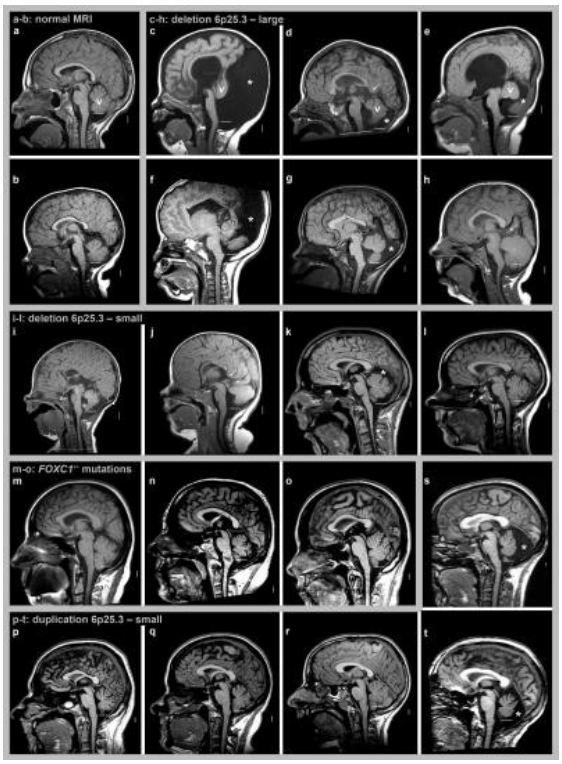
Unlikely genetic suspect implicated in common brain defect

A genetic search that wound its way from patients to mouse models and back to patients has uncovered an unlikely gene critically involved in a common birth defect which causes mental retardation, motor delays and sometimes autism, providing a new mechanism and potentially improving treatment for the disorder.

Researchers from the University of Chicago, University of Alberta and other institutions announce in the September issue of Nature Genetics--available online August 10--that the FOXC1 gene contributes to Dandy-Walker malformation (DWM), a brain defect that occurs in 1 of every 5,000 births.

The role of the gene in Dandy-Walker malformation dispels the fog surrounding what goes awry in the brains of children born with the disorder. DWM is characterized by an improperly formed cerebellum, the region at the back of the brain involved in movement and coordination. As a result children with this disorder require considerable medical care, and in some cases surgery to treat the build up of fluid around the brain, a condition called hydrocephalus.

Researchers were surprised to discover that the FOXC1 gene mediated development of the cerebellum and contributed to DWM, as the gene is never actually expressed in the brain itself. Instead, the FOXC1 gene is expressed in fetal tissue called mesenchyme, which forms the skull and other layers that surround and protect the brain. That mechanism suggests an exciting new element of embryonic brain development, said study co-author Kathleen Millen, Ph.D., assistant professor of human genetics at the University of Chicago.



This image shows MRI scans of normal patients (a, b) and patients with missing or affected FOXC1 genes or larger gene deletions. **William Dobyns, M.D. Kathleen Millen, Ph.D**

"The developing skull and all the stuff around the brain actually are as important for brain development as the brain itself," Millen said.

In the developing fetus, FOXC1 acts as a "master regulator," directing the expression of other genes that, in turn, give instructions necessary for the adjacent embryonic brain to properly form.

"It's controlling downstream genes, and some of those downstream genes we know are signaling molecules and growth factors that apparently are required for brain development," Millen said. "When you don't have them the brain gets screwed up; not because the causative gene is expressed in the brain but because it's in the surrounding tissue."

The new discovery follows research from the same group, published in 2004, that found the first genes associated with DWM. "The first gene didn't give us a huge clue, but this one gives us a major clue to the underlying cause," said study co-author William Dobyns, M.D., professor of Human Genetics, Neurology and Pediatrics at the University of Chicago.

The path to the unlikely FOXC1 gene began with a Dandy-Walker patient referred to Dobyns in 2004, shortly after the researchers had published on the first two genes associated with the disorder. While those genes were located on chromosome 3, this patient exhibited an abnormal chromosome 6, implicating a second hotspot for DWM.

The researchers narrowed their search to a region of eight genes on chromosome 6. Patients with severe DWM were missing as many as seven genes in the target region, while patients missing just one gene showed mild abnormalities detectable only by MRI brain scans.

To determine which of the eight genes were most critical in development of the disorder, researchers turned to mouse models. One mouse, selectively lacking the FOXC1 gene, was created to study eye, heart and muscle defects, but no one had studied its brain.

Millen herself said she was skeptical that the mouse lacking the FOXC1 gene would be relevant to their study, and said she bet Kimberly Aldinger, the University of Chicago neurobiology graduate student who is first author on the study, a free lunch that the gene would not be the one they were seeking. It was a bet she happily lost. "The moment we looked at the very first brain, it was so obvious they had a very messed up cerebellum and it had been completely overlooked," Millen said.

Now confident that FOXC1 was important for cerebellar development in mice, the researchers then searched for humans lacking all or part of the gene. Fortunately, they found 11 such subjects through Ordan Lehmann, associate professor of ophthalmology and medical genetics at the University of Alberta, who was studying patients with pediatric-onset glaucoma caused by FOXC1.

When the glaucoma patients were given MRI scans, the researchers observed cerebellar abnormalities that proved the involvement of FOXC1 in Dandy-Walker malformation.

"These patients were essential for blaming the brain malformation on the FOXC1 gene," Millen said. "Based on the mouse mutants we had a huge suspicion it had to be FOXC1, and the patients confirmed it."

The dramatic changes in the brains of these patients offers new insight into mechanisms contributing to glaucoma, a common disorder previously considered to be just a disease of the optic nerve – the nerve connecting the eye to the brain. Further studies of how the FOXC1 gene directs development of the cerebellum and other brain structures could also lead to new research avenues and treatments for hydrocephalous, autism and other diseases.

"Now that we understand what's going on, we can look at all the other loci and see if there are any other genes that fit this framework," Millen said. "From now on gene finding should be a lot faster because we understand the basic biology."

"This finding makes us rethink the basis of this disease," said Joseph Gleeson, M.D., an investigator with the Howard Hughes Medical Institute at the University of California, San Diego, who was not involved with the study. "It's going to be a shift from the way we were thinking about it to a new paradigm where there are a whole bunch of new ideas about how we understand Dandy-Walker malformation."

The National Institutes of Health, Autism Speaks, the Alberta Heritage for Medical Research, the Canadian Institute for Health Research, and the March of Dimes Birth Defects Foundation supported the research. Additional authors include, Victor Chizhikov of the University of Chicago, Louanne Hudgins of Stanford University Alexander Bassuk of the University of Iowa, Lesley Ades of the Children's Hospital at Westmead and the University of Sydney, and Ian Krantz of the Children's Hospital of Pennsylvania.

An HIV-blocking gel for women

New 'molecular condom' meant to prevent AIDS

SALT LAKE CITY University of Utah scientists developed a new kind of "molecular condom" to protect women from AIDS in Africa and other impoverished areas. Before sex, women would insert a vaginal gel that turns semisolid in the presence of semen, trapping AIDS virus particles in a microscopic mesh so they can't infect vaginal cells.

"The first step in the complicated process of HIV (human immunodeficiency virus) infection in a woman is the virus diffusing from semen to vaginal tissue. We want to stop that first step," says Patrick Kiser, an associate professor of bioengineering at the University of Utah's College of Engineering. "We have created the first vaginal gel designed to prevent movement of the AIDS virus. This is unique. There's nothing like it."

"We did it to develop technologies that can enable women to protect themselves against HIV without approval of their partner," he adds. "This is important – particularly in resource-poor areas of the world like sub-Sahara Africa and south Asia where, in some age groups, as many as 60 percent of women already are infected with HIV. In these places, women often are not empowered to force their partners to wear a condom."

A study testing the behavior of the new gel and showing how it traps AIDS-causing HIV particles will be published online later this week in the journal Advanced Functional Materials. Kiser is the senior author.

"Due to cultural and socioeconomic factors, women often are unable to negotiate the use of protection with their partner," says Julie Jay, the study's first author and a University of Utah doctoral candidate in pharmaceutics and pharmaceutical chemistry.

So the researchers developed a vaginal gel that a woman could insert a few hours before sex and "could detect the presence of semen and provide a protective barrier between the vaginal tissue and HIV," Jay says. "We wanted to build a gel that would stop HIV from interacting with vaginal tissue."

Kiser estimates that if all goes well, human tests of the gel would start in three to five years, and the gel would reach the market in several more years. He and Jay want to incorporate an antiviral drug into the gel so it both blocks HIV movement and prevents the virus from replicating.

A Rocky Road to Microbicides against AIDS

The effort to develop microbicides – intravaginal gels, rings and films – to prevent transmission of the AIDS virus has been halting. The few that have reached human clinical trials in Africa failed to prevent HIV transmission – either because they carried antiviral drugs that were not long-lived or strong enough, or because patients failed to use them. Some experimental microbicides increased the risk, possibly by irritating vaginal tissue and attracting immune cells that are targeted by the virus.

In 2006, Kiser and colleagues published a study on their development of another "molecular condom" to be applied vaginally as a liquid, turn into a gel coating at body temperature, then, in the presence of semen, turn liquid and release an anti-HIV drug.

Unfortunately, few antiviral drugs bind to and attack HIV in semen. And in Africa, high air temperatures prevent the gel from turning liquid so it could coat the vagina evenly, Kiser says.

The new "molecular condom" gel in the current study works in the opposite way. Like the old version, it changes in response to changes in pH – acidity or alkalinity – in the vagina caused by the introduction of semen during sex. But unlike the old gel, which became liquid at the higher (less acidic) pH of semen, the new "molecular condom" becomes a semisolid at the pH of semen, forming a mesh of "crosslinked" molecules.

The new gel is applied as a gel, and then becomes more solid and impenetrable as changes in pH alter the strength of the bond between the gel's two key components, both of which are polymers, or long, chain-like molecules made of many smaller, repeating units: PBA, or phenylboronic acid, and SHA, or salicylhydroxamic acid.

Slowing and Blocking the AIDS Virus

Kiser's team first published a study about the invention of the polymers and their behavior in 2007. A patent is pending on the invention.

The chemical bonds between the two polymers constantly attach and detach at normal, acidic vaginal pHs of about 4.8, allowing the gel to flow, Kiser says. But at a pH of 7.6 – the slightly alkaline condition when semen enters the vagina – the PBA and SHA polymers "crosslink" and stick tightly together, he adds.

Part of the new study characterized the flow of the gel.

"It flows at a vaginal pH, and the flow becomes slower and slower as pH increases, and it begins to act more solid at the pH of semen," Jay says. HIV moves slowly within the gel, even when the gel is at lower pHs (higher acidity) and still flowing, but the virus is blocked at higher pHs caused by the entry of semen into the vagina.

The crosslinked polymers form a mesh that is smaller than microscopic, and instead is nanoscopic – on the scale of atoms and molecules – with a mesh size of a mere 30 to 50 nanometers – or 30 to 50 billionths of a meter. (A meter is about 39 inches.) By comparison, an HIV particle is about 100 nanometers wide, sperm measure about 5 to 10 microns (5,000 to 10,000 nanometers) in cross section, and the width of a human hair is roughly 100 microns (100,000 nanometers).

Kiser says the gel should block other viruses and sperm, thus could work as a contraceptive and possibly prevent infection by herpes viruses and human papillomavirus (HPV), a major cause of cervical cancer.

The gel also could help prevent AIDS by blocking movement of immune system cells that try to combat infectious agents but instead get hijacked by the AIDS virus.

During the study, coauthors from Northwestern University in Chicago used a sophisticated microscope to track how fast HIV particles marked with fluorescent dye moved when they were caught in the gel, and how the speed varied with changes in pH.

The researchers compared movement of HIV particles with latex particles, which revealed that under somewhat acidic conditions, the HIV particles are slowed down in part because their surfaces react chemically with the polymers.

By adding an anti-AIDS drug such as tenofovir to the gel, "the virus would have two barriers to get through: the polymer barrier and then the drug barrier," Kiser says. Unlike an antiviral used with the old gel, tenofovir would not attack HIV directly, but protect immune cells in the vagina from infection.

Kiser says that after sex, the vagina gradually becomes acidic again, and any residual HIV particles would be inactivated both by acidity and an antiviral drug within the remaining gel, which still impedes HIV to some extent at normal vaginal acidity.

Kiser and Jay conducted the study with four other University of Utah researchers: bioengineering undergraduates Kristofer Langheinrich and Melissa Hanson, bioengineering graduate student Todd Johnson, and bioengineering researcher Meredith Clark. Other coauthors were from the Department of Cell and Molecular Biology at Northwestern University Medical School in Chicago: Thomas Hope, Shetha Shukair and Gianguido Cianci.

The study was funded by National Institutes of Health. Kiser's research team is continuing the effort to develop microbicides to prevent AIDS thanks to a $100,000 grant from the Bill and Melinda Gates Foundation.

Upcoming work includes assessing the HIV-prevention potential of other polymers, testing the safety of the new gel on vaginal cells, and studying how well the new gel blocks the transport of HIV into samples of human vaginal and penile tissue from hysterectomies and circumcisions, respectively.

Chinese acupuncture affects brain's ability to regulate pain, UM study shows

ANN ARBOR, Mich. – Acupuncture has been used in East-Asian medicine for thousands of years to treat pain, possibly by activating the body's natural painkillers. But how it works at the cellular level is largely unknown.

Using brain imaging, a University of Michigan study is the first to provide evidence that traditional Chinese acupuncture affects the brain's long-term ability to regulate pain.

The results appear online ahead of print in the September Journal of NeuroImage.

In the study, researchers at the U-M Chronic Pain and Fatigue Research Center showed acupuncture increased the binding availability of mu-opoid receptors (MOR) in regions of the brain that process and dampen pain signals – specifically the cingulate, insula, caudate, thalamus and amygdala.

Opioid painkillers, such as morphine, codeine and other medications, are thought to work by binding to these opioid receptors in the brain and spinal cord.

"The increased binding availability of these receptors was associated with reductions in pain," says Richard E. Harris, Ph.D., researcher at the U-M Chronic Pain and Fatigue Research Center and a research assistant professor of anesthesiology at the U-M Medical School.

One implication of this research is that patients with chronic pain treated with acupuncture might be more responsive to opioid medications since the receptors seem to have more binding availability, Harris says.

These findings could spur a new direction in the field of acupuncture research following recent controversy over large studies showing that sham acupuncture is as effective as real acupuncture in reducing chronic pain.

"Interestingly both acupuncture and sham acupuncture groups had similar reductions in clinical pain," Harris says. "But the mechanisms leading to pain relief are distinctly different."

The study participants included 20 women who had been diagnosed with fibromyalgia, a chronic pain condition, for at least a year, and experienced pain at least 50 percent of the time. During the study they agreed not to take any new medications for their fibromyalgia pain.

Patients had position emission tomography, or PET, scans of the brain during the first treatment and then repeated a month later after the eighth treatment.

***Additional authors**: Jon-Kar Zubieta, M.D., Ph.D., David J. Scott, Vitaly Napadow, Richard H. Gracely, Ph.D, Daniel J. Clauw, M.D.*

***Funding**: Department of Army, National Institutes of Health **Reference**: Journal of NeuroImage, Vol. 5, No. 83, 2009*

Ditching binary will make quantum computers more powerful

* 16:42 10 August 2009 **by Paul Marks**

Unlike most pieces of computer hardware, this quantum bit handles data using five basic states instead of the conventional two (Image:

Unlike most pieces of computer hardware, this quantum bit handles data using five basic states instead of the conventional two (Image:

Memo to the developers of superfast quantum computers: give up on the familiar 1s-and-0s binary system used in conventional computers. By switching to a novel five-state system, you will find it easier to build the staggeringly powerful machines.

So claim Matthew Neeley and colleagues at the University of California, Santa Barbara (UCSB).

So far, the development of quantum computers has followed the traditional binary computing model. This encodes all information using components that can be in two states, either 1 or 0.

But other possibilities exist, Neeley explains. "We could use a 'trinary' system with three digits – 0, 1 and 2 – and then the fundamental units would be trinary digits, or trits, that would essentially be three-position switches." A single "trit" would contain more information a conventional "bit".

Neeley's team have now built a quantum computer whose building blocks have five basic states.

Five-state system

Until now, quantum computers' basic components have been binary quantum bits – qubits – which encode two states in the quantum spin of atoms, electrons or photons. The ability of such particles to defy everyday logic, and exist in multiple quantum states at once, should one day enable quantum computers to perform vast numbers of calculations simultaneously.

Neeley's group used a superconducting aluminium and silicon circuit on a sapphire wafer to make five-state qubits, or "qudits", that operate at 0.025 kelvin.

"There's more information stored in a qudit than a qubit, so a given computation can be done with fewer qudits," Neeley told New Scientist.

By firing microwave photons of five different frequencies into the circuit, they were able to encourage it to jump between five discrete energy levels. "We also developed a quantum measuring technique that can distinguish between all of these levels," says Neeley.

Simultaneous existence

Because, in probabilistic terms, the qudit's five quantum states are able to exist simultaneously, the team had a working qudit on their hands.

One qudit alone is of little use, however.

Jonathan Home at the US National Institute of Standards and Technology in Boulder, Colorado, says Neeley's team needs to extend its basic system in such a way that two or more qudits can transport information between them, which would allow more complex computational operations to be undertaken.

"Designing the sort of system where two qudits interact, but still retain the interesting properties of a five-level system, will be a major challenge," Home says.

Quantum spies

The potential power of quantum computers means has attracted the interest of the US Intelligence Advanced Research Projects Agency (IARPA), which hopes to use them to break codes.

Home's team has received funding from the agency to work on a room-temperature quantum computer that allows binary qubits to interact and swap information.

Their latest results show that magnesium ions can be used to stop the qubits destabilising one another by transferring heat as well as their quantum states.

The trick, reported in this week's Science (DOI: 10.1126/science.1177077) is to use serried ranks of trapped beryllium ions as the qubits, while using neighbouring magnesium ions to absorb any heat. The heat would normally destroy quantum information as it is transported between them.

"This will pave the way to large-scale quantum computing, because it addresses the major task: information transport," says Home. *Journal reference: Science, DOI: 10.1126/science.1173440*

Doctors' opinions not always welcome in life support decisions

Some caregivers of critical care patients prefer doctors to keep their opinions on life support decisions to themselves, according to new research that challenges long-held beliefs in the critical care community.

The research, an article to be published in the August 15 issue of the American Journal of Respiratory and Critical Care Medicine, found that surrogates are virtually split when it comes to how much guidance they want to receive from physicians in making end-of-life medical choices on behalf of critically ill patients, according to lead author of the paper, Douglas B. White, of the University of Pittsburgh Medical Center.

"In fact, what we found was that, while a slight majority did prefer doctors to help them make those difficult decisions, many felt that it was a decision they wanted to make without guiding input from doctors other than an explanation of the options," said Dr. White.

At the end of life, critically ill patients frequently require surrogates to make their medical decisions for them, who, in the absence of advance directives from the patient, must rely on what they believe would have been the patients' desires. "This puts an enormous emotional burden on surrogates; not only are they losing a loved one, they also may feel burdened by guilt about allowing the patient to die." said Dr. White. "It was therefore assumed by some in the medical community that a doctor's dispassionate advice could reduce some of that burden and help surrogates make a good decision with less second-guessing themselves. However, there was little or no research to support this assumption."

Dr. White and colleagues set out to test that assumption, recently formalized as a recommendation by a number of critical care societies, by asking surrogates of critical care patients to watch and respond to two videos. The videos depicted a hypothetical ICU "family conference" in which surrogates must decide whether to continue or withdraw life support from a loved one who has a small chance of survival with continued intervention, but a high likelihood of severe functional impairment in the long-term, including dependence on a ventilator. Both videos were identical in all ways except one: in one version, the doctor says that the most important thing is for the surrogate to "make the choice that's consistent with [the patient's] values," but states that only the surrogate could make that decision; in the alternate version, the doctor offers his opinion that the patient would likely not have wanted to continue aggressive treatment given the likely outcome.

A total of 169 surrogates who were recruited from four ICUs at the University of California San Francisco Medical Center to watch the films in randomized order and respond to it. The researchers used a multi-method analysis to code the responses and validated their analyses with the surrogates themselves to ensure an accurate and complete qualitative assessment of the data.

To their surprise, Dr. White and colleagues found that only a slight majority, 56 percent, of surrogates expressed a preference for the version in which the physician offered an opinion to limit life support. A slight minority, 42 percent, preferred no recommendation, and the final two percent had no preference.

"This is an important article that has changed my clinical practice," said J. Randall Curtis, M.PH., M.D., president of the American Thoracic Society and Professor of Medicine Pulmonary and Critical Care Medicine

Section Head, Harborview Medical Center in Seattle, WA"I had previously assumed that almost all families would want physicians' recommendations, but these findings indicate that there is no such consensus among surrogates. I suspect that physicians can do more harm by withholding a recommendation that is desired than by providing a recommendation that is not desired, but this study suggests we should ask rather than assume."

Just over half (51 percent) of the surrogates expressing a preference for receiving their doctors' advice believed that it was the doctor's role to provide that opinion, whereas nearly four of five (79 percent) who preferred not to receive the advice saw it as overstepping.

"A very important part of American bioethics is respecting patient's choices," said Dr. White. "The family's most important job when acting as a surrogate decision maker is to give voice to the patient's values. I think our research highlights that the physician's job is to be flexible enough and insightful enough to respond to the surrogate's individual needs for guidance.

"It is rare that a research paper changes clinical practice, and I think this one will," said Dr. Curtis.

Link to original article: *http://www.thoracic.org/sections/publications/press-releases/resources/081509white.pdf*

Misuse of common antibiotic is creating resistant TB

Use of a common antibiotic may be undercutting its utility as a first-line defense against drug-resistant tuberculosis (TB). Fluoroquinolones are the most commonly prescribed class of antibiotics in the U.S. and are used to fight a number of different infections such as sinusitis and pneumonia. They are also an effective first line of defense against TB infections that show drug resistance. New research shows, however, that widespread general use of fluoroquinolones may be creating a strain of fluoroquinolone-resistant TB.

The results are published in the August 15 issue of the American Thoracic Society's American Journal of Respiratory and Critical Care Medicine.

"While fluoroquinolone resistance in TB strains has been reported since the mid 1990's, to our knowledge no one had investigated the direct causes of it," said Dr. We wanted to determine whether and to what extent clinical practices were having an effect of creating that resistance," said Rose A. Devasia, M.D., M.P.H., clinical instructor of Vanderbilt University.

To investigate the causes of the small but growing proportion of fluoroquinolone-resistant TB cases, Dr. Devasia and colleagues performed a retrospective case-control study using data from the Tennessee Department of Health. They analyzed the records of every newly diagnosed patient with culture-confirmed TB who was also enrolled in Tennessee's Medicaid program, TennCare between January 2002 and December 2006. Using the TennCare pharmacy database, they were able to obtain information on the patients' use of fluoroquinolone for the 12 months prior to their TB diagnosis. They used M. tuberculosis isolates taken from each patient to test for fluoroquinolone resistance in each case.

After excluding those who were not enrolled in TennCare or whose culture were either unavailable or unusable, the researchers analyzed data for 640 patients. Age, race and other demographic factors were not significantly associated with resistance, but when researchers further analyzed the data they found a linear association between previous fluoroquinolone exposure and fluoroquinolone resistance.

Overall, patients who had used fluoroquinolones within 12 months of diagnosis were almost five times as likely to have a fluoroquinolone-resistant strain of TB than those who had not used fluoroquinolones, and there was a linear association between length of fluoroquinolone use and fluoroquinolone resistance.

"Patients who had undergone shorter treatment (less than 10 days) had a relatively low rate of resistance of only 1.6 percent," said Dr. Devasia. "[But] for every additional 10 days of fluoroquinolone use, we found that patients had a 50 percent increase in the likelihood of having resistant TB. Of the116 people who had taken fluoroquinolones, 13 percent had fluoroquinolone- resistant TB."

Interestingly, Devasia and colleagues found that fluoroquinolone resistance was highest among those who had undergone treatment more than 60 days prior to TB diagnosis. "Exposure to fluoroquinolones early in the course of disease may select for and allow a fluoroquinolone-resistant strain to predominate," explained Dr. Devasia.

John Bernardo, M.D., of Boston University School of Medicine and Wing Wei Yew, M.B., of Grantham Hospital in Hong Kong, noted that pressure on doctors, particularly in settings such as emergency rooms, to inappropriately prescribe antibiotics may contribute to this growing problem. "For now, we all need to be more careful when considering the use of these drugs un the community setting and limit the use of prolonged or repeated courses of fluoroquinolones, or even avoid them altogether, in patients who are risk of having active TB," they wrote in an accompanying editorial in the same issue of the journal.

"These findings underscore the importance of considering TB in people with symptoms consistent with it and to limit the use of fluoroquinolone in those patients until TB can be definitively ruled out and that repeated

courses of fluoroquinolones for the same clinical symptoms may be an indication that TB is the real problem," said Dr. Devasia.

Link to original article: http://www.thoracic.org/sections/publications/press-releases/resources/081809devasia.pdf
Link to original editorial: http://www.thoracic.org/sections/publications/press-releases/resources/081509bernardo.pdf

Avian influenza strain primes brain for Parkinson's disease

St. Jude scientists report flu infection leaves brain more vulnerable later in life

At least one strain of the H5N1 avian influenza virus leaves survivors at significantly increased risk for Parkinson's disease and possibly other neurological problems later in life, according to new research from St. Jude Children's Research Hospital.

In the August 10 online early edition of the Proceedings of the National Academy of Sciences, researchers reported that mice which survived infection with an H5N1 flu strain were more likely than uninfected mice to develop brain changes associated with neurological disorders like Parkinson's and Alzheimer's diseases. Parkinson's and Alzheimer's involve loss of brain cells crucial to a variety of tasks, including movement, memory and intellectual functioning. The study revealed the H5N1 flu strain caused a 17 percent loss of the same neurons lost in Parkinson's as well as accumulation in certain brain cells of a protein implicated in both diseases.

"This avian flu strain does not directly cause Parkinson's disease, but it does make you more susceptible," said Richard Smeyne, Ph.D., associate member in St. Jude Developmental Neurobiology. Smeyne is the paper's senior author.

"Around age 40, people start to get a decline in brain cells. Most people die before they lose enough neurons to get Parkinson's. But we believe this H5N1 infection changes the curve. It makes the brain more sensitive to another hit, possibly involving other environmental toxins," Smeyne explained.

Smeyne noted the work involved a single strain of the H5N1 flu virus, the A/Vietnam/1203/04 strain. The threat posed by other viruses, including the current H1N1 pandemic flu virus, is still being studied.

Early indications are that the H1N1 pandemic strain carries a low neurologic risk, said Richard Webby, Ph.D., director of the World Health Organization Collaborating Center for Studies on the Ecology of Influenza in Animals and Birds, which is based at St. Jude. Webby, who is also an associate member of the St. Jude Department of Infectious Diseases, was not involved in the H5N1 study led by Smeyne.

This study also supports the theory that a hit-and-run mechanism is at work in Parkinson's disease. The investigators believe the H5N1 infection sparks an immune response that persists long after the initial threat is gone, setting patients up for further devastating losses from a second hit, possibly from another infection, drug or environmental toxin. In this case, researchers believe the flu virus is the first hit that sets up development of Parkinson's at a later time.

An estimated 4.1 million Americans, including 1 to 2 percent age 55 and older, have Parkinson's. Many suspect both genetic and environmental factors play a role in its development. The disease is linked to the death of dopamine-secreting cells in an area of the midbrain known as the substantia nigra pars compacta (SNpc). Dopamine is a neurotransmitter responsible for stimulating the motor neurons that control movement. Parkinson's is usually diagnosed after individuals lose 70 to 80 percent of the dopamine-producing cells. Treatment is available, but there is no cure.

Flu is primarily a respiratory disease, but indirect evidence dating back to 1385 links it to neurological problems, including the brain inflammation known as encephalitis. The association between flu and brain disorders like Parkinson's was strengthened by an outbreak of encephalitic lethargic, also known as von Economo's encephalopathy, following the 1918 Spanish flu pandemic. Some of those patients developed Parkinson's symptoms.

St. Jude researchers launched this study nearly three years ago in response to the threat posed by avian flu. Smeyne said there was concern about possible long-term neurological risks facing H5N1 survivors.

Previous studies had isolated H5N1 in the nervous system. But this is the first to show the path the virus takes to enter the brain as well as the aftermath of the infection. Smeyne said the virus' path from the stomach through the nervous system and into the brain is reminiscent of how Parkinson's unfolds.

In this study, mice were infected with an H5N1 flu strain isolated in 2004 from a patient in Vietnam. Robert Webster, Ph.D., said the strain remains the most virulent of the avian flu viruses. Webster, a co-author of the study, holds the Rose Marie Thomas Chair in Infectious Diseases at St. Jude.

About two-thirds of the mice developed flu symptoms, primarily weight loss. After three weeks there was no evidence of H5N1 in the nervous systems of the mice that survived.

But the inflammation the infection triggered within the brain continued for months. It was similar to inflammation associated with inherited forms of Parkinson's. Although the tremor and movement problems

disappeared as flu symptoms eased, investigators reported that 60 days later mice had lost roughly 17 percent of dopamine-producing cells in SNpc, a structure found in the midbrain.

Researchers also found evidence that the avian flu infection led to over-production of a protein found in the brain cells of individuals with both Alzheimer's and Parkinson's diseases. The protein, alpha-synuclein, collected in H5N1-infected cells throughout the brain, including the midbrain where key dopamine-producing cells are located. There was little protein accumulation in the brain cells of uninfected mice.

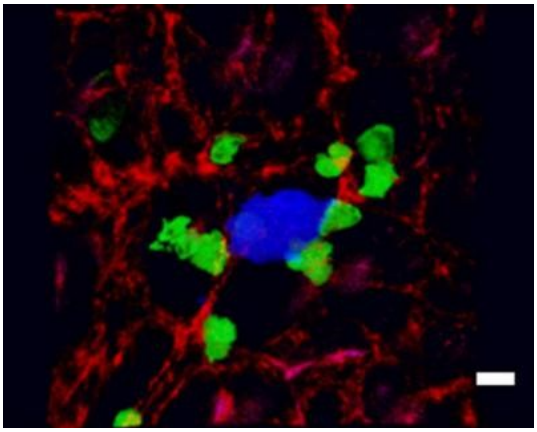
The study marks the first time scientists were able to naturally trigger the protein build-up in an experimental Parkinson's system. "The virus activates this protein," Smeyne explained.

Other authors in this paper include Haeman Jang, David Boltz and Yun Jiao (St. Jude); and Katharine Sturm-Ramirez and Kennie Shephard (formerly of St. Jude).

This work was supported in part by the National Institute of Allergy and Infectious Diseases, National Parkinson's Foundation, Michael J. Fox Foundation, National Institutes of Health and ALSAC.

Einstein researchers identify potential target for metastatic cancer

Cells thought to protect against cancer may actually promote it



BRONX, NY - The deadliest part of the cancer process, metastasis, appears to rely on help from macrophages, potent immune system cells that usually defend vigorously against disease, researchers at Albert Einstein College of Medicine of Yeshiva University report.

In a new study published online in PLoS ONE, Einstein cancer research specialist Jeffrey W. Pollard, Ph.D., and seven colleagues analyzed the movement of breast cancer cells in mice to show that a distinct population of macrophages helps malignant cells set up shop at distant sites. This process, known as metastasis, is the main reason cancer patients die.

Macrophages (green) are shown attaching to a metastatic tumor cell (blue) in the lung -- a process that promotes metastatic growth. **Albert Einstein College of Medicine**

Dr. Pollard and his colleagues propose that their discovery offers a potentially useful new target for anti-cancer therapy. What they've found is a vulnerable step in the cancer process that might be blocked by drug treatments. In three different ways, the scientists showed that metastatic tumor growth is inhibited if these unusual macrophages are killed.

They also showed that even after breast cancer cells have lodged in the animals' lungs and started aggressive growth, erasing the special macrophages dramatically slowed growth of the metastasized tumors. "This suggests that anti-macrophage therapy will have an impact in patients even with metastatic disease," Dr. Pollard said. Based on this new work, he added, "macrophages themselves, or their unique signaling pathways, represent new therapeutic targets that may be efficacious in reducing cancer mortality."

Ordinarily, macrophages are vital for maintaining health as an integral arm of the immune system, one of the body's main lines of defense. Their assigned tasks include cleaning up debris in the wake of disease or injury, alerting other immune system cells when an infection begins, and helping identify viruses and bacteria that need to be killed.

The findings of this study build on earlier cancer research by Dr. Pollard and his team that shows macrophages can act at the primary tumor site to enhance tumor progression and malignancy. Thus, they've now shown that macrophages can become traitors, enhancing the worst aspect of the disease – metastatic tumor growth.

"This new study is important because it definitively shows the effects of macrophages at distant sites, as well as the identity of the macrophage population," Dr. Pollard explained. "This is the first proof that they have impact at this location, at the site of metastatic tumor growth."

Dr. Pollard noted that "metastatic disease is the major cause of cancer mortality," in part because the distant tumors tend to resist chemotherapy and radiation treatments. Unfortunately, "the biological mechanisms that underlie metastatic disease are poorly understood," so continuing research is needed. And if metastasis can somehow be blocked -- particularly through influencing cells of the metastatic microenvironment -- the impact on cancer mortality would be enormous.

The paper, "A Distinct Macrophage Population Mediates Metastatic Breast Cancer Cell Extravasation, Establishment and Growth," was published August 10 in PLoS ONE, a journal of the Public Library of Science. The lead author is post-doctoral fellow Binzhi Qian, Ph.D., Einstein. Other co-authors are Yan Deng and Yiyu Zou, Einstein; Jae Hong Im and Ruth J. Muschel, University of Oxford Churchill Hospital in England; and Richard A. Lang, Children's Hospital Research Foundation, in Cincinnati, Ohio.

A synthetic derivative of the kudzu vine can reduce drinking and prevent relapse

**** Kudzu extracts have been used in Chinese folk medicine to treat alcoholism for about 1,000 years.***
**** Daidzin is an anti-drinking substance in kudzu.***
**** A synthetic form of daidzin, called CVT-10216, can successfully reduce drinking and prevent relapse in preclinical rodent models.***

Kudzu and its extracts and flowers have been used in traditional Chinese folk medicine to treat alcoholism for about 1,000 years. Kudzu contains daidzin, an anti-drinking substance. Daidzin inhibits human aldehyde dehydrogenase 2 (ALDH-2), which metabolizes alcohol into acetaldehyde. Inhibiting ALDH-2 promotes the accumulation of acetaldehyde, which has aversive effects. A recent test of a synthetic ALDH-2 inhibitor (CVT-10216) on rodents shows that it reduces drinking and prevents relapse by increasing acetaldehyde while drinking and later decreasing dopamine in the brain region that controls relapse during abstinence.

Results will be published in the November issue of Alcoholism: Clinical & Experimental Research and are currently available at Early View.

"I think the over-arching issue here is medical treatment," said Ivan Diamond, vice president of neuroscience at Gilead Science, Professor Emeritus of neurology, cellular and molecular pharmacology and neuroscience at the University of California, San Francisco, and corresponding author for the study.

"Alcoholism is a medical disorder, not just a problem of will power," he said. "Physicians treat medical disorders in order to prevent harm, while not necessarily curing the disease being treated – for example, drug treatment of hypertension, statins for high cholesterol, insulin for diabetes – and the same will become true for treating alcoholism. Heavy drinking causes harm. We need to prevent heavy drinking in order to prevent harm."

Diamond added that relapse may be the biggest problem facing physicians today. "We are talking about a patient who has the motivation to undergo a very unpleasant detoxification to try to stop drinking, and then gets into trouble afterward," he said. "Nearly 80 percent of abstinent alcoholics or addicts relapse within a year. Current therapies for alcoholism help, but we can do much better."

"Extracts of various parts of the kudzu vine have been used in many Chinese herbal medicine formulas and are said to be helpful in treating a variety of maladies, including alcoholism and intoxication," said Ting-Kai Li, a professor in the department of psychiatry at Duke University Medical Center, and former director of the National Institute on Alcohol Abuse and Alcoholism. "Recent research has found that several compounds of the isoflavone family - puerarin, daidzin, daidzein - in the kudzu extract decrease alcohol intake in experimental animals."

"Drs. Wing Ming Keung and Bert Vallee at Harvard were the first to confirm kudzu's effects and isolate daidzin as the most potent of the isoflavones in kudzu," added Diamond. "They went further by searching for the basis of daidzin's anti-drinking properties, discovering that daidzin was a selective inhibitor of ALDH-2. Based on x-ray crystallographic studies of daidzin binding to ALDH-2, our team set out to design a compound that would interact more efficiently with ALDH-2, finally choosing CVT-10216 as our best candidate to date."

Diamond and his colleagues administered CVT-10216 to groups of rats bred for moderate and high levels of drinking, after having exposed them to various scenarios of alcohol administration: two-bottle choice, deprivation-induced drinking, operant self-administration, and cue-induced reinstatement. The researchers then tested for blood acetaldehyde levels, alcohol-induced dopamine release in the nucleus accumbens, and effects of the inhibitor on drinking behavior and relapse.

"We had several key findings," said Diamond. "We found that, one, CVT-10216 is a highly selective reversible inhibitor of ALDH2 without apparent toxicity. This means that it does not cause serious damage to other proteins and functions. Two, treatment with our ALDH-2 inhibitor increases acetaldehyde in the test tube and in living animals." Acetaldehyde's aversive effects can include a flushing reaction and feeling ill, which tend to reduce drinking. "And three, we found that our ALDH-2 inhibitor suppresses drinking in a variety of rodent drinking models."

But that's not the whole story, Diamond added. "Most importantly, we also found that CVT-10216 prevents the usual increase in drinking (binge drinking) that occurs after five days of abstinence, and also prevents relapse to drink, even when alcohol is not present. This means that something else besides acetaldehyde helps to suppress craving for, and prevent relapse to, drinking alcohol. We believe that 'something else' is dopamine." He said that current concepts suggest that increased dopamine in the nucleus accumbens drives craving and relapse into drinking.

"Alcohol-induced increases in dopamine in the nucleus accumbens are prevented by CVT-10216 in a dose-dependent manner," said Diamond. "This means the drug has a therapeutic effect in the brain, probably on the desire to drink. Importantly, CVT-10216 does not reduce basal dopamine levels when there is no stimulation to

increase dopamine levels. This is consistent with our findings that CVT-10216 does not appear to affect moderate drinking, and does not have adverse side effects at the therapeutic doses used."

"The findings show promise that CVT-10216 might be better tolerated than Antabuse™," said Li. "How this happens is yet unknown, but suggests that the compound may be useful in treating alcohol relapse and perhaps for other psychoactive, potentially addictive compounds."

Diamond agreed: "Disulfiram or Antabuse™ has been around for 50 years," he explained. "It is called an ALDH-2 inhibitor, but it actually inhibits far more than that. Most believe that disulfiram would not be approved today as a new drug for alcoholism because of its many toxicities. Instead, we have developed CVT-10216, a reversible inhibitor with a very favorable profile, so far." Diamond hopes this novel compound will become an effective therapeutic agent for alcoholism.

"The goal of medicine is harm reduction," emphasized Diamond. "Excessive drinking causes harm while moderate drinking appears to be safe. Increasing numbers of doctors believe abstinence is an unrealistic goal. It sounds like heresy, but it isn't. Therefore, an ideal drug might be able to prevent uncontrolled relapse, convert heavy drinkers into moderate drinkers, and avoid the harmful consequences of excessive alcohol intake. If our compound works and is safe to use, then I think most physicians would not hesitate to prescribe a new drug to prevent relapse and reduce heavy drinking. My goal is to make this happen."

Denosumab increases bone density, cuts fracture risk in prostate cancer survivors

New drug could significantly improve patient quality of life

Twice-yearly treatment with denosumab, a new targeted therapy to stop bone loss, increased bone density and prevented spinal fractures in men receiving androgen-deprivation therapy for prostate cancer. The report from an international research study, the first to document reduced fracture risk in men receiving the hormone-blocking treatment, will appear in the August 20 New England Journal of Medicine and is receiving early online release.

"Androgen-deprivation therapy is the standard treatment for men with locally advanced, recurrent and metastatic prostate cancer; but many active men who have been successfully treated for their cancer develop debilitating bone fractures as a result," says Matthew Smith, MD, PhD, of the Massachusetts General Hospital (MGH) Cancer Center, who led the study as part of the Denosumab HALT Prostate Cancer Study Group. "The results of this study should be critically important in improving the quality of life of thousands of prostate cancer survivors."

About one third of the two million prostate cancer survivors in the U.S. currently receive androgen-deprivation therapy, which blocks the release of testosterone. Several medications used to treat osteoporosis, including the drugs called bisphosphonates, have been shown to reduce androgen-deprivation-related bone loss in men in earlier small clinical studies, but none of those trials were adequate to demonstrate reduced fracture risk. Denosumab – a fully human monoclonal antibody that blocks the action of osteoclasts, the cells that break down bone in the normal process of bone remodeling – is also being investigated to prevent fractures in women with osteoporosis. The current study was a Phase 3 trial supporting the application for FDA approval filed by Amgen Inc., the primary sponsor of the NEJM report.

Men undergoing androgen-deprivation therapy for nonmetastatic prostate cancer were enrolled at 156 centers in North America and Europe and randomly assigned to receive injections of either denosumab or a placebo every six months for three years. Participants were also instructed to take daily calcium and vitamin D supplements during the study period.

Among the more than 900 participants who completed the study, denosumab significantly increased bone density at all the monitored sites – including the lumbar spine, total hip and femoral neck – and reduced new vertebral fractures by 62 percent. Bone density at the radius, one of the bones in the forearm, also increased in the treatment group, an improvement not seen with other osteoporosis drugs. Few adverse events were associated with treatment, and there were no reports of osteonecrosis of the jaw, a problem reported in some patients taking bisphosphonates.

"Denosumab is an important new therapy to prevent painful fractures in prostate cancer survivors," Smith says. "An ongoing clinical trial will also evaluate whether denosumab prevents spread of prostate cancer to bone, the most common site of metastases in men with this disease." Smith is an associate professor of Medicine at Harvard Medical School.

Along with the Amgen grant, the study received support from the National Institutes of Health and the Prostate Cancer Foundation. Additional co-authors of the NEJM article include Benjamin Leder, MD, MGH Endocrinology; Blair Egerdie, MD, Urology Associates, Kitchener, Ontario; Narciso Hernandez Toriz, MD; Centro Medico Nacional Siglo XXI, Mexico City; Robert Feldman, MD, Connecticut Clinical Research Center, Middlebury; Tuevo Tammela, MD, Tempere University Hospital, Finland; Fred Saad, MD, Central Hospital of the University of Montreal; Jiri Heracek, MD, PhD, Androgeos, Prague, Czech

Republic; Maciej Szwedowski, MD, Wojewodzkie Centrum Medyczne, Opole, Poland; and Chunlei Ke, PhD, Amy Kupic, MA, and Carsten Goessl, MD, Amgen, Inc.

Antibodies to strep throat bacteria linked to obsessive compulsive disorder in mice

Study provides new insights into identifying children at risk for autoimmune brain disorders

New York, NY - A new study by researchers at Columbia University Mailman School of Public Health's Center for Infection and Immunity indicates that pediatric obsessive-compulsive disorder (OCD), Tourette syndrome and/or tic disorder may develop from an inappropriate immune response to the bacteria causing common throat infections. The mouse model findings, published online by Nature Publishing Group in this week's Molecular Psychiatry, support the view that this condition is a distinct disorder, and represent a key advance in tracing the path leading from an ordinary infection in childhood to the surfacing of a psychiatric syndrome. The research provides new insights into identifying children at risk for autoimmune brain disorders and suggests potential avenues for treatment.

OCD and tic disorders affect a significant portion of the population. More than 25% of adults and over 3% of children manifest some features of these disorders. Until now, scientists have been unable to convincingly document the association between the appearance of antibodies directed against Group A beta-hemolytic streptoccoccus (GABHS) in peripheral blood and the onset of the behavioral and motor aspects of the disorder. As a result, treatment strategies were restricted to targeting symptoms rather than causes.

Strep throat bacteria, or GABHS, are known to cause autoimmune disorders such as Sydenham chorea, with symptoms such as fever and uncontrolled tics of the face or extremities in susceptible individuals, prompting some scientists to suspect that GABHS could play a role in a syndrome known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS), a rapid-onset and episodic form of OCD and tic disorders observed in some children. The latest study by CII researchers supports the hypothesis that some neuropsychiatric syndromes may be triggered by direct action of GABHS-associated antibodies on the brain. Whether environmental factors other than GABHS can lead to similar effects is as yet unknown.

Using a mouse model of PANDAS, Mady Hornig, MD, associate professor of epidemiology at Columbia University Mailman School of Public Health, and colleagues demonstrate this suspected link between GABHS antibodies and the psychiatric symptoms of the disorder. Immunizing mice with an inactivated form of the bacteria, CII researchers found that the mice exhibited repetitive behaviors reminiscent of children with PANDAS. Injection of antibodies from the immunized mice into the bloodstream of non-immunized mice replicated these behaviors.

"These findings illustrate that antibodies alone are sufficient to trigger this behavioral syndrome," said Dr. Hornig. "Our findings in this animal model support and may explain results of Swedo and colleagues in treating children with PANDAS using plasmapheresis or intravenous immunoglobulin (IVIg). They may also have implications for understanding, preventing or treating other disorders potentially linked to autoimmunity, including autism spectrum, mood, attentional, learning, and eating disorders."

"This work provides strong corroboration for a link between exposure to infection, development of an autoimmune response, and the onset of repetitive behaviors and deficits in attention, learning, and social interaction," says CII Director W. Ian Lipkin, MD, John Snow Professor of Epidemiology, and professor of Neurology and Pathology at Columbia University. "Further investigations in this strep-triggered, autoimmune mouse model of PANDAS will promote the discovery of more effective interventions for these disabling disorders and guide the development of robust prevention strategies."

Dr. Susan Swedo, a senior investigator at NIMH who has been a leader in research into PANDAS, provides commentary on the work in this issue of Molecular Psychiatry, where the authors' work is also featured on the journal's cover.

Jefferson Headache Center study shows novel, orally inhaled migraine therapy effective

PHILADELPHIA – A new study conducted at the Jefferson Headache Center at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania shows an investigational, orally-inhaled therapy is effective in treating migraines. The multi-center, phase three FREEDOM-301 trial for the orally-inhaled migraine therapy, LEVADEX™, shows study participants had significant relief from symptoms such as pain, nausea and light and sound sensitivity when compared to placebo treatment. According to trial results, this therapy provided pain relief in 30 minutes and sustained relief for 48 hours after dosing in patients with moderate or severe migraine attacks. The drug was generally very well tolerated and there were no drug-related, serious adverse events reported.

According to the American Headache Society (AHS), migraine is a common, debilitating neurological disorder that affects approximately 30 million people in the United States. The AHS also states that most migraines last

between four and 24 hours, but some may last as long as three days. Common associated symptoms of migraine include nausea, vomiting, photophobia (sensitivity to light) and phonophobia (sensitivity to sound).
"The major advantage of LEVADEX is that it has the efficacy of intravenous DHE (dihydroergotamine) with a side-effect profile similar to placebo and better than oral triptans," said Stephen Silberstein, M.D., F.A.C.P, a clinical study investigator, director of the Jefferson Headache Center, and professor in the Department of Neurology at Jefferson Medical College of Thomas Jefferson University.

About the FREEDOM-301 Study

FREEDOM-301 is a multi-center, randomized, double-blind, placebo-controlled Phase 3 trial designed to evaluate the safety and efficacy of LEVADEX as a potential treatment for acute migraine. Primary efficacy measures include pain relief, and being free from phonophobia, photophobia and nausea at two hours after dosing. Patients enrolled in the trial were evaluated for the treatment of a single moderate or severe migraine attack and then were given the option to continue in an open label, long-term safety study. This safety study is targeting 300 patients for six months and 150 patients for 12 months, and over 500 patients are continuing in this arm of the trial. FREEDOM-301, the first Phase 3 study of LEVADEX therapy, was conducted pursuant to a Special Protocol Assessment with the U.S. Food and Drug Administration. The FREEDOM-301 trial is sponsored by MAP Pharmaceuticals, Inc.

About LEVADEX™

LEVADEX orally inhaled migraine therapy is a novel migraine therapy in Phase 3 development. Patients administer LEVADEX themselves using MAP Pharmaceuticals' proprietary TEMPO® inhaler. LEVADEX has been designed to be differentiated from existing migraine treatments. It is a novel formulation of dihydroergotamine (DHE), a drug used intravenously in clinical settings for many years to effectively and safely treat migraines. Based on clinical results, MAP Pharmaceuticals believes that LEVADEX has the potential to provide both fast onset of action and sustained pain relief and other migraine symptom relief in an easy-to-use and non-invasive at-home therapy.

Based on research to date, including the FREEDOM-301 trial, MAP Pharmaceuticals believes the unique pharmacokinetic profile of LEVADEX has the potential to effectively treat migraines, while minimizing the side effects commonly seen with DHE and other currently available medicines.

New groundbreaking treatment for oxygen-deprived newborns

Until now immediate cooling of the newborn infant was the only treatment that could possibly prevent brain damage following oxygen deprivation during delivery. New research findings from the Sahlgrenska Academy and Sahlgrenska University Hospital, in collaboration with Zhengzhou University in China, open up the possibility of a new and effective treatment that can be started as late as two days after birth.

This new treatment involves newborn infants being given a two-week course of injections of erythropoietin, a hormone that stimulates the formation of red blood cells.

"For the first time we can demonstrate that it is possible to influence the brain damage occurring as a result of oxygen deprivation during delivery considerably later than the six-hour window of opportunity for treating with cooling," says Klas Blomgren, professor of paediatrics at the Sahlgrenska Academy and specialist at Queen Silvia Children's Hospital.

The research findings, which are presented in the latest issue of the highly-respected medical journal Pediatrics, are the result of cooperation between Swedish, Austrian and Chinese researchers. The study treated just over 150 term newborn infants, half of whom were given small doses of erythropoietin every other day. Once the children reached the age of eighteen months, their neurological condition was assessed.

"Only half as many of the children treated with erythropoietin had developed a severe neurological functional disability or had died of their injuries. Thus the hormone treatment improves the prognosis considerably in the longer perspective," says Blomgren.

The children in the study had suffered moderate or severe hypoxic-ischemic encephalopathy (HIE) at birth, but it was only children with moderate HIE that were helped by this hormone treatment.

"We believe that erythropoietin has a regenerative and stimulating effect on recovery and on brain development following the injury. This appears to be a safe treatment, almost without side effects, and it is also cheaper and technically simpler to administer in comparison with cooling. This means that the treatment can be given a wide distribution, and can be used even in developing countries," says Blomgren.

For further information, contact:

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Journal: Pediatrics *Title of the article:* ***Erythropoietin Improved Neurologic Outcomes in Newborns With Hypoxic-Ischemic Encephalopathy***

Authors: Changlian Zhu, Wenqing Kang, Falin Xu, Xiuyong Cheng, Zhan Zhang, Liting Jia, Ling Ji, Xiaoyan Guo, Hong Xiong, George Simbruner, Klas Blomgren, Xiaoyang Wang

NIAID scientists study past flu pandemics for clues to future course of 2009 H1N1 virus

Flu viruses notoriously unpredictable; robust pandemic preparedness efforts crucial

A commonly held belief that severe influenza pandemics are preceded by a milder wave of illness arose because some accounts of the devastating flu pandemic of 1918-19 suggested that it may have followed such a pattern. But two scientists from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, say the existing data are insufficient to conclude decisively that the 1918-19 pandemic was presaged by a mild, so-called spring wave, or that the responsible virus had increased in lethality between the beginning and end of 1918. Moreover, their analysis of 14 global or regional influenza epidemics during the past 500 years reveals no consistent pattern of wave-like surges of disease prior to the major outbreaks, but does point to a great diversity of severity among those pandemics.

In their commentary in the Aug. 12 issue of the Journal of the American Medical Association, David M. Morens, M.D., and Jeffery K. Taubenberger, M.D., Ph.D., note that the two other flu pandemics of the 20th century, those of 1957 and 1968, generally showed no more than a single seasonal recurrence; and in each case, the causative virus did not become significantly more pathogenic over the early years of its circulation.

The variable track record of past flu pandemics makes predicting the future course of 2009 H1N1 virus, which first emerged in the Northern Hemisphere in the spring of 2009, difficult. The authors contend that characteristics of the novel H1N1 virus, such as its modest transmission efficiency, and the possibility that some people have a degree of pre-existing immunity give cause to hope for a more indolent pandemic course and fewer deaths than in many past pandemics.

Still, the authors urge that the 2009 H1N1 virus continue to be closely tracked and studied as the usual influenza season in the Northern Hemisphere draws near. Like life, the authors conclude, paraphrasing Danish philosopher Soren Kierkegaard, "influenza epidemics are lived forward and understood backward." Thus, the robust, ongoing efforts to meet the return of 2009 H1N1 virus with vaccines and other measures are essential responses to a notoriously unpredictable virus.

ARTICLE: *DM Morens and JK Taubenberger. Understanding influenza backward. Journal of the American Medical Association 302: 679-80. DOI: 10.1001/jama.302.6.679 (2009).*

WHO: *David Morens, M.D., Senior Advisor to the Director, NIAID, and Jeffery Taubenberger M.D., Ph.D., Senior Investigator, Laboratory of Infectious Diseases, NIAID, are available for interviews.*

Planetary smashup leaves trail of frozen lava

* 17:42 11 August 2009 **by Rachel Courtland**

Debris from a collision similar to the one that created Earth's moon has been found orbiting the nearby star HD 172555 (Illustration: NASA/JPL-Caltech)

A vast mess of frozen lava and vaporised rock has been found orbiting a nearby star, evidence of a cataclysmic collision between planet-like bodies outside our solar system. Such collisions are thought to have created Earth's moon and left other scars in the solar system, but it's not yet clear how common they are around other stars.

Hints of past violent collisions abound in our solar system. Many suspect the moon formed from the debris created when a Mars-sized object smashed into the Earth. Other smashups may have pulled off most of Mercury's crust, tilted Uranus on its side, and caused Venus to spin backwards.

Now a team has found evidence of an intense impact surrounding the star HD 172555, which sits some 100 light years away in the southern constellation Pavo, or Peacock.

This is the first time materials like volcanic glass and vaporised rock have been found orbiting a young star that is old enough to have formed planets, says Carey Lisse of Johns Hopkins University in Laurel, Maryland. The star is 12 million years old.

Preliminary evidence also suggests two other stars show similar hints of cataclysmic impacts, Lisse says. "We're now trying to figure out whether we've found a new class of rare but very exciting systems," Lisse told New Scientist.

Volcanic glass

Lisse and colleagues examined the spectrum of HD 172555's infrared light, captured with NASA's orbiting Spitzer Space Telescope. Bumps and dips in the spectrum can reveal the chemical composition of the star as well as the object that surround it, and the team found two unusual features.

One peak matched up with volcanic, silica-based glasses. This material is similar to obsidian, a dark glass created in volcanic eruptions, and tektites, cooled chunks created when liquid rock is ejected during impacts, cooling and hardening in flight. Another peak revealed large quantities of silicon monoxide gas – a byproduct of vaporised rock. The team also found a vast amount of cold, dark dust and rubble.

The total amount of debris adds up to a mass between that of Pluto and the moon, and points to a cataclysmic impact in which two bodies slammed into each other at a relative speed of at least 10 kilometres per second. But it is difficult to say for sure what sorts of bodies might be responsible for the collision.

A smashup sometime in the last million years between two large rocky bodies, each perhaps rivalling the size of Mercury or the moon, might explain the debris.

Other moons?

Studying systems that have suffered large collisions could reveal more about how the solar system formed, says George Rieke of the University of Arizona in Tucson, who was not affiliated with the study.

"The interesting science twist is that we are actually finding traces of the kinds of major collisions that we think shaped the Earth-moon system," Rieke says. But it is not clear whether the collision around HD 172555 created debris that would have coalesced into an object like the moon. "This could just mean that two things smashed each other to smithereens," Rieke told New Scientist.

The fact that only a few stars have so far shown evidence of a violent collision, even though hundreds seem to be surrounded by dusty discs, suggests the violent impacts that seem to have shaped our solar system might be fairly rare. "It implies at some level moons like ours may be pretty uncommon," Rieke says.

McGill/JGH researchers successfully reverse multiple sclerosis in animals

New immune-suppressing treatment forces the disease into remission in mice

A new experimental treatment for multiple sclerosis (MS) completely reverses the devastating autoimmune disorder in mice, and might work exactly the same way in humans, say researchers at the Jewish General Hospital Lady Davis Institute for Medical Research and McGill University in Montreal.

MS is an autoimmune disease in which the body's own immune response attacks the central nervous system, almost as if the body had become allergic to itself, leading to progressive physical and cognitive disability.

The new treatment, appropriately named GIFT15, puts MS into remission by suppressing the immune response. This means it might also be effective against other autoimmune disorders like Crohn's disease, lupus and arthritis, the researchers said, and could theoretically also control immune responses in organ transplant patients. Moreover, unlike earlier immune-suppressing therapies which rely on chemical pharmaceuticals, this approach is a personalized form of cellular therapy which utilizes the body's own cells to suppress immunity in a much more targeted way.

GIFT15 was discovered by a team led by Dr. Jacques Galipeau of the JGH Lady Davis Institute and McGill's Faculty of Medicine. The results were published August 9 in the prestigious journal Nature Medicine.

GIFT15 is composed of two proteins, GSM-CSF and interleukin-15, fused together artificially in the lab. Under normal circumstances, the individual proteins usually act to stimulate the immune system, but in their fused form, the equation reverses itself.

"You know those mythical animals that have the head of an eagle and the body of a lion? They're called chimeras. In a lyrical sense, that's what we've created," said Galipeau, a world-renowned expert in cell regeneration affiliated with the Segal Cancer Centre at the Jewish General and McGill's Centre for Translational Research. "GIFT15 is a new protein hormone composed of two distinct proteins, and when they're stuck together they lead to a completely unexpected biological effect."

This effect, explained Galipeau, converts B-cells -- a common form of white blood cell normally involved in immune response -- into powerful immune-suppressive cells. Unlike their better-known cousins, T-cells, naturally-occurring immune-suppressing B-cells are almost unknown in nature and the notion of using them to control immunity is very new.

"GIFT15 can take your normal, run-of-the-mill B-cells and convert them -- in a Superman or Jekyll -Hyde sort of way -- into these super-powerful B-regulatory cells," Galipeau explained. "We can do that in a petri dish. We took normal B-cells from mice, and sprinkled GIFT15 on them, which led to this Jekyll and Hyde effect.

"And when we gave them back intravenously to mice ill with multiple sclerosis, the disease went away."

MS must be caught in its earliest stages, Galipeau cautioned, and clinical studies are needed to test the treatment's efficacy and safety in humans. No significant side-effects showed up in the mice, he said, and the treatment was fully effective with a single dose.

"It's easy to collect B-cells from a patient," he added. "It's just like donating blood. We purify them in the lab, treat them with GIFT15 in a petri dish, and give them back to the patient. That's what we did in mice, and that's what we believe we could do in people. It would be very easy to take the next step, it's just a question of finding the financial resources and partnerships to make this a reality."

Bipedal Humans Came Down From The Trees, Not Up From The Ground

ScienceDaily (Aug. 11, 2009) — A detailed examination of the wrist bones of several primate species challenges the notion that humans evolved their two-legged upright walking style from a knuckle-walking ancestor.

The same lines of evidence also suggest that knuckle-walking evolved at least two different times, making gorillas distinct from chimpanzees and bonobos.

"We have the most robust data I've ever seen on this topic," said Daniel Schmitt, a Duke University associate professor of evolutionary anthropology. "This model should cause everyone to re-evaluate what they've said before." A report on the findings will appear online during the week of Aug. 10 in the research journal Proceedings of the National Academy of Sciences.

The research, led by post-doctoral research associate Tracy Kivell, was supported by the Natural Sciences and Engineering Research Council in her native Canada, General Motors' Women in Science and Mathematics, and the University of Toronto, where Kivell did her Ph.D. work.

The debate over the origins of human bipedalism began during Charles Darwin's lifetime and continues vigorously to this day, commonly dividing into two competing models, the researchers explained.

One model "envisions the pre-human ancestor as a terrestrial knuckle-walker, a behavior frequently used by our closest living relatives, the African apes," they wrote in the PNAS report. The other model traces our two-legged walking to earlier tree-climbing, a mode of locomotion that is used by all living apes.

Supporters of the knuckle-walking origin think we and African apes evolved from a common knuckle walking ancestor. That connection, they contend, is still evident in wrist and hand bone features shared by African apes and by fossil and living humans.

But Kivell found otherwise when she began comparing juvenile and adult wrist bones of more than 100 chimps and bonobos, our closest living primate kin, with those of gorillas.

Significantly, two key features associated with knuckle walking were present in only 6 percent of the gorilla specimens she studied. But she found them in 96 percent of adult chimpanzees and 76 percent of bonobos. In all, she looked at specimens from 91 gorillas, 104 chimps and 43 bonobos.

Kivell and Schmitt suggested that one explanation for the absence of these features in gorillas is that they knuckle-walk in a fundamentally different way from chimps and bonobos. Gorillas stride with their arms and wrists extended straight down and locked in what Kivell called "columnar" stances that resemble how elephants walk. By contrast, chimps and bonobos walk more flexibly, "with their wrists in a bent position as opposed to being stacked-up," she said. "And with their wrists in bent positions there will be more stresses at those joints."

As a result, chimp and bonobo wrists have special features that gorillas lack -- little ridges and concavities that serve as "bony stops" to keep their wrists from over-bending. Gorillas don't need those, she added. "When we first got together to work on this study that (difference) really jumped out in living color," Schmitt said. "Then we sat down together and asked: 'What are the differences between them?' Schmitt said. "The answer is that chimps and bonobos spend a lot of time in the trees. And gorillas do not."

Chimpanzees and bonobos have a more extended-wrist way of knuckle-walking which gives them added stability on branches, the researchers concluded. In contrast, gorillas' "columnar" style of knuckle-walking is consistent with ground transport.

Indeed, "from what we know about knuckle-walking among wild populations, gorillas and adult chimpanzees will both knuckle-walk about 85 percent of the time that they're moving," Kivell said. "But chimpanzees and bonobos are more arboreal than gorillas. So they're doing a lot more of it in the trees."

Kivell and Schmitt think this suggests independent evolution of knuckle-walking behavior in the two African ape lineages.

Some scientists point to features in the human anatomy as our own vestiges of a knuckle-walking ancestry. One notable example is the fusion a two wrist bones that could provide us extra stability, a feature we share with gorillas, chimps and bonobos. But some lemurs have that feature too, and they do a variety of different movements in the trees but do not knuckle-walk, Kivell said.

Altogether, the evidence leans against the idea that our own bipedalism evolved from a knuckle-walking ancestor, the pair wrote. "Instead, our data support the opposite notion, that features of the hand and wrist found in the human fossil record that have traditionally been treated as indicators of knuckle-walking behavior in general are in fact evidence of arboreality."

In other words, a long-ago ancestor species that spent its time in the trees moved to the ground and began walking upright.

There are no fossils from the time of this transition, which likely occurred about seven million years ago, Kivell and Schmitt said. But none of the later fossils considered to be on the direct human line were knuckle-walkers.

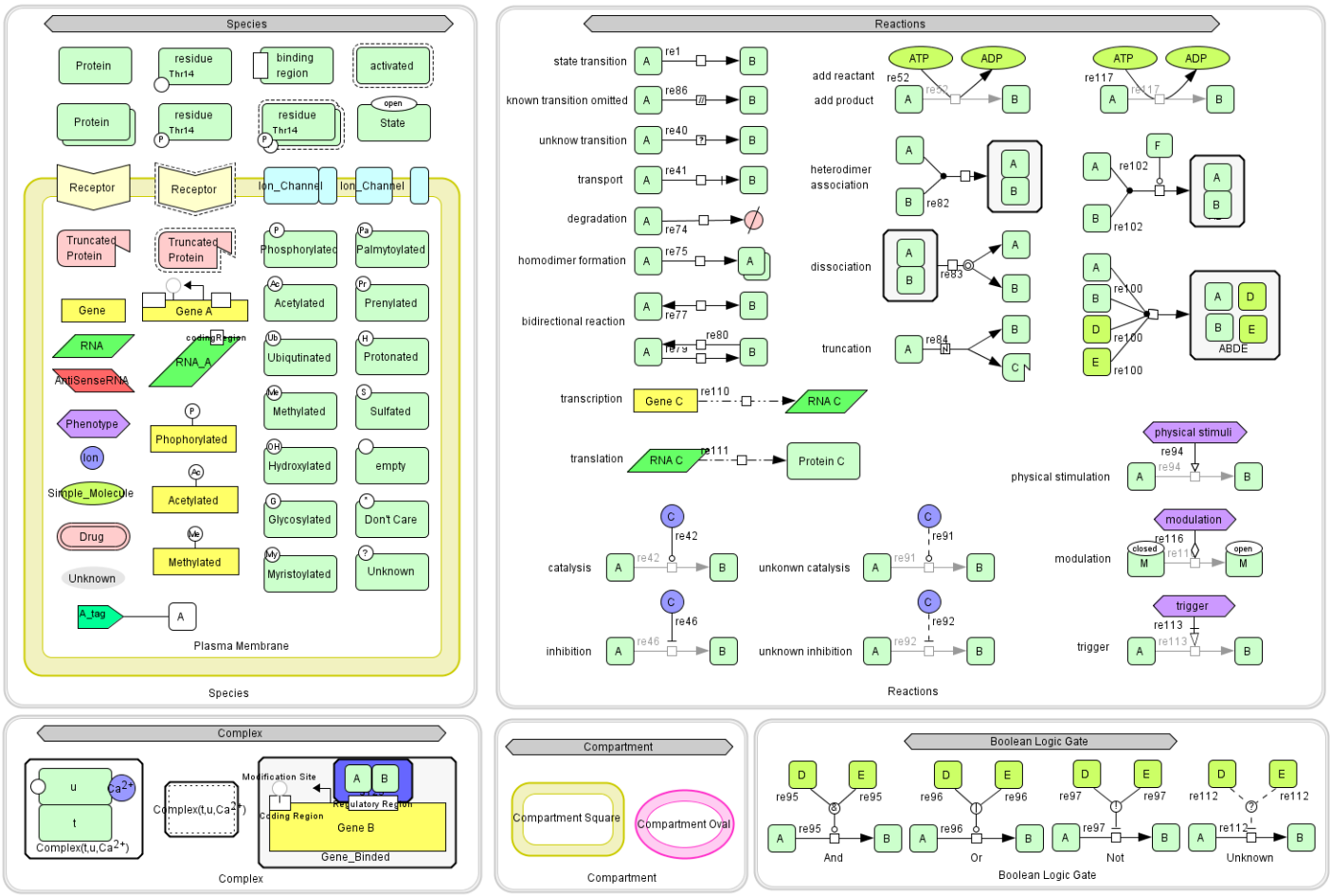
Caltech scientists help launch the first standard graphical notation for biology

Pasadena, Calif.—Researchers at the California Institute of Technology (Caltech) and their colleagues in 30 laboratories worldwide have released a new set of standards for graphically representing biological information —the biology equivalent of the circuit diagram in electronics. This visual language should make it easier to exchange complex information, so that biological models are depicted more accurately, consistently, and in a more readily understandable way.

The new standard, called the Systems Biology Graphical Notation (SBGN), was published in the August 8 issue of the journal Nature Biotechnology.

Researchers use standardized visual languages to communicate complex information in many scientific and engineering fields. A well-known example is the circuit diagram in electrical engineering. However, until now, biology lacked a standardized notation for describing biological interactions, pathways, and networks, even though the discipline is dominated by graphical information.

The SBGN project was launched in 2005 as a united effort to specifically develop a new graphical standard for molecular and systems-biology applications. The project, which was initiated by Hiroaki Kitano of the Systems Biology Institute in Tokyo, Japan, is coordinated by Nicolas Le Novère of the European Molecular Biology Laboratory's European Bioinformatics Institute in Cambridge, England, and senior research fellow Michael Hucka, codirector of the Biological Network Modeling Center at Caltech's Beckman Institute. The international team of researchers that created SBGN is composed of biochemists, modelers, and computer scientists, who developed the notation in collaboration with a broader community of researchers constituting the target user community.



"Engineers, architects, physicists, and software developers all have standard graphical notations for depicting the things they work on, which makes it possible for everyone in those fields to be on the same page, as it were," says Hucka. "I think SBGN represents the first truly broad-based attempt at establishing the same kind of standardization in biology."

SBGN will make it easier for biologists to understand each other's models and share network diagrams more easily, which, Hucka says, has never been more important than in today's era of high-throughput technologies

and large-scale network reconstruction efforts. A standard graphical notation will help researchers share this mass of data more efficiently and accurately, which will benefit systems biologists working on a variety of biochemical processes, including gene regulation, metabolism, and cellular signaling.

"Finally, and perhaps most excitingly," adds Hucka, "I believe that, just as happened with the engineering fields, SBGN will act as an enabler for the emergence of new industries devoted to the creation of software tools for working with SBGN, as well as its teaching and publication."

Previous graphical notations in biology have tended to be ambiguous, used in different ways by different researchers, and only suited to specific needs—for example, to represent metabolic networks or signaling pathways. Past efforts to create a more rigid notation failed to become accepted as a standard by the community. Hucka and his collaborators believe that SBGN should be more successful because it represents a more concerted effort to establish a standard by engaging many biologists, modelers, and software-tool developers. In fact, many of those involved in the SBGN effort are the same pioneers who proposed previous notations, demonstrating the degree to which they endorse SBGN as a new standard.

To ensure that this new visual language does not become too vast and complicated, the researchers decided to define three separate types of diagram, which describe molecular process, relationships between entities, and links among biochemical activities. These different types of diagrams complement each other by representing different "views" of the same information, presented in different ways for different purposes, but reusing most of the same graphical symbols. This approach reduces the complexity of any one type of diagram while broadening the range of what can be expressed about a given biological system.

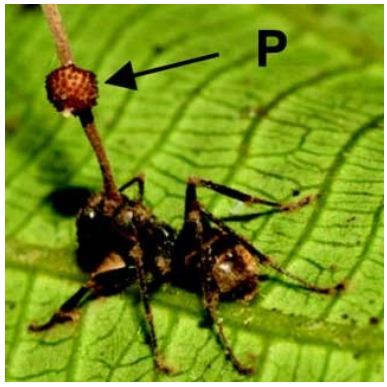
"As biology focuses more on managing complexity with quantitative and systematic methods, standards such as SBGN play an essential role. SBGN combines an intuitive notation with the rigorous style of engineering and math," says John Doyle, the John G. Braun Professor of Control and Dynamical Systems, Bioengineering, and Electrical Engineering at Caltech.

"As with SBML (the Systems Biology Markup Language), Mike and his collaborators have provided the kind of solid foundation that the whole community can build on. SBML has been a highly successful standardization effort for software interoperability, and SBGN is sure to have the same kind of impact on human communication in biology," Doyle adds.

The work at Caltech in the paper, "The Systems Biology Graphical Notation," was supported by the New Energy and Industrial Technology Development Organization and a Beckman Institute grant funding the Biological Network Modeling Center.

Parasite causes zombie ants to die in an ideal spot

A study in the September issue of The American Naturalist describes new details about a fungal parasite that coerces ants into dying in just the right spot - one that is ideal for the fungus to grow and reproduce. The study, led David P. Hughes of Harvard University, shows just how precisely the fungus manipulates the behavior of its hapless hosts.



ANT COLONIZED: A mature O. unilateralis growing from an ant it has killed a few weeks before. The "P" points out the perithecial plates where spores are released. **The American Naturalist/ University Of Chicago Press**

When a carpenter ant is infected by a fungus known as Ophiocordyceps unilateralis, the victim remains alive for a short time. The fungus, however, is firmly in the driver's seat. It compels the ant to climb from its nest high in the forest canopy down into small plants and saplings in the understory vegetation. The ant then climbs out onto the underside of a low-hanging leaf where it clamps down with its mandibles just before it dies. There it remains, stuck fast for weeks.

After the ant dies, the fungus continues to grow inside the body. After a few days, a stroma - the fungus's fruiting body - sprouts from the back of the ant's head. After a week or two, the stroma starts raining down spores to the forest floor below. Each spore has the potential to infect another unfortunate passerby.

Scientists have known for over one hundred years about this parasite's ghastly ability to turn unsuspecting ants into zombies. But Hughes and his colleagues chronicle the amazingly precise control the fungus has over its victim.

At a field site in a Thai forest, Hughes's team found that the infected carpenter ants are almost invariably found clamped onto the undersides of leaves that are 25 centimeters (about 10 inches) from the ground below. What's more, most of the dead ants were found on leaves sprouting from the northwest side of the plant. Interestingly, the researchers found that temperature, humidity and sunlight in these spots are apparently optimal for the fungus to grow and reproduce. When the researchers placed leaves with infected ants at higher locations, or on the forest floor, the parasite failed to develop properly.

"The fungus accurately manipulates the infected ants into dying where the parasite prefers to be, by making the ants travel a long way during the last hours of their lives," Hughes said.

But getting the ant to die in the right spot is only half the battle, as the researchers found when they dissected a few victims.

"The fungus has evolved a suite of novel strategies to retain possession of its precious resource," said Hughes.

As the fungus spreads within a dead ant's body, it converts the ant's innards into sugars which are used to help the fungus grow. But it leaves the muscles controlling the mandibles intact to make sure the ant keeps its death grip on the leaf. The fungus also preserves the ant's outer shell, growing into cracks and crevices to reinforce weak spots. In doing this, the fungus fashions a protective coating that keeps microbes and other fungi out. At that point, it can safely get down to the business of claiming new victims.

Carpenter ants apparently have few defenses against the fungus. The most important way they avoid infection seems to be staying as far away from victims as possible. That may be part of the reason why these ants make their nests in the forest canopy, high above fungal breeding zones. Carpenter ants also seem to avoid blazing their foraging trails under infected areas. This too might be an adaptive strategy to avoid infection, but more study is needed to confirm it, Hughes says.

The mechanisms and cues the fungus uses to control an ant's behavior remain unknown. "That is another research area we are actively pursuing right now," Hughes says. Whatever the mechanisms, this much is clear: O. unilateralis has evolved highly specialized abilities to get unsuspecting ants to do its bidding.

Sandra B. Andersen, Sylvia Gerritsma, Kalsum M. Yusah, David Mayntz, Nigel L. Hywel - Jones, Johan Billen, Jacobus J. Boomsma, and David P. Hughes, "The Life of a Dead Ant: The Expression of an Adaptive Extended Phenotype." The American Naturalist, September 2009.

Oxygen treatment hastens memory loss in Alzheimer's mice

Study has implications for postoperative elderly patients at risk for Alzheimer's disease

Tampa, FL - A 65-year-old women goes into the hospital for routine hip surgery. Six months later, she develops memory loss and is later diagnosed with Alzheimer's Disease. Just a coincidence? Researchers at the University of South Florida and Vanderbilt University don't think so. They suspect that the culprit precipitating Alzheimer's disease in the elderly women may be a routine administration of high concentrations of oxygen for several hours during, or following, surgery – a hypothesis borne out in a recent animal model study.

Dr. Gary Arendash of the Florida Alzheimer's Disease Research Center at USF and Dr. L. Jackson Roberts II at Vanderbilt University used mice genetically altered to develop abnormal levels of the protein beta amyloid, which deposits in the brain as plaques and eventually leads to Alzheimer's-like memory loss as the mice age. They found that young adult Alzheimer's mice exposed to 100-percent oxygen during several 3-hour sessions demonstrated substantial memory loss not otherwise present at their age. Young adult Alzheimer's mice exposed to normal air had no measurable memory loss, and neither did normal mice without any genetic predisposition for Alzheimer's disease.

The authors suggest that people genetically predisposed to Alzheimer's disease or with excessive amounts of beta amyloid in their brains are at increased risk of developing the disease earlier if they receive high concentrations of oxygen, known as hyperoxia. Their study is published online this month in NeuroReport.

"Although oxygen treatment beneficially increases the oxygen content of blood during or after major surgery, it also has several negative effects that we believe may trigger Alzheimer's symptoms in those destined to develop the disease," said USF neuroscientist Arendash, the study's lead author. "Our study suggests that the combination of brain beta amyloid and exposure to high concentrations of oxygen provides a perfect storm for speeding up the onset of memory loss associated with Alzheimer's Disease."

While postoperative confusion and memory problems are common and usually transient in elderly patients following surgery, some patients develop permanent Alzheimer's-like cognitive impairment that remains unexplained. Recent studies have indicated that general anesthesia administered during surgery may increase a patient's risk of Alzheimer's disease, but the laboratory studies did not use animals or people predisposed to develop the disease.

"Postoperative memory loss can be a fairly common and devastatingly irreversible problem in the elderly after major surgical procedures," said Roberts, an MD who holds an endowed chair in Pharmacology at Vanderbilt University School of Medicine. "There has been much speculation as to the cause of this memory loss, but the bottom line is that no one really knows why it happens. If all it takes to prevent this is reducing the exposure of patients to unnecessarily high concentrations of oxygen in the operating room, this would be a major contribution to geriatric medicine."

The USF-Vanderbilt study looked at 11 young adult mice genetically modified to develop memory problems as they aged, mimicking Alzheimer's disease. After behavioral tests confirmed the mice had not yet developed

memory impairment at age 3 months – about age 40 in human years – the researchers exposed half the Alzheimer's mice to 100-percent oxygen for three hours, three times over the next several months. The protocol was intended to replicate initial and supplemental exposures of elderly patients in hospital operating rooms and recovery suites to high concentrations of oxygen. The other half of the mice were exposed to 21-percent oxygen, the concentration of oxygen in typical room air.

When researchers retested the mice after the final gas exposure, they found that Alzheimer's mice exposed to 100-percent oxygen performed much worse on tests measuring their memory and thinking skills than the Alzheimer's mice exposed to normal room air. In fact, the Alzheimer's mice exposed to room air demonstrated no memory loss. Moreover, exposure of young adult mice without beta amyloid protein deposited in their brains to 100-percent oxygen did not adversely affect their memories. This is consistent with studies in humans showing that exposure of young adults to high concentrations of oxygen has no harmful effects on memory.

The researchers also demonstrated that even a single 3-hour exposure to 100-percent oxygen caused memory deficits in the Alzheimer's mice. Furthermore, when they examined the brains of these mice, they found dramatic increases in levels of isofurans, products of oxygen-induced damage from toxic free radicals. The increase was not present in the brains of normal control mice exposed to the single hyperoxia treatment.

How might high concentrations of oxygen hasten memory impairment in those destined to develop Alzheimer's disease? The researchers suggest the striking increase of isofurans during surgery may be one triggering mechanism, particularly in cardiac bypass surgery where very high blood oxygen levels are routinely attained and permanent memory loss often occurs months after the surgery. Secondly, exposure to high concentrations of oxygen prompts abnormal swelling of brain cell terminals that transmit chemical messages from one brain cell to another and may further disrupt already frayed nerve cell connections in those at risk for Alzheimer's. Third, high concentrations of oxygen combined with beta amyloid plaques constricts blood vessels and decreases blood flow to the brain more than either one alone.

The authors caution that the study in mice may or may not accurately reflect the effects of hyperoxia in human surgery patients.

"Nonetheless, our results call into question the wide use of unnecessarily high concentrations of oxygen during and/or following major surgery in the elderly," Roberts said. "These oxygen concentrations often far exceed that required to maintain normal hemoglobin saturation in elderly patients undergoing surgery."

Arendash published initial evidence in 1987 that Alzheimer's disease starts in the brain several decades before memory loss occurs. His research focuses on developing promising therapeutics in Alzheimer's mice that can quickly be transferred to human clinical trials. Roberts, an expert on the role of free radicals and oxidative injury in disease, has discovered novel products of free radical damage that may be associated with several age-related brain dysfunctions. Also participating in the hyperoxia study were Dr. Takashi Mori of Saitama Medical University (Japan) and Dr. Kenneth Hensley of the Oklahoma Medical Research Foundation.

The study was supported by grants within the Florida Alzheimer's Disease Research Center, a statewide project sponsored by the National Institute on Aging, and a National Institutes of Health Merit Award to Dr. Roberts.

Discovery may lead to powerful new therapy for asthma

Human clinical trials next for compounds that block key enzyme

GALVESTON, Texas — University of Texas Medical Branch at Galveston researchers have found that a single enzyme is apparently critical to most allergen-provoked asthma attacks — and that activity of the enzyme, known as aldose reductase, can be significantly reduced by compounds that have already undergone clinical trials as treatments for complications of diabetes.

The discovery, made in experiments conducted with mice and in human cell cultures, opens the way to human tests of a powerful new treatment for asthma, which today afflicts more than 20 million Americans. Such a development would provide a badly needed alternative to current asthma therapy, which primarily depends on hard-to-calibrate inhaled doses of corticosteroids and bronchodilators, which have a number of side effects.

"Oral administration of aldose reductase inhibitors works effectively in experimental animals," said UTMB professor Satish Srivastava, senior author of a paper on the discovery appearing in the Aug. 6 issue of the journal PLoS One. "If these drugs work as well in humans as they do in animals you could administer them either orally or in a single puff from an inhaler and get long-lasting results."

Srivastava and his colleagues (postdoctoral fellows Umesh Yadav and Leopoldo Aguilera-Aguirre, associate professor Kota Venkata Ramana, professor Istvan Boldogh and LSU Health Sciences Center assistant professor Hamid Boulares) focused on aldose reductase inhibition as a possible asthma therapy after establishing an essential role for the enzyme in other diseases also characterized by inflammation. In disorders such as colon cancer, atherosclerosis, sepsis and uveitis, the Srivastava team has found, cells are hit by a sudden overload of reactive oxygen species (varieties of oxygen and oxygen compounds that are especially eager to react with

other molecules). The result is a chain of biochemical reactions that leads the cells' genetic machinery to crank out a barrage of inflammatory signaling proteins. These summon immune system cells and generate even more reactive oxygen species, producing a vicious cycle of ever-increasing inflammation.

Aldose reductase plays an essential part in the activation of the cellular machinery that produces inflammatory proteins in these diseases, the Srivastava group discovered. "We found that if you block aldose reductase, you block the inflammation," Srivastava said. "Now, asthma, a chronic disease of inflammation is augmented by reactive oxygen species. So we thought, why not find out if aldose reductase inhibition also has an effect on asthma?"

In an initial series of in vitro experiments, the researchers applied ragweed pollen extract (ragweed pollen is notorious for provoking the allergic reactions that lead to allergies and asthmatic airway inflammation) to cultures of human airway epithelial cells —the cells that line the network of air passages within the lungs. Some of the cultures had been pretreated with an aldose reductase inhibitor, while others had not.

The untreated cells responded in much the same way airway cells do in an asthma attack, with an increased rate of apoptosis (cell suicide), a jump in the levels of reactive oxygen species, the activation of key "transcription factors" that kick-start the production of inflammatory proteins and the large-scale generation of a whole host of molecules associated with inflammation. Cells treated with aldose reductase inhibitors, by contrast, had a much lower rate of apoptosis, reduced levels of reactive oxygen species, far smaller increases in critical transcription factors and substantially lower increases in inflammatory signaling molecules.

In collaboration with Boldogh, Srivastava next investigated whether aldose reductase inhibitors could reduce the asthma-like symptoms of mice exposed to ragweed extract, a well-established clinical model mimicking the allergic airway inflammation that commonly leads to asthma in humans. When untreated mice inhaled ragweed extract, their lungs suffered an influx of eosinophils (inflammation-inducing white blood cells), a jump in inflammatory signaling molecules, a buildup of mucin (a protein component of mucus) and an increase in airway hyper-reactivity (the tendency of air passages to suddenly constrict under stress). Mice fed a dose of aldose reductase inhibitor before inhaling ragweed extract, however, showed dramatically reduced levels of these components of the asthmatic response.

"Our hypothesis performed exactly as expected, with the experiments showing that aldose reductase is an essential enzyme in the transduction pathways that cause the transcription of the cytokines and chemokines known to act in asthma pathogenesis," Srivastava said. "They attract eosinophils and cause inflammation and mucin production in the airway."

The next step, Srivastava said, will be clinical trials to determine whether aldose reductase inhibitors can relieve asthma in humans. The researcher expressed optimism about their potential outcome of the trials, as well as gratitude to the UTMB National Institute of Environmental Health Sciences Center and the sole supporter of his asthma work, the American Asthma Foundation, which last year awarded him a three-year $750,000 research grant.

"Really, a lot of the credit for this belongs to the AAF," Srivastava said. "Our primary interest is in cancer and the secondary complications of diabetes, but we were attracted to asthma pathogenesis because the AAF invited me to apply for a grant. I think they're going to be happy with the results."

Five-Second Touch Can Convey Specific Emotion, Study Finds

By NICHOLAS BAKALAR

Researchers have found experimental evidence that a touch can be worth a thousand words, that fleeting physical contact can express specific emotions — silently, subtly and unmistakably.

Scientists led by Matthew J. Hertenstein, an associate professor of psychology at DePauw University, recruited 248 students, each to touch or be touched by a partner previously unknown to them to try to communicate a specific emotion: anger, fear, happiness, sadness, disgust, love, gratitude or sympathy.

The person touched was blindfolded and ignorant of the sex of the toucher, who was instructed to try to convey one of the eight emotions, and both participants remained silent. Forty-four women and 31 men touched a female partner, while 25 men and 24 women touched a male partner.

Afterward, each person touched was given the list of eight emotions and told to pick the one conveyed. There was also a ninth choice, “none of these terms are correct,” to eliminate the possibility of forcing a choice of emotion when none were truly felt.

The touchers were instructed to touch any appropriate part of the body, and they chose variously to touch the head, face, arms, hands, shoulders, trunk and back.

Accurate understanding ranged from 50 percent to 78 percent, much higher than the 11 percent expected by chance and comparable to rates seen in studies of verbal and facial emotion.

The researchers also recorded a complex vocabulary of touch — a shake, a rub, a pat or a squeeze, small changes in the amount of pressure applied, variations in the abruptness of the stroke, changing rates at which the fingers moved across the skin, and differences in the location and duration of the contact.

Tiffany Field, director of the Touch Research Institute at the University of Miami, was impressed with the work. “This information is very interesting, and does add to the science of emotion and communication.”

But, she continued: “It’s unlikely we’d use touching as a means of expression with strangers. It’s reserved to intimate kinds of interactions.”

Dr. Field was not involved in the study, which will appear in the August issue of the journal Emotion.

Participants consistently chose certain kinds of touch to convey specific emotions. They often expressed fear, for example, by holding and squeezing with no movement, while sympathy required holding, patting and rubbing.

Men and women were equally adept at interpreting touch but used different actions to communicate emotions. Men rarely touched anyone’s face, and then only to express anger or disgust at women, and sympathy for other men. Women, on the other hand, touched faces frequently to express anger, sadness and disgust to both sexes, and to convey fear and happiness to men.

The evolutionary reasons for such a communication system are unknown, but the authors suggest that they may have the same origin as the social grooming rituals of other primates. The authors acknowledge that their data were limited to a sample of young Americans, and that cultural differences may play an important role.

Still, Dr. Hertenstein said: “These findings have strong implications for the power of touch. Most touches were only about five seconds, but in these fleeting moments, we’re capable of communicating distinct emotions, just as we are with the face. This is a sophisticated differential signaling system that we haven’t previously known about.”

Giant 'meat-eating' plant found

Matt Walker Editor, Earth News

A new species of giant carnivorous plant has been discovered in the highlands of the central Philippines.

The pitcher plant is among the largest of all pitchers and is so big that it can catch rats as well as insects in its leafy trap.

During the same expedition, botanists also came across strange pink ferns and blue mushrooms they could not identify.

The botanists have named the pitcher plant after British natural history broadcaster David Attenborough.

They published details of the discovery in the Botanical Journal of the Linnean Society earlier this year.

Word that this new species of pitcher plant existed initially came from two Christian missionaries who in 2000 attempted to scale Mount Victoria, a rarely visited peak in central Palawan in the Philippines.

The newly discovered giant pitcher (Nepenthes attenboroughii)

With little preparation, the missionaries attempted to climb the mountain but became lost for 13 days before being rescued from the slopes.

On their return, they described seeing a large carnivorous pitcher plant.

That pricked the interest of natural history explorer Stewart McPherson of Red Fern Natural History Productions based in Poole, Dorset, UK and independent botanist Alastair Robinson, formerly of the University of Cambridge, UK and Volker Heinrich, of **Bukidnon** Province, the Philippines.

All three are pitcher plant experts, having travelled to remote locations in the search for new species.

So in 2007, they set off on a two-month expedition to the Philippines, which included an attempt at scaling Mount Victoria to find this exotic new plant.

Accompanied by three guides, the team hiked through lowland forest, finding large stands of a pitcher plant known to science called Nepenthes philippinensis , as well as strange pink ferns and blue mushrooms which they could not identify.

As they closed in on the summit, the forest thinned until eventually they were walking among scrub and large boulders. “ At around 1,600 metres above sea level, we suddenly saw one great pitcher plant, then a second, then many more," McPherson recounts. "It was immediately apparent that the plant we had found was not a known species."

Pitcher plants are carnivorous. Carnivorous plants come in many forms, and are known to have independently evolved at least six separate times. While some have sticky surfaces that act like flypaper, others like the Venus fly trap are snap traps, closing their leaves around their prey.

Pitchers create tube-like leaf structures into which insects and other small animals tumble and become trapped.

The team has placed type specimens of the new species in the herbarium of the Palawan State University, and have named the plant Nepenthes attenboroughii after broadcaster and natural historian David Attenborough.

"The plant is among the largest of all carnivorous plant species and produces spectacular traps as large as other species which catch not only insects, but also rodents as large as rats," says McPherson.

The pitcher plant does not appear to grow in large numbers, but McPherson hopes the remote, inaccessible mountain-top location, which has only been climbed a handful of times, will help prevent poachers from reaching it.

During the expedition, the team also encountered another pitcher, Nepenthes deaniana, which had not been seen in the wild for 100 years. The only known existing specimens of the species were lost in a herbarium fire in 1945.

On the way down the mountain, the team also came across a striking new species of sundew, a type of sticky trap plant, which they are in the process of formally describing.

Thought to be a member of the genus Drosera , the sundew produces striking large, semi-erect leaves which form a globe of blood red foliage.

'Alien scene' of tadpoles' feast

By Rebecca Morelle Science reporter, BBC News

"Alien-like" scenes of tadpoles feasting on eggs emerging from their mother have been caught on camera.

The footage marks the success of a captive breeding programme for the critically endangered mountain chicken frog, one of the world's largest frogs.

In April, 50 of the amphibian giants were airlifted from Montserrat after a deadly fungus swept through the island, devastating the population.

Now several breeding programmes are under way to save the frogs.

Once numbers have been boosted in captivity, researchers hope to reintroduce the frogs back into the wild within the next two years.

'Alien-like' tadpole feeding frenzy

Bizarre sight

The remarkable footage was recorded at the Durrell Wildlife Conservation Trust, in Jersey, which took in 12 of the rescued frogs. Twenty-six others went to Parken Zoo in Sweden, and 12 are now housed in ZSL London Zoo.

So far, four pairs of mountain chicken frogs have started to breed - which could result in hundreds of frogs. And this has given researchers an insight into the way that these unusual amphibians care for their offspring.

Professor John Fa, director of Durrell, said: "Mountain chickens have very peculiar breeding habits because they form foam nests in burrows in the ground."

The females lay their eggs in these nests, which eventually hatch into tadpoles. But as the nests are underground, food is scarce - so the frogs need to find a way to provide nutrition for their young.

Professor Fa explained: "In the case of mountain chickens, we have discovered that the female comes into the nest and starts laying a string of infertile eggs.

"We thought that the eggs would come out and drop to the bottom of the nest and then the tadpoles would start eating them. But the footage shows about 40 tadpoles congregating around the female and eating the eggs as they come out of the female's body. "Every now and again, the female uses her back legs to push the tadpoles away from her body so another set can come up and eat as much as they can."

He added: "It is really weird - it is an alien scene. This is the first time we have caught this on film."

Frog killer

The mountain chicken frog (Leptodactylus fallax) is one of the world's most threatened frogs. The frog is so called because its meat tastes like chicken. It was once found on seven Caribbean Islands, but thanks to hunting and environmental pressures it is currently found only on Montserrat and Dominica.

Now, however, the deadly chytrid fungus, which has devastated amphibian populations around the globe, has also ravaged Dominica's mountain chickens. The fungus was first detected on the island in 2002, and within 15 months, 80% of the mountain chicken population had been obliterated.

Conservationists were extremely concerned when they found that the chytrid fungus had spread to Montserrat earlier this year, and was sweeping quickly through the last mountain chicken population.

The team made a decision to airlift some of the last healthy frogs and bring them into captivity in a bid to save the creatures from extinction.

Professor Fa said: "Things are not going terribly well in Montserrat because chytrid has now infected the safe population - or at least the one we thought was safe."

The breeding success has offered scientists a ray of hope in an otherwise bleak situation, and they are now concentrating on increasing the frogs' numbers. They hope to eventually release the captive mountain chickens back to their native home of Montserrat, and are currently looking for sites that are free of the deadly fungus.

But Professor Fa said: "If that doesn't work, if the area is infected, we will have to think again, and it could be that we take the animals to another island. "Within a year or two we have to get these animals back to the wild. The longer you keep them in captivity, the more difficult it is for them to enjoy a life in the wild again."

Do Single Women Seek Attached Men?

By John Tierney

Researchers have debated for years whether men or women are likelier to engage in “mate poaching.” Some surveys indicated that men had a stronger tendency to go after other people’s partners, but was that just because men were more likely to admit engaging in this behavior? Now there’s experimental evidence that single women are particularly drawn to other people’s partners, according to a report in the Journal of Experimental Social Psychology by two social psychologists, Melissa Burkley and Jessica Parker of Oklahoma State University.

Noting that single women often complain that “all the good men are taken,” the psychologists wondered if “this perception is really based on the fact that taken men are perceived as good.” To investigate, the researchers quizzed male and female undergraduates - some involved in romantic relationships, some unattached - about their ideal romantic partner.

Next, each of the experimental subjects was told that he or she had been matched by a computer with a like-minded partner, and each was shown a photo of an attractive person of the opposite sex. (All the women saw the same photo, as did all the men.) Half of the subjects were told that their match was already romantically involved with someone else, while the other half were told that their match was unattached. Then the subjects were all asked how interested they were in their match.

To the men in the experiment, and to the women who were already in relationships, it didn’t make a significant difference whether their match was single or attached. But single women showed a distinct preference for mate poaching. When the man was described as unattached, 59 percent of the single women were interested in pursuing him. When that same man was described as being in a committed relationship, 90 percent were interested. The researchers write:

According to a recent poll, most women who engage in mate poaching do not think the attached status of the target played a role in their poaching decision, but our study shows this belief to be false. Single women in this study were significantly more interested in the target when he was attached. This may be because an attached man has demonstrated his ability to commit and in some ways his qualities have already been ‘‘pre-screened” by another woman.

Well, that makes sense. But I asked Dr. Burkley, a professor of social psychology at Oklahoma State, if the correlation could also be due to another factor at work in some women: fear of intimacy. Could their interest in unavailable guys be what was keeping them single in the first place?

Maybe, Dr. Burkley replied. “There are many possible explanations for our results,” she told me, “and future research needs to identify exactly why single women prefer taken men. Our lab is currently conducting studies to try and tease apart the different potential explanations for our findings, but your explanation seems quite plausible.” What’s your explanation? And do you have any data — anecdotal or otherwise — to offer?

Stanford researchers call for drug labels to disclose lack of comparison with existing medications

STANFORD, Calif. — The labeling information that comes with prescription drugs tells you what's known about the medication, but researchers from the Stanford University School of Medicine think it's high time that the labeling tell you what isn't known.

The researchers want the U.S. Food and Drug Administration to require drug manufacturers to state how new medications compare with similar, existing treatments. In many instance, these statements would indicate

that there is no evidence that a new drug is more effective than older ones. They believe this information would make patients and health-care insurers less likely to pay for newer treatments without evidence that they lead to improved patient outcomes. It would also spur drug and medical-device companies to design more informative clinical trials to test a new product's superiority over existing therapies.

"Drug and device manufacturers benefit from an unacknowledged information gap that develops as more and more products are tested against placebo, but not each other," said Randall Stafford, MD, PhD, associate professor of medicine at the Stanford Prevention Research Center.

Stafford is the lead author of an essay that will be published online Aug. 12 in the New England Journal of Medicine, calling on the FDA to require more informative labeling of new drugs and medical devices. His co-authors are Philip Lavori, PhD, professor of health research and policy, and Todd Wagner, PhD, health economist at the Veterans Affairs Palo Alto Health Care System and consulting assistant professor of health research and policy at the medical school.

The researchers note that the FDA doesn't require the inclusion of statements regarding how a new drug or device compares with existing treatments. Instead, treatments are simply required to perform better than a placebo without harmful side effects. "The problem is that the public, including physicians, often view FDA approval as constituting more than it does," Stafford said. "There's an inherent tendency for physicians and patients to want the newest thing and to assume that newer and more expensive means better, although this is often not the case."

That would be fine if the new drugs were the same price as those already on the market, but new therapies "are almost always more costly than previously approved treatments, particularly so when existing drugs are available in generic form," the essay says.

The public's appetite for the latest drugs might be curbed if patients understood that new treatments aren't necessarily more effective than existing ones. The Stanford researchers recommend that the FDA require new treatments to carry a label that would read, for instance: "Although this drug has been shown to lower blood pressure more effectively than placebo, it has not been shown to be more effective than other members of the same drug class."

While some might argue that the FDA's primary role is informing the public about the safety of drugs and devices, the researchers believe that developing more informative labels is consistent with the agency's recently invigorated function as a public health agency.

Do high-fat diets make us stupid and lazy?

New research in the FASEB Journal shows that high-fat diets are just as unhealthful in the short term as they are in the long term

Short-term memory getting worse? Exercise getting harder? Examine your diet. New research published online in The FASEB Journal (http://www.fasebj.org) showed that in less than 10 days of eating a high-fat diet, rats had a decreased ability to exercise and experienced significant short-term memory loss. These results show an important link between what we eat, how we think, and how our bodies perform.

"Western diets are typically high in fat and are associated with long-term complications, such as obesity, diabetes, and heart failure, yet the short-term consequences of such diets have been given relatively little attention," said Andrew Murray, co-author of the study and currently at the University of Cambridge in the United Kingdom. "We hope that the findings of our study will help people to think seriously about reducing the fat content of their daily food intake to the immediate benefit of their general health, well-being, and alertness."

Murray and colleagues studied rats fed a low-fat diet (7.5 percent of calories as fat) and rats fed a high-fat diet (55 percent of calories as fat). The researchers discovered that the muscles of the rats eating the high-fat diet for four days were less able to use oxygen to make the energy needed to exercise, causing their hearts to worker harder - and increase in size. After nine days on a high-fat diet, the rats took longer to complete a maze and made more mistakes in the process than their low-fat-diet counterparts. Researchers then investigated the cellular causes of these problems, particularly in the mitochondria of muscle cells. They found increased levels of a protein called uncoupling protein 3, which made them less efficient at using oxygen needed to make the energy required for running.

"It's nothing short of a high-fat hangover," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. "A long weekend spent eating hotdogs, French fries, and pizza in Orlando might be a great treat for our taste buds, but they might send our muscles and brains out to lunch."

Parental influences differ in determining child's later academic success

CHAMPAIGN, Ill. – Mothers and fathers play different roles and make different contributions to a child's upbringing, but a father's influence upon a child's academic success later in life is felt the most when he's involved from the very beginning, says a University of Illinois expert in early childhood education.

While a mother's involvement in school was found to be positively related to a child's academic achievement, a father's involvement was found to be negatively related to later student achievement, according to Brent McBride, a professor of human development at Illinois.

When it comes to schooling, fathers are typically only summoned late in the game when the light is blinking red – "when the child is going to flunk, is going to get expelled, is getting held back or is exhibiting a behavior problem, which would account for the negative relationship," McBride said.

"Men typically don't become engaged in the school process until there's a problem. Then you have the big conference where both parents come in, sit down and sort everything out."

But if a father hasn't engaged with a child before they go off to school, "there's even less likelihood he's going to be engaged even when there is a problem in school," McBride said.

"That's why it's not hard to understand why men don't become involved in the school process that much, because they're not involved early on in the process."

According to McBride, there's a clear relationship between what fathers do early in a child's life and how much they're involved once their child goes off to school.

"If fathers establish early on that they're going to actively engage in the parenting process," he said, "they're much more likely to continue that engagement as they grow older."

Along with establishing a model for themselves, fathers who are devoted participants in their child's early years are also setting up expectations within the family unit that their partners see "as active engagement in the child's life," McBride said. "And when the child sees that, they grow to expect it. They know that Daddy wants to be involved, and respond to it."

McBride, who also is the director of the university's Child Development Laboratory, believes one of the reasons men have trouble having adjusting to the role of father is because fatherhood is, in some ways, less scripted than motherhood.

"If you're not used to being around children, or you don't understand how children develop, parenting may seem awkward and even somewhat intimidating," he said. "We need to help fathers realize that what they do is really important. If we wait and only get fathers involved when kids are having problems in school, that's too late."

Fathers and father figures, McBride says, can have at least as much of a unique impact on a child as mothers do, and therefore should be seen as co-equal partners in parenting.

"We shouldn't forget about what men are doing in the family constellation," he said. "When we talk about arenas or domains that have typically been the mother's expertise, we are too quick to dismiss the father as having any impact at all. It's important when we talk about issues of early parenting that we not to get locked into the 'parents equals mothers' mindset."

One of the keys to changing that mindset is working with service providers – teachers, social service workers and daycare workers – to change their perception of fathers.

"We have to work with service providers so that they recognize that if they want to get men more engaged in the process, which most professionals would concur with, then let's focus on getting them engaged from day one of a child's life," McBride said.

Typically, when children are sick, there's a "high probability that daycare or school will call the mother and not the father first," he said. Not necessarily because the mother is better informed about the child's health, McBride said, but because "that's how they're socialized to think, that Mom is the only one who can respond in that situation."

"It's a totally different mindset, one where Mommy isn't necessarily called first when something goes wrong. But they're the key to really having an effect and changing what goes on in families." McBride said these analyses suggest that we need to think more about men, fatherhood and what role they play as parents.

"We need to look at the bigger picture, because these analyses all point to the same conclusion: that men and women each contribute uniquely to child outcomes," he said. "Any chance we get to help men discover what fatherhood really means to them and give them a model toward that engagement."

The results of McBride's research were published in an article titled "The Differential Impact of Early Father and Mother Involvement on Later Student Achievement" in the May 2009 issue of the Journal of Educational Psychology.

McBride's co-authors were U. of I. students W. Justin Dyer and Ying Liu, and Geoffrey L. Brown, of the University of North Carolina at Chapel Hill.

Funding was provided by the National Science Foundation and the American Educational Research Association.

Carnitine supplements reverse glucose intolerance in animals

DURHAM, N.C. – Supplementing obese rats with the nutrient carnitine helps the animals to clear the extra sugar in their blood, something they had trouble doing on their own, researchers at Duke University Medical Center report.

A team led by Deborah Muoio (Moo-ee-oo), Ph.D., of the Duke Sarah W. Stedman Nutrition and Metabolism Center, also performed tests on human muscle cells that showed supplementing with carnitine might help older people with prediabetes, diabetes, and other disorders that make glucose (sugar) metabolism difficult.

Carnitine is made in the liver and recycled by the kidney, but in some cases when this is insufficient, dietary carnitine from red meat and other animal foods can compensate for the shortfall.

The study is published in the Aug. 21 issue of the Journal of Biological Chemistry.

After just eight weeks of supplementation with carnitine, the obese rats restored their cells' fuel- burning capacity (which was shut down by a lack of natural carnitine) and improved their glucose tolerance, a health outcome that indicates a lower risk of diabetes.

These results offer hope for a new therapeutic option for people with glucose intolerance, older people, people with kidney disease, and those with type 2 diabetes (what used to be called adult-onset diabetes).

Muoio said that soon her team of researchers will begin a small clinical trial of carnitine supplementation in people who fit the profile of those who might benefit from additional carnitine – older people (60 to 80 years) with glucose intolerance.

The Duke researchers began studying carnitine more closely when abnormalities in the nutrient emerged from blood chemistry profiles of obese and old animals. These chemical profiles report on hundreds of byproducts of cell metabolism called metabolites and give scientists an opportunity to identify markers of disease states.

Carnitine is a natural compound known for helping fatty acids enter the mitochondria, the powerhouses of cells, where fatty acids are "burned" to give cells energy for their various tasks. Carnitine also helps move excess fuel from cells into the circulating blood, which then redistributes this energy source to needier organs or to the kidneys for removal. These processes occur through the formation of acylcarnitine molecules, energy molecules that can cross membrane barriers that encase all cells.

Researchers at Duke had observed that skeletal muscle of obese rats produced high amounts of the acylcarnitines, which requires free carnitine. As these molecules started to accumulate, the availability of free, unprocessed carnitine decreased. This imbalance was linked to fuel-burning problems, that is, impairments in the cells' combustion of both fat and glucose fuel.

"We suspected that persistent increases in acylcarnitines in the rats were causing problems, and we could also see that the availability of free carnitine was decreasing with weight gain and aging," said Muoio. "It appeared that carnitine could no longer do its job when chronic metabolic disruptions were stressing the system. That's when we designed an experiment to add extra carnitine to the rats' diet."

Muoio is also a professor in the departments of medicine, pharmacology and cancer biology.

Other study authors included Robert C. Noland, Sarah E. Seiler, Helen Lum, Olga Ilkayeva, Robert Stevens, and Timothy R. Koves of the Sarah W. Stedman Nutrition and Metabolism Center. Koves is also with the Duke Department of Medicine. Robert M. Lust is with the Department of Physiology at East Carolina University in Greenville, N.C., and Fausto G. Hegardt is with the CIBER division Fisiopatología de la Obesidad y la Nutrición of the Instituto de Salud Carlos III in Spain.

The work was supported by grants from the National Institutes of Health, and the American Diabetes Association, and a John A. Hartford Duke Center for Excellence Award.

Worth the effort? Not if you're depressed

New research indicates that decreased cravings for pleasure may be at the root of a core symptom of major depressive disorder. The research is in contrast to the long-held notion that those suffering from depression lack the ability to enjoy rewards, rather than the desire to seek them.

The research, led by Vanderbilt psychologists Michael Treadway and David Zald, was published Aug. 12 by the online journal PLoS One.

"This initial study shows that decreased reward processing, which is a core symptom of depression, is specifically related to a reduced willingness to work for a reward," Treadway, a graduate student in psychology, said.

Decreased motivation to seek and experience pleasurable experiences, known as anhedonia, is a primary symptom of major depressive disorder. Anhedonia is less responsive to many antidepressants and often persists after other symptoms of depression subside. However, understanding the different components of anhedonia - the desire to obtain something pleasurable versus experiencing pleasure - has been difficult for researchers to determine in humans.

"In the last decade and a half, animal models have found that the neurotransmitter dopamine, long known to be involved in reward processing, is involved in craving or motivation, but not necessarily enjoyment," Treadway said. "To date, research into reward processing in individuals with anhedonia has focused on enjoyment of rewards, rather than assessing the drive to work for them. We think this task is one of the first to do that."

Treadway and his colleagues devised the Effort-Expenditure for Rewards Task, or EEfRT, to explore the role of reduced desire and motivation in individuals reporting symptoms of anhedonia. EEfRT involved having individuals play a simple video game that gave them a chance to choose between two different tasks, one hard, one difficult, to obtain monetary rewards. Participants were eligible but not guaranteed to receive money each time they completed a task successfully.

The "hard" task required pressing a button 100 times within 21 seconds using one's non-dominant little finger and carried a potentially higher reward than the easy task, which required pressing a button 30 times in seven seconds using one's dominant index finger. The subjects were told at the beginning of each trial whether they had a high, medium or low probability of winning a prize if they successfully completed the trial. The participants could choose which trials they completed and were given 20 minutes to perform as many tasks as possible.

The researchers found that subjects who reported symptoms consistent with anhedonia where less willing to make choices requiring greater effort in exchange for greater reward, particularly when the rewards were uncertain.

"Consistent with our hypotheses, we found that individuals with self-reported anhedonia made fewer hard-task choices," the authors wrote. "These findings are consistent with theoretical models linking anhedonia to decreased (dopamine levels)."

"By addressing the motivational dimension of anhedonia, our findings suggest a plausible theoretical connection between dopamine deficiency and reward processing in depression, which may eventually help us better understand how anhedonia responds to treatment," Treadway said.

Zald is an associate professor of psychology. Treadway and Zald's co-authors were Joshua W. Buckholtz, a Vanderbilt doctoral student in neuroscience, Ashley Schwartzmann, research analyst, and Warren Lambert, a research associate in the Department of Special Education and at the Vanderbilt Kennedy Center for Research on Human Development.

Funding from Vanderbilt University and the National Institute on Drug Abuse supported the research.

Seafood gave us the edge on the Neanderthals

* 14:14 12 August 2009 **by Ewen Callaway**

If Neanderthals ever shared a Thanksgiving feast with Homo sapiens, the two species may have had trouble settling on a menu.

Chemical signatures locked into bone suggest the Neanderthals got the bulk of their protein from large game, such as mammoths, bison and reindeer. The anatomically modern humans that were living alongside them had more diverse tastes. As well as big game, they also had a liking for smaller mammals, fish and seafood.

"It seems modern humans had a much broader diet, in terms of using fish or aquatic birds, which Neanderthals didn't seem to do," says Michael Richards, a biological anthropologist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany and the University of British Columbia in Canada.

Prehistoric menu

Such dietary differences could have played a role in the extinction of Neanderthals roughly 24,000 years ago.

"I personally think [Neanderthals] were out-competed by modern humans," says Richards. "Modern humans moved in with different, more advanced technology and the ability to consume a wider variety of foods, and just replaced them."

He and colleague Erik Trinkaus at Washington University in St Louis, Missouri, compiled chemical measurements taken from bone collagen protein belonging to 13 Neanderthals and 13 modern humans, all recovered in Europe. They also added data collected from a 40,000-year-old human recovered in Romania's Oase cave.

Because our bones are constantly destroyed and rebuilt while we are alive, the atoms that make up collagen hold a record of what we've eaten. "When you take a sample of a bone you're getting all those breakfasts, lunches and dinners for 20 years," Richards says.

Telltale atoms

Measurements of the abundance of heavy isotopes of carbon and nitrogen hold the key. Marine environments contain a higher proportion of heavy carbon atoms (carbon-13) than land ecosystems, so lots of carbon-13 in the recovered collagen points to a seafood diet. Meanwhile, heavy nitrogen (nitrogen-15) tends to build up as the atom moves up the food chain, from plants to herbivores to carnivores.

High levels of heavy nitrogen can also come from a diet with lots of freshwater fish. Aquatic food webs tend to contain more steps than terrestrial ecosystems, so large fish often have higher levels of heavy nitrogen than land predators.

By comparing the relative levels of these isotopes with those of animals found nearby, researchers can sketch the broad outlines of an ancient diet, if not every last calorie.

Carbon and nitrogen isotopes suggest that Neanderthals living between 37,000 and 120,000 years ago in what are now France, Germany, Belgium and Croatia got the bulk of their protein from large land herbivores, Richards and Trinkaus conclude. Levels of heavy nitrogen in Neanderthal bones invariably exceed levels in surrounding herbivores, and tend to match levels in that period's carnivores, such as hyenas.

Some modern humans living between 27,000 and 40,000 years ago opted for more varied diets. High levels of carbon-13 in two samples from Italy and France are evidence for a diet that probably included some marine fish or seafood.

Even other modern humans from a similar period that lived further inland seem to have enjoyed a more diverse menu. Unusually high levels of nitrogen-15 in their bones point to freshwater fish as an important source of food, Richards says.

Variety pays off

Such flexibility may explain why modern humans thrived in ancient Europe while Neanderthals perished, says Hervé Bocherens, a biological anthropologist at the University of Tübingen in Germany. "If modern humans were hunting big game, like Neanderthals, they would compete with them and deplete the resources."

When big game were scarce, modern humans could have survived and even flourished by eating fish and smaller animals. Neanderthal populations, by contrast, probably shrank and eventually disappeared in areas from which their more limited meal options disappeared.

However, Bocherens cautions against drawing too many conclusions from 13 Neanderthal skeletons, all unearthed in northern Europe. Collagen doesn't survive well in warmer climates, so researchers know less about the diet of Neanderthals in southern Europe and the Middle East, he says.

"There is evidence from a number of southern European sites in Portugal, Gibraltar, Spain and Italy that Neanderthals did exploit marine resources at times and, I would say, probably to a significant extent," says Chris Stringer, a palaeoanthropologist at the Natural History Museum in London. His team recently found cut marks on seal and dolphin bones in a Neanderthal cave in Gibraltar.

Palatable veg

Isotopes recovered from bone also ignore important sources of food that don't contain much protein. "I'm sure they're having vegetables," says Richards. "But they're not eating enough that it's being measured."

A new study of ancient DNA offers preliminary support for that conclusion. Neanderthals possessed a gene mutation that would have meant they couldn't taste bitter chemicals found in many plants.

There has been speculation that this mutation, which occurs in a taste receptor gene called TAS2R38, is beneficial to humans because it makes vitamin-packed vegetables more palatable. It probably arose in the common ancestor of modern humans and Neanderthals more than a million years ago. The gene encodes a receptor that detects a chemical called phenylthiocarbamide, which is closely related to compounds produced by broccoli, cabbage and Brussels sprouts.

If vegetables weren't part of the Neanderthal diet, the species would probably have lost the non-tasting mutation, says Carles Lalueza-Fox, a geneticist at the Institute of Biological Evolution in Barcelona, Spain, whose team sequenced TAS2R38 in 39,000-year-old DNA from a Neanderthal femur recovered in the El Sidrón cave in north-west Spain.

This Neanderthal's DNA tested positive for tasting and non-tasting versions of TAS2R38, suggesting he or she boasted copies of both alleles of the gene – and with it the ability to taste bitter foods. The presence of the non-tasting allele in this individual suggests it may have been beneficial to some Neanderthals.

"It doesn't mean they were eating Brussels sprouts or cabbage but it could be similar vegetables," Lalueza-Fox says.

Journal references: Proceedings of the National Academy of Sciences, DOI: 10.1073/pnas.0903821106
Biology Letters, DOI: 10.1098/rsbl.2009.0532

Facial expressions show language barriers too

People from East Asia tend to have a tougher time than those from European countries telling the difference between a face that looks fearful versus surprised, disgusted versus angry, and now a new report published online on August 13th in Current Biology, a Cell Press publication, explains why. Rather than scanning evenly across a face as Westerners do, Easterners fixate their attention on the eyes.

"We show that Easterners and Westerners look at different face features to read facial expressions," said Rachael E. Jack of The University of Glasgow. "Westerners look at the eyes and the mouth in equal measure, whereas Easterners favor the eyes and neglect the mouth. This means that Easterners have difficulty distinguishing facial expressions that look similar around the eye region."

The discovery shows that human communication of emotion is a lot more complex than experts had believed, according to the researchers led by Roberto Caldara at The University of Glasgow. As a result, facial expressions that had been considered universally recognizable cannot be used to reliably convey emotion in cross-cultural situations.

The researchers studied cultural differences in the recognition of facial expressions by recording the eye movements of 13 Western Caucasian and 13 East Asian people while they observed pictures of expressive faces and put them into categories: happy, sad, surprised, fearful, disgusted, angry, or neutral. The faces were standardized according to the so-called Facial Action Coding System (FACS) such that each expression displayed a specific combination of facial muscles typically associated with each feeling of emotion. They then compared how accurately participants read those facial expressions using their particular eye movement strategies.

It turned out that Easterners focused much greater attention on the eyes and made significantly more errors than Westerners did. The cultural specificity in eye movements that they show is probably a reflection of cultural specificity in facial expressions, Jack said. Their data suggest that while Westerners use the whole face to convey emotion, Easterners use the eyes more and mouth less.

A survey of Eastern versus Western emoticons certainly supports that idea.

"Emoticons are used to convey different emotions in cyberspace as they are the iconic representation of facial expressions," Jack said. "Interestingly, there are clear cultural differences in the formations of these icons." Western emoticons primarily use the mouth to convey emotional states, e.g. :) for happy and : (for sad, she noted, whereas Eastern emoticons use the eyes, e.g. ^.^ for happy and ;_; for sad.

"In sum," the researchers wrote, "our data demonstrate genuine perceptual differences between Western Caucasian and East Asian observers and show that FACS-coded facial expressions are not universal signals of human emotion. From here on, examining how the different facets of cultural ideologies and concepts have diversified these basic social skills will elevate knowledge of human emotion processing from a reductionist to a more authentic representation. Otherwise, when it comes to communicating emotions across cultures, Easterners and Westerners will find themselves lost in translation."

The researchers include Rachael E. Jack, University of Glasgow, Glasgow, Scotland, UK; Caroline Blais, Universite´ de Montreal, Montreal, Canada; Christoph Scheepers, University of Glasgow, Glasgow, Scotland, UK; Philippe G. Schyns, University of Glasgow, Glasgow, Scotland, UK; and Roberto Caldara, University of Glasgow, Glasgow, Scotland, UK.

Cave Complex Allegedly Found Under Giza Pyramids

Rossella Lorenzi, Discovery News

An enormous system of caves, chambers and tunnels lies hidden beneath the Pyramids of Giza, according to a British explorer who claims to have found the lost underworld of the pharaohs.

Populated by bats and venomous spiders, the underground complex was found in the limestone bedrock beneath the pyramid field at Giza.

"There is untouched archaeology down there, as well as a delicate ecosystem that includes colonies of bats and a species of spider which we have tentatively identified as the white widow," British explorer Andrew Collins said.

Collins, who will detail his findings in the book "Beneath the Pyramids" to be published in September, tracked down the entrance to the mysterious underworld after reading the forgotten memoirs of a 19th century diplomat and explorer.

"In his memoirs, British consul general Henry Salt recounts how he investigated an underground system of 'catacombs' at Giza in 1817 in the company of Italian explorer Giovanni Caviglia," Collins said.

The document records that the two explored the caves for a distance of "several hundred yards," coming upon four large chambers from which stretched further cave passageways.

With the help of British Egyptologist Nigel Skinner-Simpson, Collins reconstructed Salt's exploration on the plateau, eventually locating the entrance to the lost catacombs in an apparently unrecorded tomb west of the Great Pyramid.

Indeed, the tomb featured a crack in the rock, which led into a massive natural cave.

"We explored the caves before the air became too thin to continue. They are highly dangerous, with unseen pits and hollows, colonies of bats and venomous spiders," said Collins.

According to Collins, the caves -- which are tens of thousands, if not hundreds of thousands of years old -- may have both inspired the development of the pyramid field and the ancient Egyptian's belief in an underworld.

"Ancient funerary texts clearly allude to the existence of a subterranean world in the vicinity of the Giza pyramids," Collins told Discovery News. Indeed, Giza was known anciently as Rostau, meaning the "mouth of the passages." This is the same name as a region of the ancient Egyptian underworld known as the Duat.

"The 'mouth of the passages' is unquestionably a reference to the entrance to a subterranean cave world, one long rumored to exist beneath the plateau," Collins told Discovery News.

Collins' claim is expected to cause a stir in the Egyptological world.

Zahi Hawass, chief of Egypt's Supreme Council of Antiquities, has dismissed the discovery.

"There are no new discoveries to be made at Giza. We know everything about the plateau," he stated.

But Collins remarks that after extensive research, he found no mention of the caves in modern times.

"To the best of our knowledge nothing has ever been written or recorded about these caves since Salt's explorations. If Hawass does have any report related to these caves, we have yet to see it," Collins said.

Pay-per-email plan to beat spam and help charity

* 08:45 13 August 2009 **by MacGregor Campbell**

Yahoo! wants to reinvent the postage stamp to cut spam. Researchers are testing a scheme where users pay a cent to charity for each email they send – so clearing their inbox and conscience simultaneously.

You may see less spam these days, but it is more abundant than ever, making up more than 90 per cent of all email sent globally. Most is intercepted by anti-spam programs that filter mail by its origin or content.

Yahoo! Research's CentMail resurrects an old idea: that levying a charge on every email sent would instantly make spamming uneconomic. But because the cent paid for an accredited "stamp" to appear on each email goes to charity, CentMail's inventors think it will be more successful than previous approaches to make email cost. They think the cost to users is offset by the good feeling of giving to charity.

Pay per post

Some previous schemes, such as Goodmail, simply pocketed the charge for the virtual stamps. Another deterred spammers by forcing computers to do extra work per email; and Microsoft's version requires senders to decipher distorted text.

The problem with any such "economic" approach is that it costs money or effort for legitimate senders as well as spammers, Yahoo! researcher Sharad Goel explains. By passing the money onto a charity of the sender's choice, and showing the donation in a "stamp" at the bottom of every email sent, CentMail aims to make senders feel an altruistic glow to balance that perceived cost. That could also persuade people to sign up without waiting for the system to become widespread. "We think this is a more socially efficient approach to reducing spam," says Goel.

Critical mass

Once the scheme grows more popular, mail-server operators can save resources by having their systems spend less time scrutinising CentMail-accredited messages as spam suspects, its designers say.

CentMail draws inspiration from an IBM project called Charity Seals, created by Mark Wegman and Scott Fahlman. It was never implemented, though, in part because people are not used to paying for email, says Fahlman, currently at Carnegie Mellon University in Pittsburgh, Pennsylvania.

"Some people think that if you put any kind of barrier in the way of sending email, it's sacrilege," says Fahlman. But with the charity-centred approach that barrier is reduced, he says.

Charitable disagreement

Barry Leiba, also at IBM, points out that one of CentMail's core features could also be a weakness, though.

People may not wish to receive messages plugging a cause they don't agree with. "I might feel that by accepting his messages, I'm implicitly supporting his charity choices – choices that I might be vehemently against."

CentMail is currently in private beta, but Goel hopes that it will soon be released publicly and will be usable with any email address – not just Yahoo! accounts. Users will buy stamps in blocks in advance. You can sign up on the CentMail website to be told when the service goes live.

First compound that specifically kills cancer stem cells found

The cancer stem cells that drive tumor growth and resist chemotherapies and radiation treatments that kill other cancer cells aren't invincible after all. Researchers reporting online on August 13th in the journal Cell, a Cell Press publication, have discovered the first compound that targets those cancer stem cells directly.

"It wasn't clear it would be possible to find compounds that selectively kill cancer stem cells," said Piyush Gupta of the Massachusetts Institute of Technology (MIT) and the Broad Institute. "We've shown it can be done."

The team including MIT's Robert Weinberg and the Broad Institute's Eric Lander developed a new high-throughput screening method that makes it possible for the first time to systematically look for agents that kill cancer stem cells. That ability had previously eluded researchers due to the rarity of those cells within tumor cell populations and their relative instability in laboratory culture.

In the new study, the researchers manipulated cultured breast cancer cells to greatly enrich for those with the stem-like properties, including increased resistance to standard cancer drugs. They then screened a library of 16,000 natural and commercial chemical compounds for their ability to kill those stem-like cells and not other cancer cells. That screen turned up 32 contenders.

The researchers narrowed that list down to a handful of chemicals that they could readily get in sufficient quantities for further testing on normal cancer stem cells. Of those, one called salinomycin was the clear winner.

Salinomycin reduced the proportion of breast cancer stem cells by more than 100-fold compared to a commonly used chemotherapeutic drug for breast cancer called paclitaxel (aka Taxol™). Salinomycin-treated cells were less able than paclitaxel-treated ones to seed tumors when injected into mice, they report. Salinomycin treatment also slowed the growth of the animals' tumors.

Studies of salinomycin-treated human breast tumors also showed a loss in the activity of genes associated with cancer stem cells.

Exactly how salinomycin's works against cancer stem cells, the researchers don't yet know. As its name suggests, the chemical has antibiotic properties that likely aren't relevant to its newfound cancer stem cell-killing ability. It also disturbs cells' potassium balance.

It remains unclear whether salinomycin itself might find its way to the clinic, Gupta said, since many pharmaceutical steps are involved in the drug discovery process. Nevertheless, the chemical does serve as an immediate tool for manipulating cancer stem cell numbers and observing the effects on cancer's spread and progression.

The findings also highlight a new avenue for the development of cancer therapies, the researchers say.

" To date, rational cancer therapies have been designed to target specific genetic alterations present within tumors," they wrote. "The findings here indicate that a second approach may also prove useful—namely, searching for agents that target specific states of cancer cell differentiation. Accordingly, future therapies could offer greater possibilities for individualized treatment by considering both the genetic alterations and differentiation states present within the cancer cells of a tumor at the time of diagnosis."

They envision a future in which combination therapies might couple more traditional cancer drugs with those designed to hit the cancer stem cells that would otherwise get left behind.

The researchers include Piyush B. Gupta, Massachusetts Institute of Technology, Cambridge, MA, Broad Institute of MIT and Harvard, Cambridge, MA; Tamer T. Onder, Massachusetts Institute of Technology, Cambridge, MA, Whitehead Institute for Biomedical Research, Cambridge, MA; Guozhi Jiang, Massachusetts Institute of Technology, Cambridge, MA, Broad Institute of MIT and Harvard, Cambridge, MA; Kai Tao, Tufts University School of Medicine and Molecular Oncology Research Institute, Tufts Medical Center, Boston, MA; Charlotte Kuperwasser, Tufts University School of Medicine and Molecular Oncology Research Institute, Tufts Medical Center, Boston, MA; Robert A. Weinberg, Massachusetts Institute of Technology, Cambridge, MA, Whitehead Institute for Biomedical Research, Cambridge, MA, MIT Ludwig Center for Molecular Oncology, Cambridge, MA; and Eric S. Lander, Massachusetts Institute of Technology, Cambridge, MA, Whitehead Institute for Biomedical Research, Cambridge, MA, Broad Institute of MIT and Harvard, Cambridge, MA, Harvard Medical School, Boston, MA.

Why are autumn leaves red in America and yellow in Europe?

A new theory, concluded by researchers from the University of Haifa, Israel, and the University of Kuopio in Finland, reaches 35 million years back in time to solve the puzzle

Walking outdoors in the fall, the splendidly colorful leaves adorning the trees are a delight to the eye. In Europe these autumn leaves are mostly yellow, while the United States and East Asia boast lustrous red foliage. But why is it that there are such differences in autumnal hues around the world? A new theory provided by Prof. Simcha Lev-Yadun of the Department of Science Education- Biology at the University of Haifa-Oranim and Prof. Jarmo Holopainen of the University of Kuopio in Finland and published in the Journal New Phytologist proposes taking a step 35 million years back to solve the color mystery.

The green of a tree's leaves is from the larger proportion of the chlorophyll pigment in the leaves. The change in color to red or yellow as autumn approaches is not the result of the leaves' dying, but of a series of processes – which differ between the red and yellow autumn leaves. When the green chlorophyll in leaves

diminishes, the yellow pigments that already exist become dominant and give their color to the leaves. Red autumn leaves result from a different process: As the chlorophyll diminishes, a red pigment, anthocyanin, which was not previously present, is produced in the leaf. These facts were only recently discovered and led to a surge of research studies attempting to explain why trees expend resources on creating red pigments just as they are about to shed their leaves.

Explanations that have been offered vary and there is no agreement on this as of yet. One discipline suggests that the red pigment is produced as a result of physiological functions that make the re-translocation of amino acids to the woody parts of the tree more efficient in setting up its protection against the potential damage of light and cold. Other explanations suggest that the red pigment is produced as part of the tree's strategy for protecting itself against insects that thrive on the flow of amino acids. But whatever the answer is, these explanations do not help us understand why the process of creating anthocyanin, the red pigment, does not occur in Europe.

An evolutionary ecology approach infers that the strong autumn colors result from the long evolutionary war between the trees and the insects that use them as hosts. During the fall season, which is when the insects suck the amino acids from the leaves and later lay their eggs, the tree colors its leaves in red because aphids are attracted to yellow ones, so as to advertise to the insects as to the defensive quality of the tree in order to lower the tendency of the insects to occupy the leaves for nutrition and the bark for breeding. In this case too, the protective logic of red pigmentation may be sound, but the yellow leaves cannot be reconciled with this approach. But to settle this point, the new theory can be applied.

According to the theory provided by Prof. Lev-Yadun and Prof. Holopainen, until 35 million years ago, large areas of the globe were covered with evergreen jungles or forests composed of tropical trees. During this phase, a series of ice ages and dry spells transpired and many tree species evolved to become deciduous. Many of these trees also began an evolutionary process of producing red deciduous leaves in order to ward off insects. In North America, as in East Asia, north-to-south mountain chains enabled plant and animal 'migration' to the south or north with the advance and retreat of the ice according to the climatic fluctuations. And, of course, along with them migrated their insect 'enemies' too. Thus the war for survival continued there uninterrupted. In Europe, on the other hand, the mountains – the Alps and their lateral branches – reach from east to west, and therefore no protected areas were created. Many tree species that did not survive the severe cold died, and with them the insects that depended on them for survival. At the end of the repeated ice ages, most tree species that had survived in Europe had no need to cope with many of the insects that had become extinct, and therefore no longer had to expend efforts on producing red warning leaves.

According to the scientists, evidence supporting this theory can be found in the dwarf shrubs that grow in Scandinavia, which still color their leaves red in autumn. Unlike trees, dwarf shrubs have managed to survive the ice ages under a layer of snow that covered them and protected them from the extreme condition above. Under the blanket of snow, the insects that fed off the shrubs were also protected – so the battle with insects continued in these plants, making it necessary for them to color their leaves red.

Impact of cannabis on bones changes with age, study finds

Scientists investigating the effects of cannabis on bone health have found that its impact varies dramatically with age.

The study has found that although cannabis could reduce bone strength in young people, it may protect against osteoporosis, a weakening of the bones, in later life.

The team at the University of Edinburgh has shown that a molecule found naturally in the body, which can be activated by cannabis – called the type 1 cannabinoid receptor (CB1) – is key to the development of osteoporosis.

It is known that when CB1 comes into contact with cannabis it has an impact on bone regeneration, but until now it was not clear whether the drug had a positive or negative effect.

Researchers, funded by the Arthritis Research Campaign, investigated this by studying mice that lacked the CB1 receptor. The scientists then used compounds – similar to those in cannabis – that activated the CB1 receptor. They found that compounds increased the rate at which bone tissue was destroyed in the young.

The study also showed, however, that the same compounds decreased bone loss in older mice and prevented the accumulation of fat in the bones, which is known to occur in humans with osteoporosis. The results are published in Cell Metabolism.

Osteoporosis affects up to 30 per cent of women and 12 per cent of men at some point in life.

Stuart Ralston, the Arthritis Research Campaign Professor of Rheumatology at the University of Edinburgh, who led the study, said: "This is an exciting step forward, but we must recognise that these are early results and

more tests are needed on the effects of cannabis in humans to determine how the effects differ with age in people.

"We plan to conduct further trials soon and hope the results will help to deliver new treatments that will be of value in the fight against osteoporosis."

Earliest fired knives improved stone age tool kit

* 13:30 13 August 2009 **by Ewen Callaway**

Prehistoric humans harnessed fire to make sharp stone blades, say archaeologists who have recreated ancient fire-hardened tools dug up in South Africa. At 47,000 to 164,000 years old, the blades may date from the dawn of modern human behaviour, involving not just complex tool use but also language and art.

"These people were extremely smart," says Kyle Brown, an experimental archaeologist at the University of Cape Town, South Africa. "I don't think you could have passed down these skills from generation to generation without language." Such adaptations may have given the first modern humans to leave Africa the tools and know-how to conquer the world.

Heat treatment occurred to Brown – who sculpts stone tools in his field laboratory – after he had trouble transforming the local crumbly silcrete stones into anything resembling the sharp, thin blades his team recovered at sites around Still Bay, several hundred kilometres east of Cape Town. However, Brown noticed that many of the ancient blades bore the same glossy sheen as North American tools created from heat-treated stone.

"It seemed like the most logical thing to do was take some of this poor quality material that we've been collecting and put it under a fire and see what happens," he says.

Hot rocks

The rock was transformed after spending 5 to 10 hours buried beneath a fire and at temperatures between 250 and 300 °C, Brown says. "Heat treatment makes the stone harder, stiffer and more brittle," he says, "and it makes it easier to flake." Flaking is the process of chipping sharp, small pieces off a large rock.

But these experiments alone don't prove that ancient humans cooked stones before making blades. So, Brown's team looked for signs of heat treatment in artefacts 47,000 to 164,000 years old that were recovered from two Still Bay sites.

Firing leaves its mark in iron-containing rocks because heating realigns the geomagnetic orientation that was recorded when they formed. Brown's team found evidence for magnetic reorientation in all 12 of the ancient blades they tested with this method.

High heat can also eject electrons trapped in certain minerals. Electrons trickle back into the mineral once it cools, but so slowly that they can show if a rock has been heated recently. Every one of the 26 stone blades that Brown's team analysed in this way had been heated.

Proof of intent

These tests still don't prove that the blades were burned intentionally: they could have been made from unbaked stone and then caught in a bush fire. The "greasy" sheen Brown noticed on the blades gives away rocks heated before flaking, however, he says. Most of 153 stone tools his team studied showed this signature, including 164,000-year-old blades.

This pushes the earliest evidence for fire-treated tools back about 140,000 years and from Europe to Africa, not long after the emergence of Homo sapiens in eastern Africa.

Climatic shifts may have forced many of those first humans into fertile refuges in South Africa, where conditions were right for modern human behaviour to emerge, Brown says. Other evidence suggests these humans fished, painted and wore jewellery.

Ancient humans probably used heat-treated tools to hunt or butcher animals, though many of the blades are too small to wield by hand. Brown imagines weapons constructed with multiple blades that could swapped out if one broke.

Arms race

These adaptations, he argues, were part of a "tool kit" that modern humans took to other parts of the world. In Europe and west Asia, for instance, hunting and butchering with the fired blades could have given humans a competitive edge over Neanderthals, who might have ignored poor-quality rock to make their own stone weapons.

Besides cooking – which predates our species – ancient humans also controlled fire to alter the colour of ochre rock, notes John Shea, a palaeoanthropologist at Stony Brook University in New York.

However Shea questions whether heat-treated stone would have given modern humans the edge over Neanderthals. Pre-cooking stones would eat up time and energy better spent on other ways of making a living.

"It is tempting to see everything early humans did as adaptively advantageous, but this is not necessarily the case," he says.

"South Africa is about as far as one can get from Europe and the Near East and still be in Africa. It is an unlikely place to look for behavioural innovations that led to humans dispersing successfully into Eurasia," he adds. *Journal reference: Science, DOI: 10.1126/science.1175028*

Brain innately separates living and non-living objects for processing

People with blindness found to categorize objects in visual centers of brain like sighted people

For unknown reasons, the human brain distinctly separates the handling of images of living things from images of non-living things, processing each image type in a different area of the brain. For years, many scientists have assumed the brain segregated visual information in this manner to optimize processing the images themselves, but new research shows that even in people who have been blind since birth the brain still separates the concepts of living and non-living objects.

The research, published in today's issue of Neuron, implies that the brain categorizes objects based on the different types of subsequent consideration they demand—such as whether an object is edible, or is a landmark on the way home, or is a predator to run from. They are not categorized entirely by their appearance.

"If both sighted people and people with blindness process the same ideas in the same parts of the brain, then it follows that visual experience is not necessary in order for those aspects of brain organization to develop," says Bradford Mahon, postdoctoral fellow in the Department of Brain and Cognitive Sciences at the University of Rochester, and lead author of the study. "We think this means significant parts of the brain are innately structured around a few domains of knowledge that were critical in humans' evolutionary history."

Previous studies have shown that the sight of certain objects, such as a table or mountain, activate regions of the brain other than does the sight of living objects, such as an animal or face—but why the brain would choose to process these two categories differently has remained a mystery, says Mahon. Since the regions were known to activate when the objects were seen, scientists wondered if something about the visual appearance of the objects determined how the brain would process them. For instance, says Mahon, most living things have curved forms, and so many scientists thought the brain prefers to processes images of living things in an area that is optimized for curved forms.

To see if the appearance of objects is indeed key to how the brain conducts its processing, Mahon and his team, led by Alfonso Caramazza, director of the Cognitive Neuropsychology Laboratory at Harvard University, asked people who have been blind since birth to think about certain living and non-living objects. These people had no visual experience at all, so their brains necessarily determined where to do the processing using some criteria other than an object's appearance.

"When we looked at the MRI scans, it was pretty clear that blind people and sighted people were dividing up living and non-living processing in the same way," says Mahon. "We think these findings strongly encourage the view that the human brain's organization innately anticipates the different types of computations that must be carried out for different types of objects."

Mahon thinks it's possible that other parts of the human brain are innately structured around categories of knowledge that may have been important in human evolution. For instance, he says, facial expressions need a specific kind of processing linked to understanding emotions, whereas a landmark needs to be processed in conjunction with a sense of spatial awareness. The brain might choose to process these things in different areas of the brain because those areas have strong connections to other processing centers specializing in emotion or spatial awareness, says Mahon.

Mahon is now working on new experiments designed to further our understanding of how the brain represents knowledge of different classes of objects, both in sighted and blind individuals, as well as in stroke patients. *The data for the study were collected at the Center for Mind/Brain Sciences at the University of Trento in Italy.*

Bypassing Bypass Surgery

TAU grows new blood vessels to combat heart disease

Although open-heart surgery is a frequent treatment for heart disease, it remains extremely dangerous. Now groundbreaking research from Dr. Britta Hardy of Tel Aviv University's Sackler School of Medicine has shown the potential for an injected protein to regrow blood vessels in the human heart — eliminating the need for risky surgery altogether.

In heart disease, blood vessels are either clogged or die off, starving the heart of oxygen and leaving it highly susceptible to a cardiac attack. Dr. Hardy and her research partner Prof. Alexander Battler have developed a protein-based injection that, delivered straight to muscles in the body, sparks the regrowth of tiny blood vessels. These new vessels in the heart could give millions of people around the world a new lease on life.

Research on the procedure was recently published in Biochemical Pharmacology.

A treatment without side effects or inflammation

"The biotechnology behind our human-based protein therapy is very complicated, but the goal is simple and the solution is straightforward," says Dr. Hardy. "We intend to inject our drug locally to heal any oxygen-starved tissue. So far in animal models, we've seen no side effects and no inflammation following our injection of the drug into the legs. The growth of new blood vessels happens within a few weeks, showing improved blood circulation."

The protein solution can also be added as a coating to a stent. Currently, the implantation of a stent is accompanied by a high risk for blood clots, which necessitates the use of blood thinners. "We could coat a stent with our peptide, attracting endothelial stem cells to form a film on the surface of the stent," Dr. Hardy explains. "These endothelial cells on the stent would eliminate the need for taking the blood thinners that prevent blood clots from forming."

If investment goals are met, Dr. Hardy anticipates toxicity studies and Phase I trials could be complete within two years.

Saving a leg, saving a life

The research began with the hope of preventing leg amputations, positing that proteins from the human body could be used to trigger the growth of new blood vessels. Dr. Hardy started by studying a library of peptides and testing them in the laboratory. With the assistance of philanthropic funding from the Colton family in the U.S., Dr. Hardy was able to confirm initial results. She then took some of the isolated and synthesized peptides and tested them in diabetic mice whose legs were in the process of dying.

Although diabetes is known to decrease blood circulation, Dr. Hardy found that her therapy reversed the decrease. "Within a short time we saw the formation of capillaries and tiny blood vessels. After three weeks, they had grown and merged together with the rest of the circulatory system," she says. In mice with limited blood circulation, she was able to completely restore blood vessels and save their legs. It was then a short step to studying the applicability of the research to cardiac patients.

A new therapy could be commercially available soon. Unlike studies for other drugs, clinical results with the blood vessels are practically immediate. "It's pretty obvious if there is regrowth or not. Our technology promises to regrow blood vessels like a net, and a heart that grows more blood vessels becomes stronger. It's now imaginable that, in the distant future, peptide injections may be able to replace bypass surgeries," Dr. Hardy concludes.

First human gene implicated in regulating length of human sleep

Scientists have discovered the first gene involved in regulating the optimal length of human sleep, offering a window into a key aspect of slumber, an enigmatic phenomenon that is critical to human physical and mental health.

The team, reporting in the Aug. 14, 2009 issue of Science, identified a mutated gene that allows two members of an extended family to thrive on six hours of sleep a day rather than the eight to eight-and-a-half hours that studies have shown humans need over time to maintain optimal health. Working from this discovery, the scientists genetically engineered mice and fruit flies to express the mutated gene and study its impact.

While most Americans obtain less than eight hours of sleep a night (the average on non-work days is 7.4 hours), and some may feel they succeed with less when engaged in exhilarating work, domestic life or recreation, scientific evidence indicates that, over time, the body suffers from this regimen, the researchers say.

"Short term and chronic disruptions in the length of optimal sleep can have serious consequences on cognition, mood and physical health, including cancer and endocrine function," says the senior author of the study, Ying-Hui Fu, PhD, UCSF professor of neurology. However, teasing out this impact can be challenging, she says, given access to such stimuli as coffee and chocolate.

The finding, she says, offers an opportunity to unravel the regulatory mechanism of sleep. While the mutation may be rare, it could offer a probe more generally into the regulatory mechanisms of sleep quality and quantity. Understanding these mechanisms could lead to interventions to alleviate pathologies associated with sleep disturbance.

Sleep remains a relatively inscrutable biological phenomenon. Scientists know that it is regulated in large part by two processes: 1) circadian rhythms -- genetic, biochemical and physiological mechanisms that wax and wane during a 24 hour period to regulate the timing of sleep, 2) and homeostasis – unknown mechanisms that ensure that the body acquires over time the necessary amount of sleep, nudging it toward sleep when it has been deprived, prompting it out of sleep when it has received enough. This regulation of sleep intensity is measured in non rapid eye movement sleep and REM sleep. Interactions between the circadian rhythms and homeostatic mechanisms influence the timing, duration and quality of sleep and wakefulness.

But "the details in the process are really completely unknown," says Fu.

In 2001, the team discovered a mutated gene that caused some members of several families to be "morning larks," awaking around 3:30 a.m. and going to bed around 7:30 p.m. The condition, which the researchers named "familial advanced sleep phase syndrome," is believed to be primarily a variant, or mutated, form of a gene involved in regulating circadian rhythms. The total daily sleep time in people with this condition is normal.

In the current study, the team identified a small extended family in which a mother and her adult daughter had life-long shorter daily sleep requirements than most individuals. Fu's lab then studied blood samples from these women and their extended family. They identified a mutation in a gene known as hDEC2, which is a transcription factor that represses expression of certain other genes and is implicated in the regulation of circadian rhythms.

Next, the team genetically engineered mice and fruit flies to express the mutated human gene, and Ying He, PhD, a postdoctoral fellow in the Fu lab, studied its impact on their behavior and sleep patterns. Mice slept less, as seen in the extent of their scampering about in the dark (mouse preference) over the course of 24 hours and in electroencephalography (EEG) and electromyography (EMG) measurements indicating reduced nonREM and REM sleep. While lacking a Lilliputian size EEG to monitor the fruit flies, He studied the miniscule creatures' activity and sleep patterns by tracking the frequency of their movements through infrared light.

Next, the team compared the response of the genetically engineered mice and normal mice to the consequence of six hours of sleep deprivation. The engineered mice needed to compensate for their lost sleep to a much lesser extent – as seen in nonREM and REM measures – than their normal counterparts.
"These changes in sleep homeostasis in the mutant mice could provide an explanation for why human subjects with the mutation are able to live unaffected by shorter amounts of sleep throughout their lives," says Fu.

The next step, she says, is determining the DEC2's precise role. "We know the gene encodes a protein that is a transcriptional repressor and we know it makes the repressor's activity weaker. But we don't know if the weaker repressor is directly related to the shorter amount of sleep, because proteins can have many functions. It could be the protein functions as part of a larger transcriptional machinery, not necessarily as a repressor."

DEC2 could be involved in modulating "sleep quantity" alone, or it could be mediating both "sleep quantity" and "wakefulness-behavioral drive," according to Fu. The latter drive, she says, is critical for the procurement of food, shelter, and mates and could be more potent in individuals with this mutation.

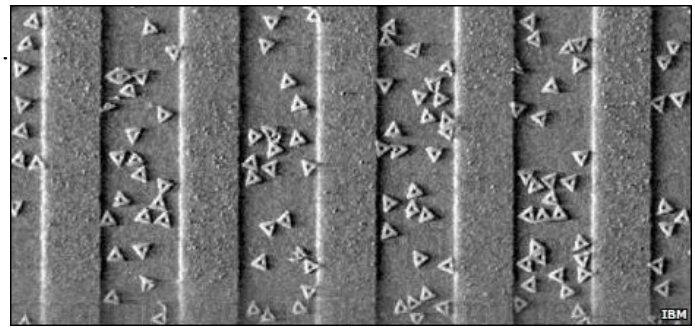
"The mouse model also provides an opportunity to investigate whether there are other behaviors or physiological conditions associated with a short sleep syndrome," says Fu. She suspects there will be.

Co-authors of the study are Christopher R. Jones, MD, at the University of Utah; Nobuhiro Fujiki, PhD, and Seiji Nishino, PhD, both of Stanford University; Ying Xu, PhD, and Jimmy Holder, MD, PhD, both at the time of the study in the Fu lab; Bin Guo, PhD, of the University of California, Berkeley; and Moritz J. Rossner, PhD, of the Max-Planck-Institute of Experimental Medicine.

The study was funded by the National Institutes of Health, a Conte Center grant, and by the Sandler Neurogenetics fund.

DNA 'organises itself' on silicon

Shapes of DNA have been used to enhance the production of circuits for next-generation computer chips.



Researchers reporting in Nature Nanotechnology have now shown how to get engineered "DNA origami" to self-organise on silicon. The origami can be designed to serve as a scaffold for electronic components just six billionths of a metre apart. Making chips with components closer together leads to smaller devices and faster computers. The six nanometre mark is nearly eight times better than the current industry produces.

Several research groups have shown that DNA itself can be used to store or manipulate data, and the juggling of DNA in a test tube or within bacteria has been shown to solve simple computational tasks. The current method, by contrast, leverages the ability to design DNA strands into regular shapes such as triangles.

Triangular "DNA origami" were made to assemble on etched carbon and silicon

Shapely

The computer industry would like to make use of next-generation materials with favourable electronic properties such as carbon nanotubes or nanowires.

Such structures are tiny and difficult to manipulate, but the chemical groups hanging off DNA helices could be used as anchor points for them. Those anchor points can be as little as six nanometres (nm) apart, making these DNA-bound circuit components smaller and thus faster than can currently be produced.

The current industry standard for etching electronic components from larger structures - a so-called "top down" approach - has components at a distance of 45nm. But the new "bottom-up" technique promises distances nearly four times better than the planned industry move to 22nm.

What makes the technique particularly useful is that the regular shapes of the circuit-loaded DNA origami allows them to fit neatly into shaped pits the researchers bored into silicon or carbon using standard techniques.

This self-assembly occurs when a liquid filled with the origami is put in contact with the etched surfaces in what the authors call a case of "bottom-up keys" fitting into "top-down locks".

Because the eventual placement of the components puts them so much closer, the approach could lead to computers that are both smaller and faster. However, the motivations are also economic - industry-wide shifts to smaller components are phenomenally expensive to the manufacturers.

"The combination of this directed self-assembly with today's fabrication technology eventually could lead to substantial savings in the most expensive and challenging part of the chip-making process," said Spike Narayan, a science and technology manager at IBM's Almaden research centre.

Fuller integration of the technique could take as much as 10 years, IBM said.

Studies do not support unhealthful relation between animal foods and breast cancer

Breast cancer is the 7th leading cause of mortality in the United States and results in approximately 41,000 deaths each year. Although genetic factors are important, there is considerable evidence that breast cancer risk is related to modifiable lifestyle factors, such as physical activity, body weight, alcohol intake, and dietary choices. The September 2009 issue of The American Journal of Clinical Nutrition reports the results of 3 human studies designed to better delineate the relation between animal foods and breast cancer risk.

"These studies highlight two very important points," said American Society for Nutrition Spokesperson Shelley McGuire, PhD. "First we all need to remember that there are really no such things as 'bad' foods. Second, observational studies that show associations between diet and health need to be considered with a proverbial grain of salt. These studies clearly provide additional and strong evidence that consumption of meat and dairy products by women does not, by itself, increase breast cancer risk. Further, moderate and mindful consumption of these foods can be very important in attaining optimal nutrition for most women who often do not consume sufficient iron and calcium."

In the first study, which was a controlled dietary intervention trial conducted in the United States, 35 obese postmenopausal women with type 2 diabetes received conjugated linoleic acid (CLA) supplements or a control supplement (safflower oil) each for 36 wk; adiposity was assessed. In another study, researchers examined the association between CLA intake from natural sources and breast cancer incidence in a large cohort of initially cancer-free Swedish women for 17.4 y. The third study assessed whether the consumption of meat, eggs, and dairy products was associated with breast cancer risk in a very large group of healthy European women followed for 8.8 y.

These studies provide no evidence that animal-food consumption increases (or decreases) risk of breast cancer, although CLA supplementation may decrease adiposity (a major risk factor for this disease). In an editorial, Linos and Willett remind us that these studies did not assess the relation between animal-food intake during early life and later breast cancer, a likely important piece of the puzzle. Nonetheless, they conclude, "These data are sufficient to exclude any major effect of consuming these foods during midlife or later on risk of breast cancer." Perhaps we finally have the answer to this long-standing question.

To access full text versions of the studies visit:http://www.nutrition.org/media/publications/ajcnSept309.pdf http://www.nutrition.org/media/publications/ajcnSept409.pdf http://www.nutrition.org/media/publications/ajcnSept509.pdf http://www.nutrition.org/media/publications/ajcnSept609.pdf

'Killer spices' provide eco-friendly pesticides for organic fruits and veggies

WASHINGTON, Aug. 16, 2009 — Mention rosemary, thyme, clove, and mint and most people think of a delicious meal. Think bigger…acres bigger. These well-known spices are now becoming organic agriculture's key weapons against insect pests as the industry tries to satisfy demands for fruits and veggies among the growing portion of consumers who want food produced in more natural ways.

In a study presented here today at the American Chemical Society's 238th National Meeting, scientists in Canada are reporting exciting new research on these so-called "essential oil pesticides" or "killer spices." These substances represent a relatively new class of natural insecticides that show promise as an environmentally-friendly alternative to conventional pesticides while also posing less risk to human and animal health, the researcher says.

"We are exploring the potential use of natural pesticides based on plant essential oils — commonly used in foods and beverages as flavorings," says study presenter Murray Isman, Ph.D., of the University of British

Columbia. These new pesticides are generally a mixture of tiny amounts of two to four different spices diluted in water. Some kill insects outright, while others repel them.

Over the past decade, Isman and colleagues tested many plant essential oils and found that they have a broad range of insecticidal activity against agricultural pests. Some spiced-based commercial products now being used by farmers have already shown success in protecting organic strawberry, spinach, and tomato crops against destructive aphids and mites, the researcher says.

"These products expand the limited arsenal of organic growers to combat pests," explains Isman. "They're still only a small piece of the insecticide market, but they're growing and gaining momentum."

The natural pesticides have several advantages. Unlike conventional pesticides, these "killer spices" do not require extensive regulatory approval and are readily available. An additional advantage is that insects are less likely to evolve resistance — the ability to shrug off once-effective toxins — Isman says. They're also safer for farm workers, who are at high risk for pesticide exposure, he notes.

But the new pesticides also have shortcomings. Since essential oils tend to evaporate quickly and degrade rapidly in sunlight, farmers need to apply the spice-based pesticides to crops more frequently than conventional pesticides. Some last only a few hours, compared to days or even months for conventional pesticides. As these natural pesticides are generally less potent than conventional pesticides, they also must be applied in higher concentrations to achieve acceptable levels of pest control, Isman says. Researchers are now seeking ways of making the natural pesticides longer-lasting and more potent, he notes.

"They're not a panacea for pest control," cautions Isman. Conventional pesticides are still the most effective way to control caterpillars, grasshoppers, beetles and other large insects on commercial food crops, he says. "But at the end of the day, it comes down to what's good for the environment and what's good for human health."

The "killer spices" aren't just limited to agricultural use. Some show promise in the home as eco-friendly toxins and repellents against mosquitoes, flies, and roaches. Unlike conventional bug sprays, which have a harsh odor, these natural pesticides tend to have a pleasant, spicy aroma. Many contain the same oils that are used in aromatherapy products, including cinnamon and peppermint, Isman notes.

Manufacturers have already developed spice-based products that can repel ticks and fleas on dogs and cats without harming the animals. Researchers are now exploring the use of other spice-based products for use on fruits and vegetables to destroy microbes, such as E. coil and Salmonella, which cause food poisoning.

Other scientists are currently exploring the insect-fighting potential of lavender, basil, bergamot, patchouli oil, and at least a dozen other oils from exotic plant sources in China. Funding for this study was provided by EcoSMART®, a botanical pesticide company based in Alpharetta, Ga.

Needle-free, inhalant powder measles vaccine could save thousands of lives

WASHINGTON, Aug. 16, 2009 — The first dry powder inhalable vaccine for measles is moving toward clinical trials next year in India, where the disease still sickens millions of infants and children and kills almost 200,000 annually, according to a report presented here today at the 238th National Meeting of the American Chemical Society (ACS).

Robert Sievers, Ph.D., who leads the team that developed the dry-powder vaccine, said it's a perfect fit for use in back-roads areas of developing countries. Those areas often lack the electricity for refrigeration, clean water and sterile needles needed to administer traditional liquid vaccines.

"Childhood vaccines that can be inhaled and delivered directly to mucosal surfaces have the potential to offer significant advantages over injection," Sievers said. "Not only might they reduce the risk of infection from HIV, hepatitis, and other serious diseases due to unsterilized needles, they may prove more effective against disease."

"Many serious infections, such as the measles virus, can enter the body through inhalation. Measles vaccine dry powders have the potential to effectively vaccinate infants, children and adults by inhalation, avoiding the problems associated with liquid vaccines delivered by injection," he added.

Although made for developing countries, the technology eventually could become the basis for a new generation of inhalable — and ouchless vaccines — in the United States and elsewhere. So far, an inhalable vaccine is available for only one disease. It is a wet mist vaccine for influenza.

Sievers, once an atmospheric scientist and who now is with Department of Chemistry and Biochemistry and Center for Pharmaceutical Biotechnology, University of Colorado, Boulder, took inspiration for the new vaccine from research on how people inhale tiny airborne droplets of air pollutants.

To create an inhalable vaccine, Sievers and his team of students and researchers developed a patented process known as the "Carbon Dioxide-Assisted Nebulization with a Bubble Dryer," called CAN-BD. The

weakened measles virus is mixed with "supercritical" carbon dioxide — part gas, part liquid — to produce microscopic bubbles and droplets, which then are dried to make an inhalable powder.

The powder is puffed into a small, cylindrical, plastic sack, with an opening like the neck of a plastic water bottle, and administered. "By taking one deep breath from the sack, a child could be effectively vaccinated," Sievers said.

In animal tests, the inhaler has been just as effective in delivering measles vaccine as the traditional injection, the researchers say. They now are working on an inexpensive dry powder inhaler that would deliver measles or influenza vaccines to developing nations and could be used elsewhere. In replacing injections, the new method also would help reach those who refuse inoculations because of their fear of needles. The researchers say that the vaccine could be produced for about 26 cents a dose.

If the inhaler passes final safety and effectiveness tests, the Serum Institute of India Ltd. expects a demand growing to 400 million doses of measles vaccine a year, according to Sievers.

"Human clinical trials are expected to begin next year in India, after animal safety studies are completed this year," Sievers said. "About two-thirds of the world's deaths due to measles occur in that nation. Worldwide, several hundred people die every day from measles-related disease," he added.

In earlier research in the 1980s in Mexico during a measles outbreak, 3 million children received a measles vaccine by inhaling a wet mist aerosol and those who took part in the test had a lower rate of developing measles than those who received a vaccine by injection, according to Sievers. "The problem with that method," he said, "was that the wet mists required power or batteries to generate the aerosol and the liquid vaccines had to be freshly made up and kept on ice and the nebulizer that delivers the dose had to be cleaned. The new, inexpensive dry aerosol dispenser doesn't need to be cleaned and doesn't require power," he said.

The study has been conducted with a grant from the Foundation for the National Institutes of Health as part of the Grand Challenges in Global Health Initiative of the Bill and Melinda Gates Foundation.

Agricultural methods of early civilizations may have altered global climate, study suggests

Massive burning of forests for agriculture thousands of years ago may have increased atmospheric carbon dioxide enough to alter global climate and usher in a warming trend that continues today, according to a new study that appears online Aug. 17 in the journal Quaternary Science Reviews.

Researchers at the University of Virginia and the University of Maryland-Baltimore County say that today's 6 billion people use about 90 percent less land per person for growing food than was used by far smaller populations early in the development of civilization. Those early societies likely relied on slash-and-burn techniques to clear large tracts of land for relatively small levels of food production.

"They used more land for farming because they had little incentive to maximize yield from less land, and because there was plenty of forest to burn," said William Ruddiman, the lead author and a professor emeritus of environmental sciences at the University of Virginia. "They may have inadvertently altered the climate."

Ruddiman is a climate scientist who specializes in investigating ocean-sediment and ice-core records. In recent years he has searched across scientific disciplines – anthropology, archaeology, population dynamics, climatology – to gain insight into how humans may have affected climate over the millennia.

He said that early populations likely used a land-clearing method that involved burning forests, then planting crop seed among the dead stumps in the enriched soil. They would use a large plot until the yield began to decline, and then would burn off another area of forest for planting.

They would continue this form of rotation farming, ever expanding the cleared areas as their populations grew. They possibly cleared five or more times more land than they actually farmed at any given time. It was only as populations grew much larger, and less land was available for farming or for laying fallow, that societies adopted more intensive farming techniques and slowly gained more food yield from less land.

Ruddiman notes that with the highly efficient and intensive farming of today, growing populations are using less land per capita for agriculture. Forests are returning in many parts of the world, including the northeastern United States, Europe, Canada, Russia and even parts of China.

The positive environmental effects of this reforestation, however, are being canceled out by the large-scale burning of fossil fuels since the advent of the Industrial Revolution, which began about 150 years ago. Humans continue to add excessive levels of carbon dioxide to the atmosphere, contributing to a global warming trend, Ruddiman said.

Five years ago, Ruddiman made headlines with a hypothesis that humans began altering global climate thousands of years ago, not just since the Industrial Revolution. That theory has since been criticized by some climate scientists who believe that early populations were too small to create enough carbon dioxide to alter climate.

According to projections from some models of past land use, large-scale land clearing and resulting carbon emissions have only occurred during the industrial era, as a result of huge increases in population.

But Ruddiman, and his co-author Erle Ellis, an ecologist at UMBC who specializes in land-use change, say these models are not accounting for the possibly large effects on climate likely caused by early farming methods.

"Many climate models assume that land use in the past was similar to land use today; and that the great population explosion of the past 150 years has increased land use proportionally," Ellis said. "We are proposing that much smaller earlier populations used much more land per person, and may have more greatly affected climate than current models reflect."

Ruddiman and Ellis based their finding on several studies by anthropologists, archaeologists and paleoecologists indicating that early civilizations used a great amount of land to grow relatively small amounts of food. The researchers compared what they found with the way most land-use models are designed, and found a disconnect between modeling and field-based studies.

"It was only as our populations grew larger over thousands of years, and needed more food, that we improved farming technologies enough to begin using less land for more yield," Ruddiman said. "We suggest in this paper that climate modelers might consider how land use has changed over time, and how this may have affected the climate."