## Grazing animals help spread plant disease

CORVALLIS, Ore. – Researchers have discovered that grazing animals such as deer and rabbits are actually helping to spread plant disease – quadrupling its prevalence in some cases – and encouraging an invasion of annual grasses that threaten more than 20 million acres of native grasslands in California.

The findings run contrary to what had been predicted by other theories, which had suggested that "consumers" such as deer would help to contain or reduce disease. They point once again to the complexity of natural ecosystems and the many ways in which plants, animals and even viruses interact with each other.

The work will be published this week in Proceedings of the National Academy of Sciences, by researchers from Oregon State University, Cornell University and the University of North Carolina.

"We usually think of a disease and its host as very tightly coupled, like a flu virus that infects humans," said Elizabeth Borer, an assistant professor of zoology at OSU. "But in natural ecosystems we're finding it's not nearly that simple, and to understand how plant pathogens work we have to consider the entire food web and many plant/animal interactions of which we are barely aware."

The work is of particular importance, researchers said, because so many elements of ecosystems are undergoing rapid change, from human manipulation, climate change, increase or decrease in various species, new invasive species, and other factors. Any one of those changes could have ripple effects with seemingly unrelated diseases or other issues that are poorly understood – an increase in the abundance of white-footed mice, for instance, has been shown to increase Lyme disease risk in humans.

In this study, scientists examined the effect of herbivores and omnivores such as mule deer, rabbits and feral pigs on the prevalence of barley and cereal yellow dwarf viruses, which can infect more than 100 crop and non-crop plant species, reducing their growth and seed yield. This virus is a major concern for cereal crop production around the world.

In places where most plant eaters were kept out of test plots, the prevalence of this virus was only about 5 percent. It rose to 18 percent, a 3.6-fold increase, in areas that the animals grazed.

The grazers did not directly spread the plant virus, researchers said. Rather, they increased the amounts of annual grasses that are preferred by the aphids which play a role in transmission of this viral plant disease. That allowed for a much greater prevalence of the virus in areas where grazing took place.

"Even in complex natural communities, alternations to food web composition such as consumer invasion or extinction can lead to significant impacts that cascade through entire communities, including changes in infection risk," the researchers wrote in their report.

## Scientists isolate genes that made 1918 flu lethal

MADISON - By mixing and matching a contemporary flu virus with the "Spanish flu" - a virus that killed between 20 and 50 million people 90 years ago in history's most devastating outbreak of infectious disease - researchers have identified a set of three genes that helped underpin the extraordinary virulence of the 1918 virus.

Writing today in the Proceedings of the National Academy of Sciences, a team led by University of Wisconsin-Madison virologists Yoshihiro Kawaoka and Tokiko Watanabe identifies genes that gave the 1918 virus the capacity to reproduce in lung tissue, a hallmark of the pathogen that claimed more lives than all the battles of World War I combined.

"Conventional flu viruses replicate mainly in the upper respiratory tract: the mouth, nose and throat. The 1918 virus replicates in the upper respiratory tract, but also in the lungs," causing primary pneumonia among its victims, says Kawaoka, an internationally recognized expert on influenza and a professor of pathobiological sciences in the UW-Madison School of Veterinary Medicine. "We wanted to know why the 1918 flu caused severe pneumonia."

Autopsies of 1918 flu victims often revealed fluid-filled lungs severely damaged by massive hemorrhaging. Scientists assumed that the ability of the virus to take over the lungs is associated with the pathogen's high level of virulence, but the genes that conferred that ability were unknown.

Discovery of the complex and its role in orchestrating infection in the lungs is important because it could provide a way to quickly identify the potential virulence factors in new pandemic strains of influenza, Kawaoka says. The complex could also become a target for a new class of antiviral drugs, which is urgently needed as vaccines are unlikely to be produced fast enough at the outset of a pandemic to blunt its spread.

To find the gene or genes that enabled the virus to invade the lungs, Kawaoka and his group blended genetic elements from the 1918 flu virus with those of a currently circulating avian influenza virus and tested the variants on ferrets, an animal that mimics human flu infection.

For the most part, substituting single genes from the 1918 virus onto the template of a much more benign contemporary virus yielded agents that could only replicate in the upper respiratory tract. One exception,

however, included a complex of three genes that, acting in concert with another key gene, allowed the virus to efficiently colonize lung cells and make RNA polymerase, a protein necessary for the virus to reproduce.

"The RNA polymerase is used to make new copies of the virus," Kawaoka explains. Without the protein, the virus is unable to make new virus particles and spread infection to nearby cells.

In the late 1990s, scientists were able to recover genes from the 1918 virus by looking in the preserved lung tissue of some of the pandemic's victims. Using the relic genes, Kawaoka's group was able to generate viruses that carry different combinations of the 1918 virus and modern seasonal influenza virus.

When tested, most of the hybrid viruses only infected the nasal passages of ferrets and didn't cause pneumonia. But one did infect the lungs, and it carried the RNA polymerase genes from the 1918 virus that allowed the virus to make the key step of synthesizing its proteins.

In 2004, Kawaoka and his team identified another key gene from the 1918 virus that enhanced the pathogen's virulence in mice. That gene makes hemagglutinin, a protein found on the surface of the virus and that confers on viral particles the ability to attach to host cells.

"Here, I think we are talking about another mechanism," Kawaoka says. The RNA polymerase is used to make copies of the virus once it has entered a host cell. The role of hemagglutinin is to help the virus gain access to cells.

*In addition to the study's lead authors, Watanabe and Kawaoka, co-authors of the new PNAS paper are Shinji Watanabe, Jin Hyun Kim and Masato Hatta, also of UW-Madison; and Kyoko Shinya of Kobe University. The work was funded by the Japanese Ministry of Education, Culture, Sports, Science and Technology and by grants-in-aid from the Ministry of Health, Labor and Welfare of Japan.* –*Terry Devitt, 608-262-8282, trdevitt@wisc.edu*

## Flowering plants speed post-surgery recovery

### *The perfect gift for hospital patients*

MANHATTAN, KS - Contact with nature has long been suspected to increase positive feelings, reduce stress, and provide distraction from the pain associated with recovery from surgery. Now, research has confirmed the beneficial effects of plants and flowers for patients recovering from abdominal surgery.

***These are flowers from a bouquet at the Eastern Market in Washington, D.C.*** **Photo by Queerbubbles**

A recent study by Seong-Hyun Park and Richard H. Mattson, researchers from the Department of Horticulture, Recreation and Forestry at Kansas State University, provides strong evidence that contact with plants is directly beneficial to a hospital patient's health. Using various medical and psychological measurements, the study set out to evaluate if plants in hospital rooms have therapeutic influences.

Studies show that when patients have great stress associated with surgery, they typically experience more severe pain and a slower recovery period. Some of these problems are treated through the use of anesthetics and analgesics, but, if not properly administered, the drugs can have side effects ranging from vomiting and headaches to drug dependency or even fatality. It is therefore beneficial to patients and care providers to develop approaches that improve the overall patient experience but don't rely on pharmaceuticals.

The study, published in the October 2008 issue of HortTechnology, was conducted on 90 patients recovering from an appendectomy. Patients were randomly assigned to hospital rooms with or without plants during their postoperative recovery periods. Data collected for the study included information on the length of hospitalization, administration of drugs for postoperative pain control, vital signs, ratings of pain intensity, distress, fatigue and anxiety, and the patient's room satisfaction questionnaire.

Patients with plants in their rooms had significantly fewer intakes of pain medication, more positive physiological responses (lower blood pressure and heart rate), less pain, anxiety, and fatigue, and better overall positive and higher satisfaction with their recovery rooms than their counterparts in the control group without plants in their rooms.

An interesting note to this study - the majority of patients who had plants in their rooms reported that the plants were the most positive qualities of their rooms (93%), whereas patients without plants in their rooms said that watching television was the most favorable aspect of their rooms (91%).

The study suggests that potted plants offer the most benefit, as opposed to cut flowers, because of their longevity. Nursing staff reported that as patients recovered, they began to show interaction with the plants, including watering, pruning, and moving them for a better view or light. A number of studies have also shown that indoor plants make air healthier and provide an optimum indoor environment by increasing humidity, and reducing the quantity of mold spores and airborne germs.

This nonpharmacological approach to recovery is good news for patients, doctors, and insurers alike in terms of cost effectiveness and medical benefits. The study provides strong evidence that contact with plants is directly beneficial to patients' health, providing meaningful therapeutic contact for patients recovering from painful surgery.

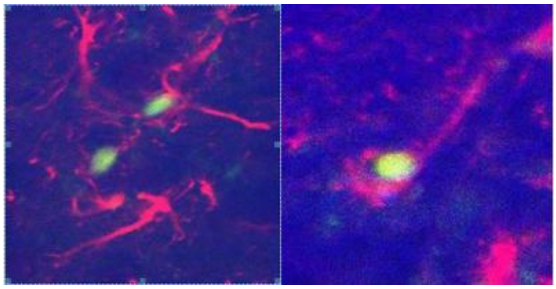
*The complete study and abstract are available on the ASHS HortTechnology electronic journal web site: http://horttech.ashspublications.org/cgi/content/abstract/18/4/563*

*Founded in 1903, the American Society for Horticultural Science (ASHS) is the largest organization dedicated to advancing all facets of horticultural research, education, and application. More information at ashs.org*

## Hebrew University scientists succeed through stem cell therapy in reversing brain birth defects

Jerusalem – Scientists at the Hebrew University of Jerusalem have succeeded in reversing brain birth defects in animal models, using stem cells to replace defective brain cells.

The work of Prof. Joseph Yanai and his associates at the Hebrew University-Hadassah Medical School was presented at the Tel Aviv Stem Cells Conference last spring and is expected to be presented and published nest year at the seventh annual meeting of the International Society for Stem Cell Research in Barcelona, Spain.



***New brain cells (green stain) induced in the heroin damaged brain by transplantation of neural stem cells.*** **The Hebrew University of Jerusalem**

Involved in the project with Prof. Yanai are Prof. Tamir Ben-Hur, head of the Department of Neurology at the Hebrew University-Hadassah Medical School, and his group, as well as Prof. Ted Slotkin at Duke University in North Carolina, where Prof. Yanai is an adjunct professor.

Neural and behavioral birth defects, such as learning disabilities, are particularly difficult to treat, compared to defects with known cause factors such as Parkinson's or Alzheimer's disease, because the prenatal teratogen – the substances that cause the abnormalities -- act diffusely in the fetal brain, resulting in multiple defects.

Prof. Yanai and his associates were able to overcome this obstacle in laboratory tests with mice by using mouse embryonic neural stem cells. These cells migrate in the brain, search for the deficiency that caused the defect, and then differentiate into becoming the cells needed to repair the damage.

Generally speaking, stem cells may develop into any type of cell in the body, however at a certain point they begin to commit to a general function, such as neural stem cells, destined to play a role in the brain/ nervous system. At more advanced developmental stages, the neural stem cells take on an even more specific role as neural or glial (supporting) cells within the brain/ nervous system.

In the researchers' animal model, they were able to reverse learning deficits in the offspring of pregnant mice who were exposed to organophosphate (a pesticide) and heroin. This was done by direct neural stem cell transplantation into the brains of the offspring. The recovery was almost one hundred percent, as proved in behavioral tests in which the treated animals improved to normal behavior and learning scores after the transplantation. On the molecular level, brain chemistry of the treated animals was also restored to normal.

The researchers went one step further. Puzzled by the stem cells' ability to work even in those cases where most of them died out in the host brain, the scientists went on to discover that the neural stem cells succeed before they die in inducing the host brain itself to produce large number of stem cells which repair the damage. This discovery, finally settling a major question in stem cell research, evoked great interest and was published earlier this year in one of the leading journals in the field, Molecular Psychiatry.

The scientists are now in the midst of developing procedures for the least invasive method for administering the neural stem cells, which is probably via blood vessels, thus making the therapy practical and clinically feasible.

Normally, stem cells are derived from individuals genetically different from the patient to be transplanted, and therefore the efficacy of the treatment suffers from immunological rejection. For this reason, another important avenue of the ongoing study, toward the same goals, will be to eliminate the immunological rejection of the transplant, which will become possible by taking cells from the patient's own body -- from a place where they are easily obtained -- by manipulating them to return to their stem cell phase of development, and then transplanting them into the patient's brain via the blood stream. One important advantage of this approach will be to eliminate the controversial ethical issues involved in the use of embryo stem cells.

*The research on the project has been supported by the US National Institutes of Health, the US-Israel Binational Science Foundation and the Israel anti-drug authorities.*

## Study shows competition, not climate change, led to Neanderthal extinction

***Press release from PLoS ONE***

In a recently conducted study, a multidisciplinary French-American research team with expertise in archaeology, past climates, and ecology reported that Neanderthal extinction was principally a result of competition with Cro-Magnon populations, rather than the consequences of climate change.

The study, reported in the online, open-access journal PLoS ONE on Dec. 24, figures in the ongoing debate on the reasons behind the eventual disappearance of Neanderthal populations, which occupied Europe prior to the arrival of human populations like us around 40,000 years ago. Led by Dr William E. Banks, the authors, who belong to the French Centre National de la Recherche Scientifique, l'Ecole Pratique d'Hautes Etudes, and the University of Kansas, reached their conclusion by reconstructing climatic conditions during this period and analyzing the distribution of archaeological sites associated with the last Neanderthals and the first modern human populations with an approach typically used to study the impact of climate change on biodiversity.

This method uses geographic locations of archaeological sites dated by radiocarbon, in conjunction with high-resolution simulations of past climates for specific periods, and employs an algorithm to analyze relationships between the two datasets to reconstruct potential areas occupied by each human population and to determine if and how climatic conditions played a role in shaping these areas. In other words, by integrating archaeological and paleoenvironmental datasets, this predictive method can reconstruct the regions that a past population could potentially have occupied. By repeating the modeling process hundreds of times and evaluating where the errors occur, this machine-learning algorithm is able to provide robust predictions of regions that could have been occupied by specific human cultures.

This modeling approach also allows the projection of the ecological footprint of one culture onto the environmental conditions of a later climatic phase—by comparing this projected prediction to the known archaeological sites dated to this later period, it is possible to determine if the ecological niche exploited by this human population remained the same, or if it contracted or expanded during that period of time.

Comparing these reconstructed areas for Neanderthals and anatomically modern humans during each of the climatic phases concerned, and by projecting each niche onto the subsequent climatic phases, Banks and colleagues determined that Neanderthals had the possibility to maintain their range across Europe during a period of less severe climatic conditions called Greenland Interstadial 8 (GI8).

However, the archaeological record shows that this did not occur, and Neanderthal disappearance occurs at a point when we see the geographic expansion of the ecological niche occupied by modern humans during GI8. The researchers' models predict the southern limit of the modern human territory to be near the Ebro River Valley in northern Spain during the preceding cold period called Heinrich Event 4 (H4), and that this southern boundary moved to the south during the more temperate phase GI8.

The researchers conclude that the Neanderthal populations that occupied what is now southern Spain were the last to survive because they were able to avoid direct competition with modern humans since the two populations exploited distinct territories during the cold climatic conditions of H4. They also point out that during this population event contact between Neanderthals and modern humans may have permitted cultural and genetic exchanges.

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*Citation: Banks WE, d'Errico F, Peterson AT, Kageyama M, Sima A, et al. (2008) Neanderthal Extinction by Competitive Exclusion. PLoS ONE 3(12): e3972. doi:10.1371/journal.pone.0003972 http://dx.plos.org/10.1371/journal.pone.0003972*

## European Neanderthals had ginger hair and freckles

***Neanderthals living in Europe were fair skinned, freckled and had ginger hair, a study has revealed.***

**By Edward Owen** in Madrid Last Updated: 6:51PM GMT 29 Dec 2008

In a major breakthrough, Spanish scientists have discovered the blood group and two other genes of the early humans who lived 43,000 ago. After analysing the fossil bones found in a cave in north-west Spain, the experts concluded they had human blood group "O" and were genetically more likely to be fair skinned, perhaps even with freckles, have red or ginger hair and could talk.

The investigating team from Spain's government scientific institute, CSIC, used the very latest forensic techniques to remove the bones for analysis to prevent them getting contaminated with modern DNA.

Carles Lalueza, an evolutionary biologist with the investigation, said: "What we were trying to do was to create the most realistic image of the Neanderthals with details that are not visible in the fossils, but which form part of their identity." The report, published in BMC Evolutionary Biology, concludes that: "These results suggest the genetic change responsible for the O blood group in humans predates the human and Neanderthal divergence" but came "after humans separated from their common ancestor ... chimpanzees."

The Spanish scientists also describe how they also discovered two other genes. One gene known as MC1R suggests the Neanderthals had fair skin and even freckles like redheads. Another, a variety of FOXP2, is related to speaking and the capacity to create a language and therefore suggests they could communicate orally.

Neanderthals are believed to have numbered about 15,000 and lived in Europe and Asia for about 200,000 years until they became extinct about 30,000 years ago.

Since 2000, archeo-paleontologists, wearing special sealed white suits, masks and helmets have been painstakingly sifting through 1,500 bone fragments found in the "Tunnel of Bones" in the Sidrón cave complex in Borines, Asturias, north-west Spain. Unnatural striations in the bones suggest that the Neanderthals practised cannibalism and broke the bones to pick out succulent bone marrow.

But why this group died, without wild animals discovering and contaminating their remains, or why indeed the Neanderthals in general became extinct, still remains a mystery. "Really we can't establish a direct relation with why the Neanderthals disappeared," says Antonio Rosas.

One theory is that they succumbed to an ice age or another, more sinister, is that they were wiped out by the arrival of our more direct human ancestors from Africa.

## Study Investigates the Cost Effectiveness of Spinal Surgery

### *Rush University Medical Center is only Chicago site in landmark trial*

Chicago – Back pain affects more than 80 percent of people and costs more than $100 billion annually in the U.S. But is the surgery cost effective? A study by researchers at Rush University Medical Center suggests that for patients with spinal stenosis, a laminectomy, or surgical removal of some soft bone and tissue, is a reasonable value. However, for patients with spinal stenosis with associated slipped vertebrae, the benefits of spinal fusion surgery may not be enough to offset costs. The study is published in the December 16 issue of the Annals of Internal Medicine. Rush was one of 13 sites throughout the country and the only Chicago site that followed patients in the Spine Patient Outcomes Research Trial (SPORT).

“This study is significant because it is the first to systematically track people’s health care expenditures and health outcomes,” said Dr. Gunnar Andersson, former chairman of the department of Orthopedics at Rush and study investigator. “More than 650,000 surgical procedures are performed annually for back pain in the United States with costs exceeding $20 billion. Whether this investment provides good value is largely unknown.”

The study looked at two conditions, spinal stenosis that is treated most commonly with laminectomy, which is a procedure where orthopedic surgeons remove the portion of the vertebral bone called the lamina and soft tissue to relieve pressure on the nerves in the spine. The second condition that was analyzed is spinal stenosis with slipped vertebrae also known as spinal stenosis with degenerative spondylolisthesis, which is most commonly treated with spine fusion surgery.

More than 3,900 patients participated in the randomized, controlled trial of surgery versus non-operative treatment. 320 patients underwent laminectomy and 344 patients had spinal fusion.

Researchers used the Quality Adjusted Life Year (QALY) scale to measure benefit to patients in comparison to the direct and indirect costs of the surgical procedures over a two-year period after surgery. The researchers calculate that stenosis surgery using laminectomy cost is $77,000 per QALY gained. In contrast, spinal fusion surgery for stenosis with slipped vertebrae cost about $115,000 per QALY gained. In the U.S., $100,000 is the threshold at which procedures are considered to be cost effective.

The initial two-year analysis indicates that decompressive surgery without fusion for spinal stenosis offers good value and that fusion surgery for spondylolithesis offers less value for its cost than most accepted interventions. A definitive assessment of cost effectiveness awaits longer term outcome data, which will be analyzed further as the trial continues.

“With the number of spine surgery cases in the U.S. increasing and the rising costs of health care expenditures, it is extremely important for us to understand the economic value of common surgical procedures,” said Andersson. “Cost effectiveness is a critical component of providing patients with quality care.”

“With the SPORT trial we have an innovative and collaborative multicenter study of elective orthopedic interventions,” said Andersson. “As we continue to analyze the outcomes of these procedures over the next decade, we will have more long-term results that will benefit back pain patients.”

“For many patients suffering from back pain, getting rid of the pain is worth any cost,” said Andersson.

## Viruses, start your engines!

### *Researchers find what drives one of nature's powerful, nanoscale motors*

Peering at structures only atoms across, researchers have identified the clockwork that drives a powerful virus nanomotor. Because of the motor's strength - to scale, twice that of an automobile - the new findings could inspire engineers designing sophisticated nanomachines. In addition, because a number of virus types may possess a similar motor, including the virus that causes herpes, the results may also assist pharmaceutical

companies developing methods to sabotage virus machinery. Researchers from Purdue University in West Lafayette, Ind., and the Catholic University of America in Washington, D.C., collaborated on the study that appears in the Dec. 26, 2008, issue of the journal Cell.

"The discovery of how this virus motor functions represents a significant milestone in the investigation of viral processes," says David Rockcliffe, the program director who oversees a National Science Foundation (NSF) grant that partly funded the research. "This research is a breakthrough that not only may lead to the development of a means of arresting harmful infections, but it also points to possible ways in which nano-devices could be fashioned,"

The virus in the study, called T4, is not a common scourge of people, but its host is: the bacterium Escherichia coli (E. coli). Purdue researchers studied the virus structures, such as the motor, while the Catholic University researchers isolated the virus components and performed biochemical analyses.

"T4 is what's called a 'tailed virus'," says Purdue biologist Michael Rossmann, one of the lead researchers for the study. "It is actually one of the most common types of organisms in the oceans of the world. There are many different, tailed, bacteria viruses--or phages--and all of these phages have such a motor for packaging their DNA, their genome, into their pre-formed heads."

The virus is well known to scientists. "T4 has rich history going back to 1940s when the original genetic tools to understand virus assembly were developed," adds biologist Venigalla Rao of Catholic University, also a lead researcher on the study. "T4 has been an important model system to tease out the details of basic mechanisms by which viruses assemble into infectious particles."

For the recent study, analyses involved two sophisticated instruments capable of studying structures at the nanometer (billionth of a meter) scale. One of the techniques, x-ray crystallography, showed the ordered arrays of atoms in the various structures, while another, called cryo-electron microscopy, let the researchers study the broader shape of the structures without the need for coating or drying out the specimens.

Having already determined the structures of a number of other viral components and how they self-assemble, in this study the researchers focused their attention on the small motor that some viruses use to package DNA into their "heads", protein shells also called capsids.

Not all viruses have a motor such as the one found in the T4 virus, but some viruses that cause human diseases posses molecular motors with similar functions, and likely have similar structures. T4 uses its motor to pack about 171,000 basepairs of genetic information to near-crystalline density within its 120 nanometer by 86 nanometer capsid. The researchers found that the motor is located at the intersection of the capsid and the virus "tail" and is made of a circular array of proteins called gene product 17 (gp17). Five, two-part, gp17 proteins combine to form a pair of conjoined rings, arrayed so that their upper segments form an upper ring and their lower segments form a lower ring.

As a T4 virus assembles itself, the lower ring of the motor structure attaches to a strand of DNA, while the upper ring attaches to a capsid. The upper and lower rings have opposite charges, which allow the motor to contract and release, alternately tugging at the DNA like a ring of hands pulling on a rope. The process draws the DNA strand upwards into the capsid where it is protected from damage, enabling the virus to survive and reproduce. After the DNA is inside the capsid, the motor falls off, and a virus tail attaches to the capsid.

Until now, researchers did not know how T4, or any other virus, accomplished the DNA packaging. According to Rao, "Since the assembly of herpes viruses closely resembles that of T4, this research might provide insights on how to manipulate herpes infections."

While many questions remain, adds Rossmann, the virus may lend itself to a variety for medical purposes. One example Rossmann cites is as a potential new weapon to fight dangerous microbes.

"Bacteriophages like T4 are a completely alternative way of dealing with unwanted bacteria. The virus can kill bacteria in its process of reproduction, so use of such viruses as antibiotics has been a long looked-for alternative to overcome the problems which we now have with antibiotics."

## Moderate Drinking Can Reduce Risks Of Alzheimer's Dementia And Cognitive Decline

### *But Abusing Alcohol can Damage Brain, Loyola Researchers say*

MAYWOOD, Ill. -- Moderate drinkers often have lower risks of Alzheimer's disease and other cognitive loss, according to researchers who reviewed 44 studies.

In more than half of the studies, published since the 1990s, moderate drinkers of wine, beer and liquor had lower dementia risks than nondrinkers. In only a few studies were there increased risks.

"Alcohol is a two-edged sword," said Michael Collins, Ph.D., a professor and neuroscientist at Loyola University Chicago Stritch School of Medicine and lead author of the refereed report in the journal Alcoholism: Clinical and Experimental Research. "Too much is bad. But a little might actually be helpful." Moderate alcohol consumption generally is defined as 1 drink or less per day for women and 1-2 drinks or less per day for

men. The article will be published in the February 2009 issue of the journal, and is available on line now. The article summarizes a roundtable, organized by Collins, held at the Research Society on Alcoholism meetings in Chicago in 2007.

"The pathological damage and vast social havoc from addiction to and abuse of alcohol are well known, and of necessity should continue to receive primary attention by doctors, scientific researchers and health professionals," Collins and colleagues write. "However, light-to-moderate responsible alcohol consumption "appears to carry certain health benefits."

Long-term alcohol abuse can cause memory loss and impair cognitive function. It's unknown why moderate alcohol use appears to have the opposite effect. One theory is that the well-known cardiovascular benefits of moderate alcohol consumption also can reduce the risk of mini strokes that cause dementia.

Collins and another Loyola professor, neuroscientist Edward Neafsey, Ph.D., suggest a second possible explanation. Small amounts of alcohol might, in effect, make brain cells more fit. Alcohol in moderate levels stresses cells and thus toughens them up to cope with major stresses down the road that could cause dementia.

For most people who drink responsibly and in moderation, there's probably no reason to quit. But because of the potential for alcohol to be abused, Collins and Neafsey do not recommend that abstainers begin drinking. The researchers note there are other things besides moderate drinking that can reduce the risk of dementia, including exercise, green tea, education and a Mediterranean diet high in fruits, vegetables, cereals, beans, nuts and seeds. Moreover, there are times when people should never drink, including adolescence, pregnancy and before driving, Collins said.

## Vitamins C and E and beta carotene again fail to reduce cancer risk in randomized controlled trial

Women who took beta carotene or vitamin C or E or a combination of the supplements had a similar risk of cancer as women who did not take the supplements, according to data from a randomized controlled trial in the December 30 online issue of the Journal of the National Cancer Institute.

Epidemiological studies have suggested that people whose diets are high in fruits and vegetables, and thus antioxidants, may have a lower risk of cancer. Results from randomized trials that address the issue, however, have been inconsistent and have rarely supported that observation.

In the current study, Jennifer Lin, Ph.D., of the Brigham and Women's Hospital and Harvard Medical School in Boston, and colleagues tested the impact of antioxidant supplements on cancer incidence in a randomized controlled trial. A total of 7,627 women who were at high risk of cardiovascular disease were randomly assigned to take vitamin C, vitamin E, or beta-carotene.

With an average of 9.4 years of follow-up time, there was no statistically significant benefit from antioxidant use compared with placebo in terms of disease risk or mortality due to cancer. Overall, 624 women developed cancer and 176 died from cancer during the follow-up time. Compared with placebo, the relative risk of a new cancer diagnosis was 1.11 for women who took vitamin C, 0.93 for women who took vitamin E, and 1.00 for women who took beta carotene. None of these relative risks was statistically significantly different from 1.

"Supplementation with vitamin C, vitamin E, or beta carotene offers no overall benefits in the primary prevention of total cancer incidence or cancer mortality," the authors conclude. "In our trial, neither duration of treatment nor combination of the three antioxidant supplements had effects on overall fatal or nonfatal cancer events. Thus, our results are in agreement with a recent review of randomized trials indicating that total mortality was not affected by duration of supplementation and single or combined antioxidant regimens."

In an accompanying editorial, Demetrius Albanes, M.D., of the National Cancer Institute, reviewed data from previous randomized controlled trials that examined supplement use and cancer incidence. He noted that while the trial data reported by Lin are negative with respect to lowering cancer risk, there is valuable information uncovered that should not be overlooked. There was a trend for a reduction in colon cancer with vitamin E supplementation, which has been observed in other studies. Additionally, beta carotene use was associated with a modest excess of lung cancer, which is consistent with previous reports.

"Null trials or those with unexpected outcomes should not, however, be viewed as failures; they have and will continue to shed light on the causes of cancer and help us discover the means for its prevention," the editorialist concludes.

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*Editorial: NCI Press Office, ncipressofficers@mail.nih.gov, 301-496-6641*
*Article: Lin J et al.,Vitamins C and E and Beta Carotene Supplementation and Cancer Risk: A Randomized Controlled Trial. J Natl Cancer Inst 2009:101:14-23.*
*Editorial: Albanes D, Vitamin Supplements and Cancer Prevention: Where Do Randomized Controlled Trials Stand? J Natl Cancer Inst 2009:101:2-4.*

## How to knit a brain

* 30 December 2008 **by Michael Brooks**

AS SOON as she saw her first images of the brain, Marjorie Taylor was spellbound. The vibrant pinks and blues, the intricate detailing - somehow they spoke to her. "I couldn't help but look at them with the eye of a quilter," says Taylor, a psychologist at the University of Oregon. "I thought the folds of the cerebral cortex would be great in velvet."

And so was born a new genre of visual art: scientifically accurate fabric brains. True to her original vision, Taylor's first piece was a quilt with a cerebral cortex in blue velvet on a silver background. She has since completed three more brain-themed quilts. "Not very many," she admits. "They take a long time to do."

Taylor isn't the only fabric artist who draws inspiration from neuroscience. Psychiatrist Karen Norberg of the National Bureau of Economic Research in Cambridge, Massachusetts, also creates anatomically correct fabric brain art. Independently of Taylor, she decided to make an accurate model of the human brain - in wool.

It took a year to knit, and the result is astonishing. The cortex of Norberg's larger-than-life brain has realistic folds, while the internal structure is correct down to the nearest stitch. All the parts are properly connected, as can be revealed by undoing a well-concealed zip that connects the two hemispheres.

Like all the best art, the brain is a one-off. "This is one of a kind," says Norberg. "It's a labour of love."

The woollen brain is now housed at the ***Museum of Science in Boston***, while Taylor's works hang in various offices and institutes around the University of Oregon. "Someday we hope to bring all the pieces together for a show," says Taylor. For now, images of both women's work can be seen at the online Museum of Scientifically Accurate Fabric Brain Art (***http://harbaugh.uoregon.edu/Brain/index.htm***), curated by neuro-economist Bill Harbaugh of the University of Oregon.

Neither artist is resting on her textile laurels. At the moment, Taylor is using a traditional Nova Scotian technique to make a rug depicting an fMRI scan of the brain lighting up in response to spoken words. Norberg is working on quilts showing the chemical structure of various brain hormones and neurotransmitters. "It seems to work well to represent them using a very traditional quilting pattern," she says.

Norberg and Taylor don't take their art too seriously. Norberg accepts that there is something faintly ridiculous about knitting a brain. And yet, she says, it was surprisingly instructive. "It's a way to learn microanatomy and neurodevelopment." Taylor also sees the humorous side. "I do think it's beautiful, but there is something funny about it," she says. But she too remains defiant about her hobby. "There are plenty of rugs that show flowers and cats and lighthouses," she points out. "Why not fMRI scans?"

## Radical alternatives proposed for cannabis controls

* 30 December 2008 **by Andy Coghlan**

WHAT should we do to minimise the harm cannabis can cause to the health and welfare of users and to society at large? The answer, according to a report by a group of prominent academics and government advisers, is to change the law to allow the state to prepare and distribute the drug for recreational use.

This controversial proposal comes from a commission assembled by the Beckley Foundation, a British charity dedicated to exploring the science of psychoactive substances. "The damage done by prohibition is worse than from the substance itself," says Amanda Feilding, the founder of the Beckley Foundation.

The Beckley commission's ideas will be aired in March at a meeting in Vienna, Austria, of the UN Commission on Narcotic Drugs. The UNCND will report to a meeting of the UN general assembly later this year that will set international policy on drug control for the decade to come.

Marijuana is now the world's most widely used illicit drug. The latest figures from the UN Office on Drugs and Crime (UNODC) indicate that in 2006-7 some 166 million people aged 15 or above, or 3.9 per cent of this age group, used it regularly. Just 1 per cent of the world population uses other illegal drugs. Cannabis use is particularly widespread in rich countries. Around 40 per cent of Americans and one-third of Australians say they have tried it.

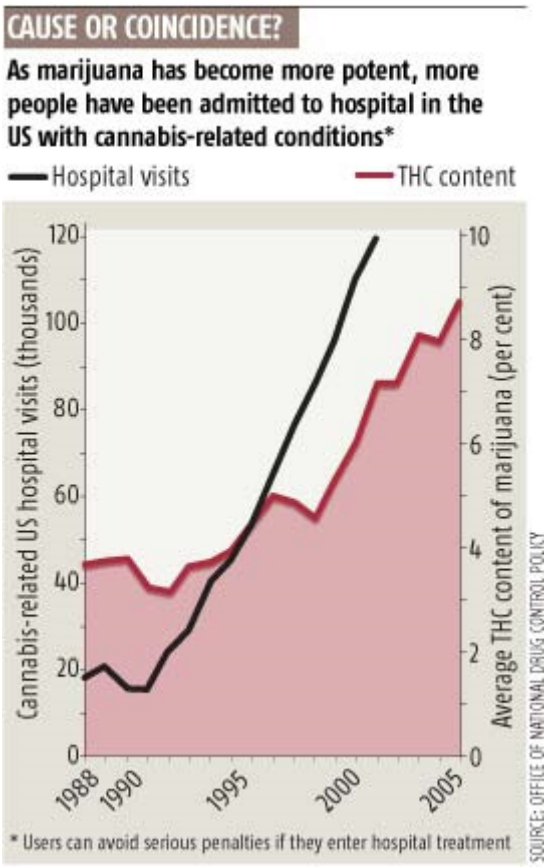
The evidence assembled by the Beckley commission left it in no doubt that cannabis damages the health of heavy users, especially those who start as teenagers. Such users are at increased risk of suffering from psychosis, and lung and heart disorders. They are also more likely to drop out of school early, be involved in traffic accidents, and be poor parents (see "How bad is it?"). The report also found evidence that cannabis may

act as a "gateway drug", increasing the likelihood that users will go on to try more damaging drugs such as heroin or cocaine.

The report details a sharp rise in the potency of marijuana, with levels of delta-9-tetrahydrocannabinol (THC) - the chemical that gets cannabis users "stoned" - typically double to treble what they were a decade ago. This, it says, is partly the result of a switch to growing the plant indoors under continuous lighting.

Potent varieties, sometimes known as "skunk" or "sinsemilla", now make up 80 per cent of the market in the UK and the Netherlands according to a report published by the UK home office. These varieties also lack a compound called cannabidiol found in other cannabis strains, which when present may help prevent THC triggering psychotic episodes. About 9 per cent of regular cannabis users become dependent - experiencing withdrawal if they stop using - and suffer ill health as a result of their drug use, the Beckley authors say.

Despite the undoubted dangers associated with marijuana, the Beckley report concludes that it is far less harmful to users and to society in general than other illicit drugs such as heroin and cocaine, and far less damaging than the legal drugs tobacco and alcohol. There have been only two documented deaths from marijuana overdose, the report notes. This contrasts with 200,000 deaths from all causes each year attributed to other illegal drugs, 2.5 million deaths annually related to alcohol and 5 million to smoking.




***Cause or coincidence***

Because possession of cannabis is illegal, its harmful consequences extend beyond possible damage to immediate health, the Beckley report points out. In particular, users are at risk of punishment and acquiring a criminal record. "If you don't think being arrested is a harm, you are unpersuadable," says criminologist Peter Reuter of the University of Maryland, a co-author of the report. "In the US, 750,000 people were arrested in 2006, and I think that's a substantial harm."

The report recommends that marijuana should be sold legally, subject to strict standards to ensure it is not strong enough to cause psychological problems. This, it says, would allow a strict age bar to be imposed that would prevent children from buying it, and put the criminal gangs who peddle it out of business. Cannabis buyers would not be offered other drugs by the licensed dealers, removing this as a possible route of progression from cannabis to other drugs.

The framework for drug laws worldwide is now set by the 1961 Single Convention on Narcotic Drugs, which has been signed by the overwhelming majority of nations. Though the convention requires that all signatories make possession of cannabis illegal, some have experimented with decriminalisation. The Netherlands, for example, no longer arrests and punishes people found to have small amounts of cannabis, though large-scale supply remains illegal and in the hands of criminal gangs.

The legalisation proposed by the Beckley group is likely to face strong opposition in Vienna both from the UN Office on Drugs and Crime and from many governments. The fear is that easing up on cannabis will undermine the whole international effort to combat recreational drug use. "Cannabis is the most vulnerable point of the whole multilateral edifice," Antonio Maria Costa, executive director of the UNODC, said in a speech in March 2008.

The US has set its face firmly against any move towards legalisation, fearing that this would produce a nation of dope-heads. A document launched in July 2008 by the US Office of National Drug Control Policy (ONDCP) declared marijuana to be "the greatest cause of illegal drug abuse".

Dave Murray, head of research at the ONDCP, told New Scientist that strict enforcement of anti-drug laws had helped cut teenage use of marijuana by 25 per cent between 2001 and 2008. In the absence of prohibition, it would have been difficult to achieve that," he says.

By contrast, the Beckley authors, among others, argue that punishment does not reduce cannabis use and itself causes harm. Their view is backed by a study in 2000 by Simon Lenton of the National Drug Research Institute in Perth, Western Australia, which compared what happened to people in Western Australia, where cannabis possession attracts a criminal conviction and penalty, with those in South Australia who were given non-punitive infringement notices. He found that 32 per cent of those "criminalised" reported adverse

employment consequences compared with 2 per cent of "infringers". The criminalised users were also far more likely to be involved in crime again, and to suffer housing and relationship problems.

Feilding accepts that there may be few takers in Vienna for her group's proposals. But the mere fact that an alternative to the strict prohibition of cannabis will even be considered is a breakthrough in itself, she says.

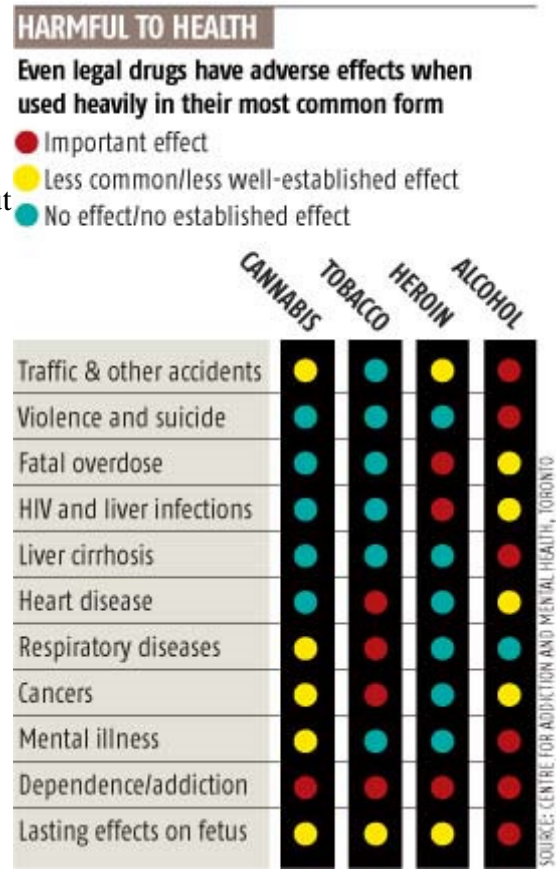
**How bad is it?**

The most damaging of the possible ill effects of cannabis use is psychosis. "You're 40 per cent more likely to get psychotic disturbances if you're a user from early life," says Les Iverson at the University of Oxford, who is a member of the UK government's Advisory Committee on the Misuse of Drugs (ACMD). He points out however, that cannabis is not necessarily the cause in all these cases.

Dave Murray, head of research at the US Office of National Drug Control Policy, says that in the US the rise in strength and market dominance of potent marijuana strains has paralleled a rise in emergency hospital admissions of people suffering psychoses after cannabis use.

Another worry with cannabis is that it is a "gateway" drug encouraging use of more damaging substances. Murray says that cannabis users who start young are between 9 and 15 times as likely to become heroin or cocaine users. "We can't say one causes the other, but there's a strong correlation," he notes.

There is also the danger of traffic accidents: cannabis intoxication raises a driver's risk of crashing by 1.3 to 3 times. By contrast, alcohol intoxication raises the accident risk by up to 15 times.




About 9 per cent of regular cannabis users become dependent, compared with 32 per cent of tobacco smokers, 23 per cent of heroin users, 17 per cent of cocaine users and 15 per cent of those drinking alcohol. Respiratory and lung cancer risks are also raised for cannabis users, and they can sustain damage to verbal learning ability, memory and attention. According to the Beckley report, permanent changes in receptors of the hippocampus, prefrontal cortex and cerebellum have been seen in heavy cannabis users. There are also links between early cannabis use and poor school performance. Whether this is a result of cannabis itself, or because they share some other common cause, such as poverty, is not known. Overall, an analysis of 20 drugs by David Nutt at the University of Bristol, UK, who chairs the ACMD, rated cannabis as the 11th most harmful drug, well behind alcohol and tobacco.

## Ancient Earth was a barren waterworld

* 30 December 2008 **by David Shiga**

DRY land may be something of a novelty. Until around 2.5 billion years ago our planet was almost completely covered by water, a model of the early Earth suggests. Today, some 28 per cent of Earth's surface is above sea level. Exactly how the ratio of land to sea has varied through Earth's history is unclear, but it is generally agreed that the amount of continental crust has increased over time.

Now, calculations by Nicolas Flament of the University of Sydney, Australia, and colleagues suggest that Earth was a water-world until about 2.5 billion years ago, with land making up only 2 to 3 per cent of its surface (Earth and Planetary Science Letters, DOI: 10.1016/j.epsl.2008.08.029).

The team assumed that back then Earth's mantle was up to 200 °C hotter than it is now, mainly because there was then a larger quantity of radioactive elements decaying and producing heat. A hotter mantle would have made the crust beneath the oceans hotter and thicker than it is today, buoying it up relative to the continents. The resulting shallower ocean basins would have held less water, leading to the flooding of what is now land. In addition, the hotter mantle would cause the continental crust of the time to spread laterally, making it lower-lying and flatter than today, and so more likely to flood.

Then, as the mantle cooled, land would have gradually appeared as the oceans became deeper and regions of high relief on the continental crust formed. The team believe that this transition may help to explain why levels of oxygen in the atmosphere rose around this time. During the water-world period, any oxygen produced by photosynthesising bacteria would have been quickly used up through reactions with decaying organic matter in the oceans. When the newly emerged land eroded, it produced sediment that, once washed into the oceans, would have buried the organic matter, preventing any further reactions with oxygen, and so allowing it to build up in the atmosphere.

This would have allowed oxygen-breathing organisms to flourish, say the team. The eroded sediment would also have caused an explosion in life by fertilising the oceans with phosphorus - an important nutrient. And newly formed coastal regions would have provided plenty of shallow habitats for photosynthesis.

Stephen Mojzsis of the University of Colorado, Boulder, agrees that the early continental regions could have been mostly flooded at this time. However, he suspects the land fraction was not quite as low as 2 to 3 per cent because many rocks of this age appear to have formed from sediment washed off dry land.

## Beer marinade cuts steak cancer risk

IF YOU are frying a steak and mindful of your health, then marinate it in either beer or red wine. So say food scientists who measured amounts of a family of carcinogens found in fried steaks after steeping them in booze.

Cooking food increases levels of cancer-causing compounds called heterocyclic amines (HAs). Fried and grilled meat are particularly high in these compounds, because fiery temperatures convert the sugars and amino acids in muscle tissue into HAs. Various substances can reduce HA content: an olive oil, lemon juice and garlic marinade cut HAs in grilled chicken by 90 per cent, while red wine reduced HAs in fried chicken.

Now Isabel Ferreira and colleagues at the University of Porto in Portugal have looked at the effects of beer and red wine marinades on fried steak. Six hours of marinating in beer or red wine slashed levels of two types of HA by up to 90 per cent compared with unmarinated steak (Journal of Agricultural and Food Chemistry, DOI: 10.1021/jf801837s).

For a third type of HA, beer was more efficient at reducing its content than wine, cutting levels significantly in 4 hours, while wine took 6. Beer contains more water-retaining sugars than wine and Ferreira says that may hinder the transport of water-soluble molecules to the steak's surface, where high heat converts them into HAs. Tasters also preferred the smell, taste and appearance of beer-marinated steak.

**Really?**

## The Claim: New Year's Is the Most Dangerous Time of the Year to Be on the Road

**By ANAHAD O'CONNOR**


**Leif Parsons**

**THE FACTS** With all the open bars, people on the road and rejoicing in the streets, it is easy to imagine that New Year's is a risky time. Holidays are the most hazardous time for drivers, a result of sharp increases in traveling and drunken driving. And when it comes to New Year's, research over the years offers sobering statistics.

According to research by the Insurance Institute for Highway Safety, which examined accident data in the United States from 1986 to 2002, the day of the year with the most fatalities from accidents is the Fourth of July, with an average of 161. Not far behind are July 3 (149) and Dec. 23 (145). New Year's Day is fourth, with 142.

A closer look reveals something peculiar: New Year's Day is the deadliest for pedestrians. In the study period, 410 of those killed on New Year's were pedestrians, slightly more than on Halloween (401). For New Year's, the problem was largely that of increased drinking and celebrations. Half the deaths involved alcohol impairment, and 58 percent of the pedestrians who were killed had a high blood-alcohol concentration, the study found.

Something to keep in mind as the Champagne flows Wednesday night.

**THE BOTTOM LINE** New Year's Day is not the most hazardous day for drivers, but it's up there.

**Personal Health**

## 'Cookbook Medicine' Won't Do for Elderly

**By JANE E. BRODY**

The Martha Stewart Center for Living at Mount Sinai Medical Center in New York is like no medical clinic I've ever seen. It is brightly lighted and quiet- there is no television blasting. It has wide corridors and plenty of comfortable chairs with sturdy arms, and yet few people wait more than 10 minutes to see a doctor or nurse practitioner.

The center, which opened in 2007, was designed especially for primary care of older adults, many of whom have complex chronic medical problems like diabetes, heart disease and hypertension as well as debilitating conditions like arthritis and osteoporosis.

Just as a child is not a small adult and requires specialized care, adults over the age of, say, 65, are not just old adults and should not be treated like patients half their age.

The population of aging Americans is expected to mushroom in the years ahead. Geriatricians, the experts in elder care, are already in short supply, and their numbers will continue to shrink. But knowing the kind of care

that these specialists provide may help older people and those who look after them learn to seek it out wherever they go.

"Cookbook medicine may be appropriate for younger people but is not always appropriate for older people," Dr. Mark Lachs, a geriatrician at Weill-Cornell Medical Center in New York, said in an interview. He sees two dangers in how older adults are treated: overtreatment and undertreatment.

"If a high-functioning 80- or 90-year-old develops angina, aggressive treatment would be appropriate," Dr. Lachs said. "Care should not be withheld solely on the basis of age."

On the other hand, overtesting and overtreating older patients can result in debilitating side effects. Before deciding on tests and treatment, he said, "the doctor must take into account the whole picture of the patient, the patient's family and life situation."

**Screening for Lifestyle**

Dr. R. Sean Morrison is one of the geriatricians at Mount Sinai. "The overall goal is to help older adults achieve the best quality of life possible, given the limits of medical technology and knowledge," he said.

When I asked how he would approach a new patient of 85, Dr. Morrison said he would start with a series of questions: "Tell me about yourself. What do you like to do? What are the things you would like to do that you cannot do anymore? What is your medical history? What medications do you currently take? What brings you here today?"

The geriatric exam itself would depend on the patient's answers. "If the patient is a healthy 75-year-old who plays golf and tennis and has no functional limitations," Dr. Morrison said, "the focus would be on preventive screening and advance care planning.

"But if the patient has functional limitations, the focus would be to restore and improve what can be restored and improved, such as reducing the risk of falls, addressing any acute medical conditions, and streamlining medications for chronic health problems so that the right drugs are taken for the right conditions."

"You want a doctor who asks more than just about your medical conditions," he added. The doctor should ask about the effect of medical conditions on quality of life, and then should explore what improvements are possible. "The focus of care should be on quality of life," he said. "Too often, doctors lose sight of this goal when the focus is on treating specific diseases."

The doctor should address a patient's most serious health threats, of course, but also the patient's most serious concerns. Is the patient troubled by problems like fatigue, pain or shortness of breath, or having problems with medications?

For example, he said, if a patient has serious arthritis and hypertension and cannot go to places without a readily accessible bathroom on the first floor because she takes a diuretic for high blood pressure, perhaps the blood pressure medication should be changed. The patient may prefer a different drug that carries a slightly greater risk of stroke if it means a better quality of life.

**The Exam**

"When going to a new doctor, an older patient should receive a comprehensive assessment, not just a physical exam," Dr. Chad Boult, a geriatrician at the Johns Hopkins School of Public Health, said in an interview. "The patient should be asked, What is important to you about your health now? What is your life like - your exercise habits, diet, use of alcohol and tobacco? Is your environment safe and convenient?"

There are three areas that should be explored during a geriatric exam that are often missed if the doctor focuses on a specific illness, Dr. Morrison said:

**Dementia**. He asks the patient: "Are you having trouble with your memory? Is it O.K. if I check with a family member about this?" He said there were often treatable causes for memory problems, like thyroid disease, medication side effects or depression.

**Risk of falls.** Checking balance, gait and strength is easy, he said. "I would meet you in the waiting room, watch how you stand up from a chair and walk to the exam room. I'd throw a pen on the floor and ask you to pick it up. I'd ask you to sit in a chair and stand up three times as quickly as you can. Can you get up and down without using the arms of the chair? If the patient uses a cane, how is it used and is it the right height?"

**Incontinence.** "There's a tremendous social stigma associated with incontinence even when there are medical reasons for it," Dr. Morrison said. It is as common as hypertension and diabetes among the elderly, but patients rarely discuss it with their doctors unless asked about it, he said.

Dr. Boult said that patients' feet were often overlooked, leading to problems that can become life-limiting. Many older people cannot reach their feet to clean them and cut their toenails, and they develop painful sores.

**Other Considerations**

Dr. Morrison said that before recommending screening tests like mammograms for breast cancer and PSA tests for prostate cancer, the question to ask is, "What are we going to do with the test results? If we're not

going to act on them, screening should be stopped." If a patient has chronic conditions that limit life expectancy, he said, there is no point in screening for most cancers.

On the other hand, he said, two medical procedures can greatly improve the quality of life for older adults: joint replacement and cataract surgery. Too often, patients think such surgeries aren't worth the bother because they won't be around much longer. He described a woman who at 82 was having trouble walking but chose not to have a knee replacement. Now 102, the patient told him, "I should have listened to you years ago."

Like this woman at 82, many older people are quite healthy, Dr. Boult said.

But about one-quarter of the older population has multiple chronic conditions and spends 80 percent of Medicare dollars, he added. "These patients need coordinated care, a system of regular monitoring, and regular access to a primary care doctor who can detect problems early before they require expensive, dramatic treatments."

**Vital Signs**

## Having a Baby: Vitamin D Deficiency Is Tied to C-Sections

**By NICHOLAS BAKALAR**

Vitamin D deficiency may increase the likelihood of having a Caesarean section, a new study has found.

At the turn of the 20th century, according to background information in the report, deformed bones in the pelvis often led to a C-section, a problem that virtually disappeared with the vitamin D fortification of milk and other foods. But this study, published online Dec. 23 in The Journal of Clinical Endocrinology & Metabolism, suggests that vitamin D deficiency in pregnancy is still a problem.

The researchers studied 253 births at a Boston hospital from 2005 to 2007. After controlling for other variables, the scientists found that women with low blood levels of vitamin D were almost four times as likely to have an emergency C-section as those with normal levels. Vitamin D deficiency has been associated with muscle weakness and high blood pressure, which might help explain the finding.

Dr. Michael Holick, a professor of medicine at Boston University and the senior author of the study, offered straightforward advice for pregnant women. "Take a thousand-unit supplement of vitamin D, available at any pharmacy, on top of any prenatal vitamins you're taking, so that you're getting 1,400 units a day," he said. "There is no downside to doing this."

## Grape-seed extract kills laboratory leukemia cells, proving value of natural compounds

PHILADELPHIA – An extract from grape seeds forces laboratory leukemia cells to commit cell suicide, according to researchers from the University of Kentucky. They found that within 24 hours, 76 percent of leukemia cells had died after being exposed to the extract.

The investigators, who report their findings in the January 1, 2009, issue of Clinical Cancer Research, a journal of the American Association for Cancer Research, also teased apart the cell signaling pathway associated with use of grape seed extract that led to cell death, or apoptosis. They found that the extract activates JNK, a protein that regulates the apoptotic pathway.

While grape seed extract has shown activity in a number of laboratory cancer cell lines, including skin, breast, colon, lung, stomach and prostate cancers, no one had tested the extract in hematological cancers nor had the precise mechanism for activity been revealed.

"These results could have implications for the incorporation of agents such as grape seed extract into prevention or treatment of hematological malignancies and possibly other cancers," said the study's lead author, Xianglin Shi, Ph.D., professor in the Graduate Center for Toxicology at the University of Kentucky.

"What everyone seeks is an agent that has an effect on cancer cells but leaves normal cells alone, and this shows that grape seed extract fits into this category," he said. Shi adds, however, that the research is not far enough along to suggest that people should eat grapes, grape seeds, or grape skin in excess to stave off cancer. "This is very promising research, but it is too early to say this is chemo-protective."

Hematological cancers - leukemia, lymphoma and myeloma - accounted for an estimated 118,310 new cancer cases and almost 54,000 deaths in 2006, ranking these cancers as the fourth leading cause of cancer incidence and death in the U.S.

Given that epidemiological evidence shows that eating vegetables and fruits helps prevent cancer development, Shi and his colleagues have been studying chemicals known as proanthocyanidins in fruits that contribute to this effect. Shi has found that apple peel extract contains these flavonoids, which have antioxidant activity, and which cause apoptosis in several cancer cell lines but not in normal cells. Based on those studies, and findings from other researchers that grape seed extract reduces breast tumors in rats and skin tumors in mice, they looked at the effect of the compound in leukemia cells.

Using a commercially available grape seed extract, Shi exposed leukemia cells to the extract in different doses and found the marked effect in causing apoptosis in these cells at one of the higher doses.

They also discovered that the extract does not affect normal cells, although they don't know why.

The researchers then used pharmacologic and genetic approaches to determine how the extract induced apoptosis. They found that the extract strongly activated the JNK pathway, which then led to up-regulation of Cip/p21, which controls the cell cycle.

They checked this finding by using an agent that inhibited JNK, and found that the extract was ineffective. Using a genetic approach – silencing the JNK gene – also disarmed grape seed extract's lethal attack in leukemia cells. "This is a natural compound that appears to have relatively important properties," Shi said.

## A new light on the anti-tumor mechanisms of Scutellaria barbata

半枝蓮

Medicinal plants have been used as traditional remedies for hundreds of years. Among them, S. barbata has been traditionally used in treatment of hepatitis, inflammation, osteomyelitis and gynecological diseases in China. Studies indicate that extracts from S. barbata have growth inhibitory effects on a number of human cancers. Reports are available on the treatment of lung, breast and digestive system cancer, hepatoma, and chorioepithelioma with S. barbata extracts. However, the underlying mechanism of the antitumor activity of S. barbata extracts remains unclear.

A research article to be published on December 28, 2008 in the World Journal of Gastroenterology addresses this question. The research team led by Dr. Zhi-Jun Dai from the Medical School of Xi'an Jiaotong University studied the growth inhibitory effects of S. barbata and determined its mechanism of antitumor activity in mouse liver cancer cell line H22.

They found that ESB could inhibit the proliferation of H22 cell in a time dependent manner. Among the various phases of cell cycle, the percentage of cells in S phase was significantly decreased, while the percentage of cells in G1 phase was increased. Flow cytometry assay also showed ESB had positive effect on apoptosis. Typical apoptotic morphology such as condensation and fragmentation of nuclei and blebbing membrane of the apoptotic cells could be observed through transmission electron microscope and fluorescence microscope. Further investigating the molecular mechanism behind ESB-induced apoptosis, cells treated with ESB underwent a rapid loss of mitochondrial transmembrane potential(delta psi m), release of mitochondrial cytochrome c into cytosol, induction of caspase-3 activity in a dose-dependent manner. This may offer new evidence for S. barbata in the treatment of hepatoma in clinical practice.

*Reference: Dai ZJ, Wang XJ, Li ZF, Ji ZZ, Ren HT, Tang W, Liu XX, Kang HF, Guan HT, Song LQ. Scutellaria barbate extract induces apoptosis of hepatoma H22 cells via the mitochondrial pathway involving caspase-3. World J Gastroenterol 2008; 14(48): 7321-7328 http://www.wjgnet.com/1007-9327/14/7321.asp*

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## USC dentist links Fosomax-type drugs to jaw necrosis

### *Study is among first to link short term drug use for osteoporosis to bone death*

Researchers at the University Of Southern California, School Of Dentistry release results of clinical data that links oral bisphosphonates to increased jaw necrosis. The study is among the first to acknowledge that even short-term use of common oral osteoporosis drugs may leave the jaw vulnerable to devastating necrosis, according to the report appearing in the January 1 Journal of the American Dental Association (JADA).

Osteoporosis currently affects 10 million Americans. Fosomax is the most widely prescribed oral bisphosphonate, ranking as the 21st most prescribed drug on the market since 2006, according to a 2007 report released by IMS Health.

"Oral Bisphosphonate Use and the Prevalence of Osteonecrosis of the Jaw: An Institutional Inquiry" is the first large institutional study in the U.S. to investigate the relationship between oral bisphosphonate use and jaw bone death, said principal investigator Parish Sedghizadeh, assistant professor of clinical dentistry with the USC School of Dentistry.

After controlling for referral bias, nine of 208 healthy School of Dentistry patients who take or have taken Fosamax for any length of time were diagnosed with osteonecrosis of the jaw (ONJ). The study's results are in contrast to drug makers' prior assertions that bisphosphonate-related ONJ risk is only noticeable with intravenous use of the drugs, not oral usage, Sedghizadeh said. "We've been told that the risk with oral bisphosphonates is negligible, but four percent is not negligible," he said.

Most doctors who have prescribed bisphosphonates have not told patients about any oral health risks associated with the use of the drugs, despite even short-term usage posing a risk due to the drug's tenacious 10-year half

life in bone tissue. Lydia Macwilliams of Los Angeles said no one told her about the risk posed by her three years of Fosamax usage until she became a patient of Sedghizadeh at the School of Dentistry. "I was surprised," she said. "My doctor who prescribed the Fosamax didn't tell me about any possible problems with my teeth."

Macwilliams was especially at risk for complications because she was to have three teeth extracted. The infection is a biofilm bacterial process, meaning that the bacteria infecting the mouth and jaw tissues reside within a slimy matrix that protects the bacteria from many conventional antibiotic treatments, and bisphosphonate use may make the infection more aggressive in adhering to the jaw, Sedghizadeh said. The danger is especially pronounced with procedures that directly expose the jaw bone, such as tooth extractions and other oral surgery. After her extractions, two of the three extraction sites had difficulty healing due to infection, Macwilliams said. Luckily, with treatment as well as the rigorous oral hygiene regimen USC dentists developed especially for patients with a history of bisphosphonate usage, the remaining sites slowly but fully healed. "It took about a year to heal," she said, "but it's doing just fine now."

Sedghizadeh hopes to have other researchers confirm his findings and thus encourage more doctors and dentists to talk with patients about the oral health risks associated with the widely used drugs. The results confirm the suspicions of many in the oral health field, he said. "Here at the School of Dentistry we're getting two or three new patients a week that have bisphosphonate-related ONJ," he said, "and I know we're not the only ones seeing it."

## Did a Comet Hit Earth 12,000 Years Ago?

***Nanodiamonds found across North America suggest that major climate change could have been cosmically instigated***

**By David Biello**

Roughly 12,900 years ago, massive global cooling kicked in abruptly, along with the end of the line for some 35 different mammal species, including the mammoth, as well as the so-called Clovis culture of prehistoric North Americans. Various theories have been proposed for the die-off, ranging from abrupt climate change to overhunting once humans were let loose on the wilds of North America. But now nanodiamonds found in the sediments from this time period point to an alternative: a massive explosion or explosions by a fragmentary comet, similar to but even larger than the Tunguska event of 1908 in Siberia.

Sediments from six sites across North America—Murray Springs, Ariz.; Bull Creek, Okla.; Gainey, Mich.; Topper, S.C.; Lake Hind, Manitoba; and Chobot, Alberta—yielded such teensy diamonds, which only occur in sediment exposed to extreme temperatures and pressures, such as those from an explosion or impact, according to new research published today in Science.

***DEEP IMPACT?: This 40 centimeter band of dark sediment uncovered at Murray Spring, Ariz., may indicate a cosmic impact or explosion that kicked off a period of global cooling and a mass extinction in North America.***

**Courtesy of Doug Kennett**

The discovery lends support to a theory first advanced last year in that some type of cosmic impact or impacts—a fragmented comet bursting in the atmosphere or raining down on the oceans—set off the more than 1,300-year cooling period in the Northern Hemisphere known as the Younger Dryas for the abundance of an alpine flower's pollen found during the interval.

The cooling period interrupted an extended warming out of an ice age predicted by slight changes in Earth's orbit (known as Milankovitch cycles) that continues today. And it remains an unexplained anomaly in the climate record.

But a series of cometary fragments exploding over North America might explain a layer of soil immediately prior to the cooling containing unusually high levels of iridium—an element more common in cosmic wanderers like meteoroids than in Earth's crust. Paired with the fact that this layer occurs directly before the extinction of at least 35 genera of large mammals, including mammoths, it is strong circumstantial evidence for a cosmic event.

"Very strong impact indicators are found in the sediments directly above, and often shrouding in the case of Murray Springs, the remains of these animals and the people who were hunting them," says archaeologist and study co-author Doug Kennett of the University of Oregon in Eugene, the son in the father–son team helping to advance the new impact theory. "Is it a comet? Is it a carbonaceous chondrite? Was it fragmented? Was it focused? Based on the distribution of the diamonds, it was certainly large scale."

Preliminary searches further afield—Europe, Asia and South America—have turned up similar minerals and elements in sediments of the same age, Kennett says, and his own work on California's Channel Islands tells a tale of a massive burn-off, followed by erosion and a total change in the flora of the region.

"It's consistent with a fragmentary body breaking up with air shocks and possible surface impacts in various parts of North America. It could be above the ice sheet or offshore in the ocean," he says, explaining why no impact crater(s) has been found to date. "Immediate effects on the ground include high temperatures and pressures triggering major transformations of the vegetation, knocking trees over but also burning."

And that would make the climate shift of the Younger Dryas a closer cousin to the massive asteroid impact that wiped out the dinosaurs 65 million years ago. "This is an event that happened on one day," Kennett notes. "We're going to need high-resolution climate records, archaeological records, paleontological records to try to explore the effects."

## Toxicity mechanism identified for Parkinson's disease

Neurologists have observed for decades that Lewy bodies, clumps of aggregated proteins inside cells, appear in the brains of patients with Parkinson's disease and other neurodegenerative diseases.

The presence of Lewy bodies suggests underlying problems in protein recycling and waste disposal, leading to the puzzle: how does disrupting those processes kill brain cells?

One possible answer: by breaking a survival circuit called MEF2D. Researchers at Emory University School of Medicine have discovered that MEF2D is sensitive to the main component of Lewy bodies, a protein called alpha-synuclein.

In cell cultures and animal models of Parkinson's, an accumulation of alpha-synuclein interferes with the cell's recycling of MEF2D, leading to cell death. MEF2D is especially abundant in the brains of people with Parkinson's, the researchers found. The results are scheduled for publication in the Jan. 2, 2009 issue of Science.

"We've identified what could be an important pathway for controlling cell loss and survival in Parkinson's disease," says senior author Zixu Mao, PhD, associate professor of pharmacology at Emory University School of Medicine.

Further research could identify drugs that could regulate MEF2D, allowing brain cells to survive toxic stresses that impair protein recycling, he suggests.

Most cases of Parkinson's disease are termed sporadic, meaning that there is no obvious genetic cause, but there are inherited forms of Parkinson's. Some of these can be linked to mutations in the gene for alpha-synuclein or triplications of the gene. The mutations and triplications cause the brain to produce either a toxic form of alpha-synuclein or more alpha-synuclein than normal.

"Somehow it's toxic, but alpha-synuclein isn't part of the cell's machinery of death and survival," Mao says.

He and his colleagues began examining how alpha-synuclein influenced MEF2D after a report from another laboratory on disposal of alpha-synuclein by chaperone-mediated autophagy (CMA).

During CMA, certain selected proteins are funneled into lysosomes, compartments of the cell devoted to chewing up discarded proteins. Mao and colleagues found that lysosomes isolated from cells will absorb MEF2D protein, and interfering with CMA chemically causes MEF2D levels to rise.

MEF2D is a transcription factor, a protein that controls whether several genes are turned on or off. Previous studies have shown MEF2D is needed for proper development and survival of brain cells. To function, MEF2D must be able to bind DNA.

The authors found that when CMA is disrupted, most of the accumulated MEF2D can't bind DNA. This may indicate that the protein is improperly folded or otherwise modified.

"Even though there's a lot of it, something is making the MEF2D protein inactive," Mao says.

Mao and his colleagues found that mice that artificially overproduce alpha-synuclein (a model of Parkinson's disease) have elevated levels of apparently inactive MEF2D in their brains. In addition, MEF2D protein levels were higher in the brains of Parkinson's patients than in controls.

Following the influence of alpha-synuclein on MEF2D may be a way to connect the various genetic and environmental risk factors for Parkinson's, even if CMA is not the sole mechanism, Mao says.

"It may be that various stresses impact MEF2D in different ways," he says. "We think this work provides an explanation that ties several important observations together."

*The first and second authors of the paper were postdoctoral researchers Qian Yang, MD, PhD, and Hua She, PhD, in Mao's laboratory. Additional authors were Marla Gearing, Emory School of Medicine, Emanuela Colla and Michael Lee, Johns Hopkins University, and John J. Shacka, University of Alabama, Birmingham.*

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*Reference: Yang Q., et al., Regulation of Neuronal Survival Factor MEF2D by Chaperone-Mediated Autophagy, Science, Jan 2, 2009.*

# 'Bug' could combat dengue fever

***Humans could be protected from dengue fever by infecting the mosquitoes carrying it with a parasite which halves their lifespan, say researchers.***

Australian scientists, writing in the journal Science, found that Wolbachia bacteria spread well through laboratory-bred mosquitoes. Only older mosquitoes pass on dengue - so killing them could cut disease.

Experts said it remained to be seen how well the bacteria would spread outside the laboratory.

The virus might also adapt to survive, they added.

Many thousands of cases of dengue fever occur worldwide each year, mainly in warmer tropical countries.

The virus is passed to humans when mosquitoes carrying it feed on their blood, and while there have been efforts to eradicate them using insecticides, these have been fraught with problems, including the ability of the mosquito to become resistant to the chemicals used.

The potential of Wolbachia as a way of controlling mosquito populations has been suggested for some time, but the latest study offers hope - albeit under laboratory conditions - that it might work. The researchers from the University of Queensland in Brisbane picked a strain of Wolbachia known to halve the lifespan of its host.

The mosquito which carries the dengue virus is not naturally susceptible to the bacteria, so the researchers adapted it to create a successful infection.

The bacteria can be passed from infected female to offspring, and even though the cost in terms of lifespan should mean that infected insects should die out, Wolbachia has another trick up its sleeve.

It makes subtle changes to infected males which mean they can only produce offspring with infected females.

**Older danger**

As expected, the infection thrived in the laboratory population of mosquitoes, and halved their lifespan to just a few weeks. This is potentially significant because, after a mosquito acquires the dengue virus by biting an infected animal or human, there is a period of incubation lasting from a week to three weeks before it can pass on the infection when biting.

This means that only mosquitoes older than this are likely to be dangerous to humans and even these are likely to die swiftly, reducing their ability to infect.

The researchers suggested that the parasite represented a potentially inexpensive way to tackle the problem, particularly in urban areas, where other methods of control were difficult.

Dr Andrew Read and Dr Matthew Thomas, specialists in infectious disease dynamics from the Pennsylvania State University in the US, said "substantial" reductions in disease transmission could occur, but there were still obstacles to success. "Determining whether it can remove enough infectious mosquitoes will be a challenge," they wrote.

If the bacterial strain chosen was too virulent it would spread very slowly and large numbers of infected mosquitoes might need to be released, they said.

It was also possible that dengue virus strains would adapt to require a shorter incubation period, they said.