was simply a feathered dinosaur that might have been capable of some aerial behavior, though perhaps not powered flight. In short, despite feathers, it was not the archetypal bird.

Dr. Erickson said in an interview that studied under a polarizing microscope, the dense microstructure of the bone showed few traces of blood vessels. He said this was evidence of a slow metabolism by which the individual probably took more than two years to reach adult size. Birds have especially fast metabolisms, making them able to leave the nest in days or a few weeks.

Mark A. Norell, a co-author who specializes in dinosaur research at the American Museum of Natural History in New York, said the findings showed that "the transition to physiological and metabolic birds happened well after Archaeopteryx." As a result, he added, the evolutionary emergence of birds "is still a huge mystery."

Both Dr. Norell and Dr. Erickson emphasized that their findings did not undermine the theory widely held among paleontologists that birds evolved from what are known as theropod dinosaurs. Birds, in that sense, are avian dinosaurs, although some ornithologists insist that is a stretch.

Paleontologists and ornithologists who had no part in the research said the findings were an important step in dinosaur-bird studies, but not surprising.

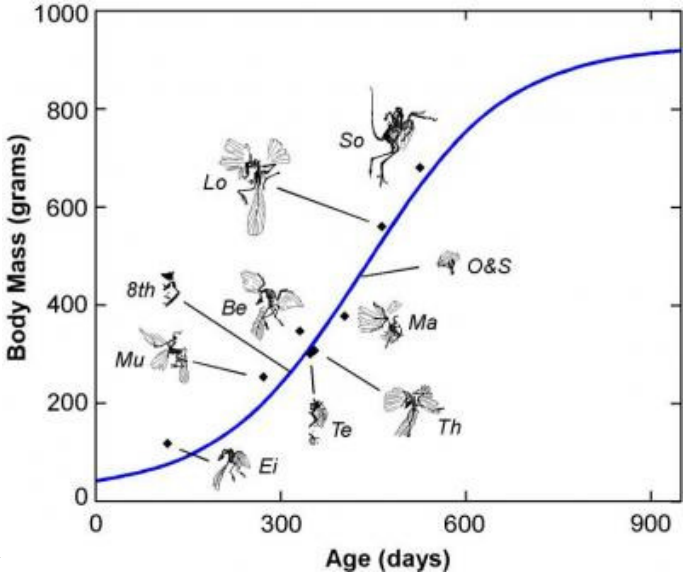
"Archaeopteryx has always been seen as a marvelous example of a transitional species," said Helen James, an ornithologist at the National Museum of Natural History in Washington. "You would expect to find its physiology to be transitional from what we see in modern birds and modern reptiles."

Lawrence M. Witmer, a paleontologist at Ohio University who conducts other Archaeopteryx research, said that he was not surprised to learn that the species was "not fully avian," but that it had many features seen in later birds, indicating that it had not been displaced as "a very basal member" of the avian family tree.

In the new research, the scientists worked with Zhonghe Zhou of the Institute of Vertebrate Paleontology and Paleoanthropology in Beijing, conducting similar bone examinations on several specimens found recently in China of feathered dinosaur species. They concluded that confuciusornis was the first known species in which the transition to a bird's growth rate occurred.

Confuciusornis lived about 130 million years ago. Although its growth rate was somewhat slower than that of most same-size living birds, this species had no teeth, no long tail and seemed to grow more rapidly than Archaeopteryx and other known specimens in between. More advanced bird fossils, with bones well supplied with blood vessels, appeared somewhat less than 100 million years ago.

In fact, it was the numerous discoveries in China that prompted the first close examination of Archaeopteryx bones. Two years ago, Oliver W. M. Rauhut of the Bavarian State Collection for Paleontology and Geology in Munich gave the scientists permission to conduct the research on the museum's fossil, which like all the known specimens was of a juvenile. Museum technicians extracted samples - hardly larger than specks of lint - from already damaged parts of a thighbone.




***Archaeopteryx growth curve showing that all fossils are juveniles. (Specimen designations: Ei = Eichstäat, Mu = Munich, 8th = 8th Exemplar, Te = Teyler, Th = Thermopolis, Be = Berlin, Ma = Maxberg, O&S = Exemplar der Familien Ottmann & Steil, Lo = London, So = Solnhofen)*** **Gregory Erickson**

The bone growth rate, the scientists determined, was unbirdlike but reflected metabolic rates greater than those in nondinosaurian reptiles; that is, they were more warmblooded than coldblooded. In that respect,

Archaeopteryx appeared to be intermediate between reptiles and birds, growing at a probable rate close to that of marsupials, they said. Comparisons with other birdlike dinosaur specimens indicated that the bone structure of this Archaeopteryx was not abnormal.

“Theories regarding the subsequent steps that lead to the modern avian condition need to be re-evaluated,” the scientists concluded in the journal article, “to help understand what is turning out to be a complex evolutionary story.”

## Last time carbon dioxide levels were this high: 15 million years ago, scientists report

You would have to go back at least 15 million years to find carbon dioxide levels on Earth as high as they are today, a UCLA scientist and colleagues report Oct. 8 in the online edition of the journal Science.

"The last time carbon dioxide levels were apparently as high as they are today — and were sustained at those levels - global temperatures were 5 to 10 degrees Fahrenheit higher than they are today, the sea level was approximately 75 to 120 feet higher than today, there was no permanent sea ice cap in the Arctic and very little ice on Antarctica and Greenland," said the paper's lead author, Aradhna Tripati, a UCLA assistant professor in the department of Earth and space sciences and the department of atmospheric and oceanic sciences.

"Carbon dioxide is a potent greenhouse gas, and geological observations that we now have for the last 20 million years lend strong support to the idea that carbon dioxide is an important agent for driving climate change throughout Earth's history," she said.

By analyzing the chemistry of bubbles of ancient air trapped in Antarctic ice, scientists have been able to determine the composition of Earth's atmosphere going back as far as 800,000 years, and they have developed a good understanding of how carbon dioxide levels have varied in the atmosphere since that time. But there has been little agreement before this study on how to reconstruct carbon dioxide levels prior to 800,000 years ago.

Tripati, before joining UCLA's faculty, was part of a research team at England's University of Cambridge that developed a new technique to assess carbon dioxide levels in the much more distant past — by studying the ratio of the chemical element boron to calcium in the shells of ancient single-celled marine algae. Tripati has now used this method to determine the amount of carbon dioxide in Earth's atmosphere as far back as 20 million years ago.

"We are able, for the first time, to accurately reproduce the ice-core record for the last 800,000 years - the record of atmospheric C02 based on measurements of carbon dioxide in gas bubbles in ice," Tripati said. "This suggests that the technique we are using is valid. We then applied this technique to study the history of carbon dioxide from 800,000 years ago to 20 million years ago," she said. "We report evidence for a very close coupling between carbon dioxide levels and climate. When there is evidence for the growth of a large ice sheet on Antarctica or on Greenland or the growth of sea ice in the Arctic Ocean, we see evidence for a dramatic change in carbon dioxide levels over the last 20 million years.

"A slightly shocking finding," Tripati said, "is that the only time in the last 20 million years that we find evidence for carbon dioxide levels similar to the modern level of 387 parts per million was 15 to 20 million years ago, when the planet was dramatically different."

Levels of carbon dioxide have varied only between 180 and 300 parts per million over the last 800,000 years - until recent decades, said Tripati, who is also a member of UCLA's Institute of Geophysics and Planetary Physics. It has been known that modern-day levels of carbon dioxide are unprecedented over the last 800,000 years, but the finding that modern levels have not been reached in the last 15 million years is new.

Prior to the Industrial Revolution of the late 19th and early 20th centuries, the carbon dioxide level was about 280 parts per million, Tripati said. That figure had changed very little over the previous 1,000 years. But since the Industrial Revolution, the carbon dioxide level has been rising and is likely to soar unless action is taken to reverse the trend, Tripati said.

"During the Middle Miocene (the time period approximately 14 to 20 million years ago), carbon dioxide levels were sustained at about 400 parts per million, which is about where we are today," Tripati said. "Globally, temperatures were 5 to 10 degrees Fahrenheit warmer, a huge amount."Tripati's new chemical technique has an average uncertainty rate of only 14 parts per million. "We can now have confidence in making statements about how carbon dioxide has varied throughout history," Tripati said.

In the last 20 million years, key features of the climate record include the sudden appearance of ice on Antarctica about 14 million years ago and a rise in sea level of approximately 75 to 120 feet.

"We have shown that this dramatic rise in sea level is associated with an increase in carbon dioxide levels of about 100 parts per million, a huge change," Tripati said. "This record is the first evidence that carbon dioxide may be linked with environmental changes, such as changes in the terrestrial ecosystem, distribution of ice, sea level and monsoon intensity."

Today, the Arctic Ocean is covered with frozen ice all year long, an ice cap that has been there for about 14 million years. "Prior to that, there was no permanent sea ice cap in the Arctic," Tripati said.

Some projections show carbon dioxide levels rising as high as 600 or even 900 parts per million in the next century if no action is taken to reduce carbon dioxide, Tripati said. Such levels may have been reached on Earth 50 million years ago or earlier, said Tripati, who is working to push her data back much farther than 20 million years and to study the last 20 million years in detail.

More than 50 million years ago, there were no ice sheets on Earth, and there were expanded deserts in the subtropics, Tripati noted. The planet was radically different.

Tripati's research focuses on the development and application of chemical tools to study climate change throughout history. She studies the evolution of climate and seawater chemistry through time.

"I'm interested in understanding how the carbon cycle and climate have been coupled, and why they have been coupled, over a range of time-scales, from hundreds of years to tens of millions of years," Tripati said.

*Co-authors on the Science paper are Christopher Roberts, a Ph.D. student in the department of Earth sciences at the University of Cambridge, and Robert Eagle, a postdoctoral scholar in the division of geological and planetary sciences at the California Institute of Technology. The research was funded by UCLA's Division of Physical Sciences and the United Kingdom's National Environmental Research Council. In addition to being published on the Science Express website, the paper will be published in the print edition of Science at a later date.*

## Liver cells grown from patients' skin cells

### *Treatment of liver diseases possible*

Scientists at The Medical College of Wisconsin in Milwaukee have successfully produced liver cells from patients' skin cells opening the possibility of treating a wide range of diseases that affect liver function. The study was led by Stephen A. Duncan, D. Phil., Marcus Professor in Human and Molecular Genetics, and professor of cell biology, neurobiology and anatomy, along with postdoctoral fellow Karim Si-Tayeb, Ph.D., and graduate student Ms. Fallon Noto.

"This is a crucial step forward towards developing therapies that can potentially replace the need for scarce liver transplants, currently the only treatment for most advanced liver disease," says Dr. Duncan.

Liver disease is the fourth leading cause of death among middle aged adults in the United States. Loss of liver function can be caused by several factors, including genetic mutations, infections with hepatitis viruses, by excessive alcohol consumption, or chronic use of some prescription drugs. When liver function goes awry it can result in a wide variety of disorders including diabetes and atherosclerosis and in many cases is fatal.

The Medical College research team generated patient–specific liver cells by first repeating the work of James Thomson and colleagues at University of Wisconsin-Madison who showed that skin cells can be reprogrammed to become cells that resemble embryonic stem cells. They then tricked the skin–derived pluripotent stem cells into forming liver cells by mimicking the normal processes through which liver cells are made during embryonic development. Pluripotent stem cells are so named because of their capacity to develop into any one of eh more than 200 cell types in the human body.

At the end of this process, the researchers found that they were able to very easily produce large numbers of relatively pure liver cells in laboratory culture dishes. "We were excited to discover that the liver cells produced from human skin cells were able to perform many of the activities associated with healthy adult liver function and that the cells could be injected into mouse livers where they integrated and were capable of making human liver proteins," says Dr. Duncan.

Several studies have shown that liver cells generated from embryonic stem cells could potentially be used for therapy. However, the possible use of such cells is limited by ethical considerations associated with the generation of embryonic stem cells from preimplantation embryos and the fact that embryonic stem cells do not have the same genetic make-up as the patient.

Although the investigations are still at an early stage the researchers believe that the reprogrammed skin cells could be used to investigate and potentially treat metabolic liver disease. The liver may be particularly suitable for stem-cell based therapies because it has a remarkable capacity to regenerate. It is interesting to note that the regenerative nature of the liver was referenced in the ancient Greek tale of Prometheus. When Prometheus was caught stealing the gift of fire from Zeus, he was punished by having his liver eaten daily by an eagle. This provided the eagle with an everlasting meal because each night the liver of Prometheus would re-grow.

The liver is a central regulator of the body's metabolism and is responsible for controlling sugar and cholesterol levels, secretion of a variety of hormones, production of blood clotting factors, and has an essential role in preventing toxins from damaging other organs in the body.

It is possible that in the future a small piece of skin from a patient with loss of liver function could be used to produce healthy liver cells, replacing the diseased liver with normal tissue.

*Recently, the National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases through the American Recovery and Reinvestment Act have provided the MCW researchers, in collaboration with Markus Grompe, M.D., at the Oregon Health and Science University, a $1 million research grant to pursue the possibility of using reprogrammed skin cells to study and treat metabolic liver disease. Using this support, as well as donations from individuals throughout Milwaukee, the Medial College researchers are currently producing reprogrammed cells from patients suffering from diabetes, hyperlipidemia, and hypercholesterolemia in an effort to identify new treatments for these diseases.*

## Amyotrophic lateral sclerosis may involve a form of sudden, rapid aging of the immune system

### *Studies in laboratory mice and humans suggest that the immune system ages prematurely and malfunctions*

LOS ANGELES – Premature aging of the immune system appears to play a role in the development of amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, according to research scientists from the Maxine Dunitz Neurosurgical Institute at Cedars-Sinai Medical Center, the Weizmann Institute of Science in Israel, and Sheba Medical Center in Israel.

A study published in the Journal of Cellular and Molecular Medicine shows that CD4+ T cells, which grow and mature in the thymus before entering the bloodstream, are reduced in number in patients who have ALS as the thymus shrinks and malfunctions. Theoretically, devising therapies to support or replace these cells could be a strategy in treating the disease.

The research was led by Michal Schwartz, Ph.D., a visiting professor at the Center of Neuroimmunology and Neurogenesis in the Department of Neurosurgery at Cedars-Sinai and professor of neuroimmunology at the Weizmann Institute in Rehovot, Israel.

The findings are consistent with evidence collected over a decade by Schwartz's group suggesting that a well-functioning immune system plays a pivotal role in maintaining, protecting and repairing cells of the central nervous system. Studies conducted in animals have shown that boosting immune T-cell levels may reduce symptoms and slow progression of certain neurodegenerative diseases.

Results from the current study suggest that premature aging of the immune system and thus a decrease in protection from immune T cells could contribute to the aggressive and rapid progression of amyotrophic lateral sclerosis, which attacks motor neurons – nerve cells responsible for muscle strength and voluntary movements. The researchers found that thymic malfunction occurs simultaneously with motor neuron dysfunction, both in laboratory mice bred to mimic amyotrophic lateral sclerosis and in humans suffering from the disease.

Motor neurons extend from the brain to the spinal cord and from the spinal cord to the muscles of the body. Amyotrophic lateral sclerosis damages motor neurons in the spinal cord, leading to their death, the inability to control muscle action, and the wasting away of muscle tissue. About 5,600 people are diagnosed with amyotrophic lateral sclerosis each year. Up to 10 percent of cases are inherited because of certain gene mutations but the majority occur in the general population with no known cause.

Life expectancy varies greatly but generally ranges from two to five years after diagnosis. More than half of patients survive more than three years, and about 5 percent live 20 years, according to the ALS Association. The disease has been known to spontaneously stop progressing, and in rare cases, the symptoms have actually reversed. Amyotrophic lateral sclerosis is often referred to as Lou Gehrig disease in recognition of the baseball great whose career with the New York Yankees was cut short by the disease in 1939. He died two years later.

The thymus gland, where immune cells called T lymphocytes mature before entering the bloodstream, normally reaches its peak in size and production in childhood. It then slowly shrinks, becoming virtually nonexistent in the elderly, but the lifespan of newly produced T cells ranges from three to 30 years.

This study found that the thymus glands of mice and patients with the disease undergo accelerated degeneration. In addition to using laboratory tests that provide a noninvasive measure of thymic function, the researchers performed imaging scans on three relatively young patients and found no evidence of thymic remnants. Additional studies showed that patients with the disease had dramatically reduced numbers of five genes that are known to support immune responses. Patients also were found to have a significant deficiency of another gene that may make T cells susceptible to a process that causes cell death.

"If T-cell malfunction is confirmed to be a contributing factor to ALS, as we propose, therapeutic strategies may be aimed at overcoming this deficiency through rebuilding, restoring or transplanting the thymus," said Schwartz, the journal article's senior author.

*The study was supported by the Israeli ALS Research Association, the Israeli Academy of Science, the Maxine Dunitz Neurosurgical Institute, and the Marciano Family Foundation.*

***Citation**: The Journal of Cellular and Molecular Medicine, "Thymic Involution in Amyotrophic Lateral Sclerosis," published online July 24, 2009.*

## Chronic fatigue syndrome linked to 'cancer virus'

* 19:00 08 October 2009 **by Ewen Callaway**

Chronic fatigue syndrome, the debilitating condition once dismissed as "yuppie flu", has been linked to a virus that is also common in people with a certain type of prostate cancer.

It's still not clear if the virus, called XMRV, causes chronic fatigue syndrome (CFS), or is just more common in people with the disorder. But the discovery is sure to reignite the debate over whether CFS is fundamentally a psychological condition or a physiological one.

"It's a contentious area that lies somewhere between medicine and psychiatry," says Simon Wessely, a psychiatrist at King's College London who has been vilified by patient groups for his scepticism of cut-and-dried explanations for CFS and his assertion that psychological factors may play an important role.

CFS is characterised by cramps, sleeplessness, weakness and headaches. It affects more than a million Americans and a quarter of a million Britons, yet its cause remains elusive.

**Virus clues**

Previously a number of viruses, including herpesviruses, enteroviruses and Epstein-Barr virus – which also causes glandular fever, or mononucleosis – have been suggested as triggers for CFS. But these have only been found in a small minority of people with the disorder.

A team led by Judy Mikovits at the Whittemore Peterson Institute in Reno, Nevada, decided to investigate whether XMRV (or xenotropic murine leukaemia virus-related virus, to give it its full name) might be linked to CFS after the virus was reported in 2006 to be present in the tumour tissue of patients with a hereditary form of prostate cancer. It is still not clear what effect the virus has on people. But the fact that this type of prostate cancer and CFS have both been linked to changes in the same antiviral enzyme led Mikovits to wonder whether XMRV could playing a role in CFS too.

**Sensitive test**

When her team analysed blood taken from 101 CFS patients, 68, or two thirds, tested positive for XMRV genes, compared with just eight out of 218 healthy controls. The next step will be working out whether XMRV causes CFS or just grows particularly well in people who have it.

Mikovits suspects that XMRV causes CFS. She says her team has found antibodies against XMRV in 95 per cent of the nearly 300 patients they have tested, but these results have yet to published in a journal. Antibodies are a more sensitive test than looking for viral genes, as they pick up people who have had XMRV in the past, not just those who still have it.

What's more, some characteristics of the virus match up with the syndrome's symptoms, she says. Viruses related to XMRV can cause blood vessels around the body to leak, a common symptom of CFS. Mikovits also notes that in mice, a protein that coats the shell of the virus causes the animals' nerves to degenerate. A class of immune cells called natural killer cells, which are thought to go wrong in CFS, are known to be susceptible to infection by the virus.

"XMRV infection of [natural killer] cells may affect their function," says Jonathan Kerr, a researcher at St George's, University of London, who was not involved in the study. "This does fit." He adds, however, that "an independent study to confirm these findings is very much needed".

**Childhood trauma**

That sentiment is echoed by John Coffin, a virologist at Tufts University in Boston. "This looks like a very, very interesting start," he says. "It's not impossible that this could cause a disease with neurological and immunological consequences, but we don't know for sure."

Wessely points out, however, that XMRV fails to account for the wide variety of other factors associated with the CFS, including childhood trauma and other infections such as viral meningitis. "Any model that is going to be satisfactory has to explain everything, not just little bits," he says.

If XMRV does turn out to contribute to CFS, this could point to new treatments. In the UK, patients are prescribed exercise and cognitive therapy, which seems to work for some patients, but not for most. Such failings underscore the need for therapies that go after the root cause of chronic fatigue syndrome – whatever it turns out to be. *Journal reference: Science, DOI: 10.1126/science.1179052*

## Learning to juggle grows brain networks for good

* 18:00 11 October 2009 **by Jessica Hamzelou**

Juggling boosts the connections between different parts of the brain by tweaking the architecture of the brain's "white matter" – a finding that could lead to new therapies for people with brain injuries.

White matter describes all areas of the brain that contain mostly axons – outgrowths of nerve cells that connect different cells. It might be expected that learning a new, complex task such as juggling should

strengthen these connections, but previous work looking for changes in the brains of people who had learned how to juggle had only studied increases in grey matter, which contains the nerve cells' bodies.

Now Jan Scholz and his colleagues at the University of Oxford have discovered that juggling changes white matter, too. They gave 24 young men and women training packs for juggling and had them practise for half an hour a day for six weeks. Before and after this training period, the researchers scanned the brains of the jugglers along with those of 24 people who didn't do any juggling, using a technique called diffusion tensor imaging that reveals the structure of white matter.

They found that there was no change in the brains of the non-jugglers, but the jugglers grew more white matter in a part of the parietal lobe – an area involved in connecting what we see to how we move.

The same transformation was seen in all the jugglers, regardless of how well they could perform. This suggests that it's the learning process itself that is important for brain development, not how good you are.

**Learning matters**

Arne May of the University Medical Centre Hamburg-Eppendorf in Germany, who led the previous work on juggling and grey matter, finds this result "fascinating". "It suggests that learning a skill is more important than exercising what you are good at already – the brain wants to be puzzled and learn something new," he says.

Like May, Scholz's group found increases in grey matter, but differences in the size and timing of the grey- and white-matter changes suggest they are independent. Nevertheless, both are probably necessary to learn how to juggle, argues Scholz.

"More white matter on its own might mean you can move more quickly, but you'd need the grey matter to make sure your hands were in the right place," he says.

**Don't use it, don't lose it**

The group scanned the jugglers' brains again after four weeks without juggling. They found that the new white matter had stayed put and the amount of grey matter had even increased. This could be why, when we learn a new skill, we retain some ability, no matter how long ago we last practised.

"It's like riding a bike," Scholz says. "Either you can juggle or you can't. It takes a lot of training to learn, but once it clicks, you don't forget it."

Scholz also hopes that it might be possible to develop juggling-based training programmes to help people with brain injuries, or that further study of how juggling changes the architecture of the brain may lead to the discovery of drugs that could boost this plasticity. "If we could use training or drugs to help stroke patients regenerate damaged parts of their brains, that would be fantastic," he says.

*Journal reference: Nature Neuroscience, DOI: 10.1038/nn.2412*

## Patients who received donated pacemakers survive without complications

### *Study of 12 patients in the Philippines shows safety and efficacy of reusing devices*

ANN ARBOR, Mich. – Patients who received refurbished pacemakers donated from Detroit area funeral homes survived without complications from the devices, according to a case series reported by the University of Michigan Cardiovascular Center.

The pacemakers were implanted in 12 patients at the University of Philippines- Philippine General Hospital who could not afford advanced cardiac care and were confined to their beds as they waited for a permanent pacemaker.

All donated pacemakers functioned normally at six months, and most importantly there were no device complications such as infections. The study appears online ahead of print in the Oct. 13 issue of the Journal of the American College of Cardiology.

The argument for pacemaker reuse has been debated for decades. But the idea is gaining ground as U-M cardiology experts report promising results of providing donated pacemakers to underserved nations.

"In light of the widening health care disparity seen between the industrialized world and developing nations, we feel that pacemaker reuse is an ethical obligation to address the medical needs of those who could not afford therapy otherwise," says co-author Timir Baman, M.D., cardiology fellow at the U-M Cardiovascular Center.

Based on surveys showing a majority of heart patients were interested in donating their pacemakers after death, U-M has launched Project My Heart Your Heart.

Project My Heart Your Heart is a joint collaboration between the University of Michigan Cardiovascular Center, Michigan funeral homes, and World Medical Relief, a Detroit-based non-profit organization that specializes in the delivery of used medical equipment.

"Ongoing research is needed to evaluate the feasibility of regional and potentially nationwide pacemaker donation programs," says co-author Kim Eagle, M.D., director of the U-M Cardiovascular Center.

In recent decades, industrialized nations have seen a drop in deaths from heart attacks and strokes, but those in low- and middle-income nations continue to experience an epidemic of cardiovascular disease.

The prevalence of cardiovascular disease is expected to increase 137 percent between 1990 and 2020 for those living in low- and middle- income countries, authors write. It's estimated that as many as 1 million people worldwide die annually from slow heart rates.

"Many of these countries lack the financial resources to address this epidemic of cardiovascular disease," says co-author Hakan Oral, M.D., director of electrophysiology at the U-M cardiovascular center. "As a result, resources are often directed away from high-cost treatment strategies, such as implantable cardiac rhythmn management devices."

Pacemakers and other implantable cardiac devices are implanted to regulate an irregular or slow heart beat, or act as an insurance policy by automatically shocking the heart back to a normal rhythm. They can last up to 10 years and cost $10,000 to $50,000.

Only pacemakers with 70 percent battery life were included in the study and informed consent was obtained from all patients' families in order to remove and donate the pacemakers after death. A total of 50 pacemakers were donated by funeral homes to WMR. Of them, 12 with adequate battery life were implanted in poor patients at Philippine General Hospital in Manila.

U-M is exploring partnerships with the Philippine General, Vietnam Heart Institute in Hanoi, and Komfo Medical Center in Ghana, which is in the process of developing an arrhythmia therapy program, for allocation of used pacemakers. The international hospitals have had on-site reviews for quality and clinical excellence by U-M cardiology experts.

In the next phase, the U-M Cardiovascular Center will seek approval from the U.S. Food and Drug Administration to embark on a large scale clinical trial to show that pacemaker reuse is safe and effective.

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***Resources**: U-M Cardiovascular Center http://www.med.umich.edu/cvc/*

***Project My Heart Your Heart** http://www.med.umich.edu/myheartyourheart/*