



The Vitamin & Herb Stores

**Human Technology Research Synopsis**

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**Public release date: 21-Aug-2009**

## Off-label use: Oft not evidence base

Physicians lack knowledge of off-label drug use and FDA approval status

CHICAGO - In a recent national survey, a substantial minority of physicians erroneously believed that certain off-label uses of prescription drugs were approved by the Food and Drug Administration. This mistaken belief could encourage them to prescribe these drugs, despite the lack of scientific evidence supporting such use.

"Off-label prescribing is common, but researchers have not always known why. Our research shows that some off-label prescribing might be driven by mistaken beliefs about FDA approval and the level of evidence supporting off-label drug use," said G. Caleb Alexander, MD, MS, Assistant Professor of Medicine at the University of Chicago Medical Center and corresponding author of the research, which will be published under an embargo in *Pharmacoepidemiology and Drug Safety* on August 21, 2009. "The results indicate an urgent need for more effective methods of informing physicians about the level of evidence supporting off-label drug use—especially for common off-label uses that are ineffective or carry unacceptable risks of harm."

**Overall, physicians were able to correctly identify the FDA-approval status of just over half (mean 55%) of the 22 drug-indication pairs (i.e., a particular drug prescribed for a particular condition) that were included in the survey.**

In many cases, the proportion of physicians who erroneously believed a particular drug was FDA approved for a specific indication was higher among physicians who had prescribed the drug for that indication.

**For example, 26% of all physician respondents erroneously believed that lorazepam was FDA approved for chronic anxiety. That figure rose to 33% for physicians who had prescribed lorazepam for chronic anxiety.**

**And 13% of all physician respondents erroneously believed that quetiapine (Seroquel®) was FDA approved for dementia with agitation. That figure rose to 19% for physicians who had prescribed quetiapine for dementia with agitation.** At the time of the study there was even an FDA-advisory specifically urging caution regarding the off-label use of quetiapine in patients with dementia.

The survey of 1,199 physicians (599 primary care physicians and 600 psychiatrists) was conducted in 2007-2008 and included 22 drug-indication pairs. The indications varied in their FDA approval status from on-label use to off-label use supported by medical evidence to off-label use deemed to be ineffective. (The level of evidence supporting or not supporting each specific use was based on Drugdex, an independent drug compendium.)

The FDA makes it clear that they regulate the marketing of prescription drugs, not prescribing. The agency approves drugs for marketing with an official "label" that stipulates an indication, dose, intended population, duration of use, and other specifications. However, physicians and other licensed prescribers are free to prescribe any approved drug for any indication, whether or not the indication is included on the drug's FDA-approved label.

"Some physicians and health care experts maintain that physicians should know the evidence, not the FDA labeling. However, knowledge about FDA labeling can be important because FDA approval of a drug for a specific indication indicates a clear threshold of evidence supporting that use," said Donna Chen, MD, Assistant Professor of Biomedical Ethics, Public Health Sciences, and Psychiatry at the University of Virginia. Dr. Chen is the lead author of the research, entitled "U.S. physician knowledge of the FDA-approved indications and evidence base of commonly prescribed drugs: results of a national survey".

**A study published in the Archives of Internal Medicine by other investigators in 2006 indicated that**

**approximately 21% of drug uses in the United States occur for off-label purposes, with 73% of those cases lacking scientific evidence of the drug's effectiveness. The highest rates of off-label use were for anticonvulsants (74%), antipsychotics (60%) and antibiotics (41%).**

"We hope our research will increase awareness of off-label prescribing and highlight the pressing need for more evidence-based use of prescription drugs," Alexander said. "Although some off-label uses are well-supported, many are not. New ways are needed to help physicians tap the scientific evidence supporting various prescription drug uses."

Some disadvantages of off-label use

- May diminish public expectation that drugs will be evaluated for safety and efficacy before use
- Blunts industry incentives to perform studies required for FDA label changes
- Drugs used off label may have unrecognized safety and efficacy problems
- Promotes use of drugs in populations (e.g., children, the elderly) for which they have not been tested

Source: G. Caleb Alexander, MD, MS, Assistant Professor of Medicine at the University of Chicago Medical Center

Some advantages of off-label use

- Allows for clinical innovation, especially for patients who do not respond to standard treatments
- May be only available option for uncommon conditions or for patient populations that have not been studied
- Allows physicians to anticipate growing evidence of efficacy prior to formal evaluation
- Increases return on investment for pharmaceutical firms

Source: G. Caleb Alexander, MD, MS, Assistant Professor of Medicine at the University of Chicago Medical Center

**Public release date: 25-Aug-2009**

## **Research shows why low vitamin D raises heart disease risks in diabetics**

By Jim Dryden

Aug. 21, 2009 -- **Low levels of vitamin D are known to nearly double the risk of cardiovascular disease in patients with diabetes, and researchers at Washington University School of Medicine in St. Louis now think they know why.**

A healthy macrophage cell, at left, with sufficient vitamin D. On the right, a macrophage with inadequate vitamin D has become clogged with cholesterol, an early marker of atherosclerosis.

**They have found that diabetics deficient in vitamin D can't process cholesterol normally, so it builds up in their blood vessels, increasing the risk of heart attack and stroke.** The new research has identified

a mechanism linking low vitamin D levels to heart disease risk and may lead to ways to fix the problem, simply by increasing levels of vitamin D.

"Vitamin D inhibits the uptake of cholesterol by cells called macrophages," says principal investigator Carlos Bernal-Mizrachi, M.D., a Washington University endocrinologist at Barnes-Jewish Hospital. "When people are deficient in vitamin D, the macrophage cells eat more cholesterol, and they can't get rid of it. The macrophages get clogged with cholesterol and become what scientists call foam cells, which are one of the earliest markers of atherosclerosis."

Macrophages are dispatched by the immune system in response to inflammation and often are activated by diseases such as diabetes. Bernal-Mizrachi and his colleagues believe that in diabetic patients with inadequate vitamin D, macrophages become loaded with cholesterol and eventually stiffen blood vessels and block blood flow.

Bernal-Mizrachi, an assistant professor of medicine and of cell biology and physiology, studied macrophage cells taken from people with and without diabetes and with and without vitamin D deficiency. His team, led by research assistants Jisu Oh and Sherry Weng, M.D., exposed the cells to cholesterol and to high or low vitamin D levels. When vitamin D levels were low in the culture dish, macrophages from diabetic patients were much more likely to become foam cells.

In the Aug. 25 issue of the journal *Circulation*, which currently is available online, the team reports that vitamin D regulates signaling pathways linked both to uptake and to clearance of cholesterol in macrophages.

"Cholesterol is transported through the blood attached to lipoproteins such as LDL, the 'bad' cholesterol," Bernal-Mizrachi explains. "As it is stimulated by oxygen radicals in the vessel wall, LDL becomes oxidated, and macrophages eat it uncontrollably. LDL cholesterol then clogs the macrophages, and that's how atherosclerosis begins."

That process becomes accelerated when a person is deficient in vitamin D. And people with type 2 diabetes are very likely to have this deficiency. Worldwide, approximately one billion people have insufficient vitamin D levels, and in women with type 2 diabetes, the likelihood of low vitamin D is about a third higher than in women of the same age who don't have diabetes.

The skin manufactures vitamin D in response to ultraviolet light exposure. But in much of the United States, people don't make enough vitamin D during the winter — when the sun's rays are weaker and more time is spent indoors.

The good news is when human macrophages are placed in an environment with plenty of vitamin D, their uptake of cholesterol is suppressed, and they don't become foam cells. Bernal-Mizrachi believes it may be possible to slow or reverse the development of atherosclerosis in patients with diabetes by helping them regain adequate vitamin D levels.

"There is debate about whether any amount of sun exposure is safe, so oral vitamin D supplements may work best," he says, "but perhaps if people were exposed to sunlight only for a few minutes at a time, that may be an option, too."

He has launched a new study of diabetics who are both deficient in vitamin D and have high blood pressure. He wants to learn whether replacing vitamin D will lower blood pressure and improve blood flow. For this study, Bernal-Mizrachi is recruiting patients with type 2 diabetes ages 30 to 80 who are not taking insulin to control their blood sugar. Study volunteers also must have high blood pressure.

**Public release date: 25-Aug-2009**

## **Long-term tamoxifen use increases risk of an aggressive, hard to treat type of second breast cancer**

Study finds a more than four-fold increased risk of ER negative second cancers

SEATTLE – While long-term tamoxifen use among breast cancer survivors decreases their risk of developing the most common, less aggressive type of second breast cancer, such use is associated with a more than four-fold increased risk of a more aggressive, difficult-to-treat type of cancer in the breast opposite, or contralateral, to the initial tumor. These findings by Christopher Li, M.D., Ph.D., and colleagues at Fred Hutchinson Cancer Research Center were published online Aug. 25 in the journal *Cancer Research*.

Hormonal therapy with drugs like tamoxifen is one of the most common treatments for breast cancer because it has been shown to reduce the risk of dying from the disease but, as this study suggests, it does have risks.

Comparing breast-cancer patients who received the estrogen-blocking drug tamoxifen to those who did not, the researchers found that while the drug was associated with a 60 percent reduction in estrogen receptor-positive, or ER positive, second breast cancer – the more common type, which is responsive to estrogen-blocking therapy – it also appeared to increase the risk of ER negative second cancer by 440 percent. "This is of concern, given the poorer prognosis of ER-negative tumors, which are also more difficult to treat," said Li, an associate member of the Hutchinson Center's Public Health Sciences Division.

These findings confirm preliminary research by Li and colleagues, published in 2001, which was the first to suggest a link between long-term tamoxifen use and an increased risk of ER-negative second cancers. "The earlier study had a number of limitations. For example, we did not have information on the duration of tamoxifen therapy the women received," Li said. "The current study is larger, is based on much more detailed data, and is the first study specifically designed to determine whether tamoxifen use among breast cancer survivors influences their risk of different types of second breast cancers," Li said.

This new study assessed history of tamoxifen use among 1,103 breast cancer survivors from the Seattle-Puget Sound region who were initially diagnosed with ER positive breast cancer between the ages of 40 and 79. Of these, 369 of the women went on to develop a second breast cancer. Nearly all of the women in the study who took adjuvant hormonal therapy used tamoxifen specifically. Detailed information about tamoxifen use was ascertained from telephone interviews and medical record reviews.

While the study confirmed a strong association between long-term tamoxifen therapy and an increased risk of ER-negative second cancer, it does not suggest that breast cancer survivors should stop taking hormone therapy to prevent a second cancer, Li said.

"It is clear that estrogen-blocking drugs like tamoxifen have important clinical benefits and have led to major improvements in breast cancer survival rates. However, these therapies have risks, and an increased risk of ER negative second cancer may be one of them. Still, the benefits of this therapy are well established and doctors should continue to recommend hormonal therapy for breast cancer patients who can benefit from it," Li said.

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## **Hormone therapy for prostate cancer patients with heart conditions linked to increased death risk**

Men with coronary artery disease-induced congestive heart failure or heart attack who receive hormone therapy before or along with radiation therapy for treatment of prostate cancer have an associated increased risk of death, according to a study in the August 26 issue of JAMA.

Patients with localized prostate cancer have several options available for treatment, including the use of brachytherapy (treatment in which radioactive seeds are implanted in the prostate), both as monotherapy and in conjunction with external beam radiation therapy, according to background information in the article. Neoadjuvant (treatment that is given before or with the primary treatment) hormonal therapy (HT) is used as a means for prostate gland cytorreduction (decrease in number of cells, as in a tumor) in order to eliminate pubic arch (an arch formed by the pubic bones) interference and improve the ability to perform brachytherapy. Previous research has suggested that "hormonal therapy when added to radiation therapy (RT) for treating unfavorable-risk prostate cancer leads to an increase in survival except possibly in men with moderate to severe comorbidity [co-existing illnesses]. However, it is unknown which comorbid conditions eliminate this survival benefit," the authors write.

Akash Nanda, M.D., Ph.D., of Brigham & Women's Hospital–Dana-Farber Cancer Institute, Boston, and colleagues assessed whether neoadjuvant HT use in men with prostate cancer treated with brachytherapy affects the risk of all-cause death of men with known coronary artery disease–induced conditions, including congestive heart failure and heart attack. The study included 5,077 men (median [midpoint] age, 69.5 years) with localized or locally advanced prostate cancer who were treated with or without a median of 4 months of neoadjuvant HT followed by RT between 1997 and 2006 and were followed up until July 2008.

During the study period, 419 men died. Of those, 200 had no underlying comorbidity, 176 had one coronary artery disease risk factor, and 43 had a history of known coronary artery disease resulting in congestive heart failure or heart attack. Analyses of the data indicated that "when considering comorbidity groups separately, neoadjuvant HT use was not associated with an increased risk of all-cause mortality in men with no comorbidity (9.6 percent vs. 6.7 percent) or a single coronary artery disease risk factor (10.7 percent vs. 7.0 percent) after median follow-ups of 5.0 years and 4.4 years, respectively," the researchers write.

However, for men with coronary artery disease–induced congestive heart failure or heart attack, after a median follow-up of 5.1 years, **neoadjuvant HT use was associated with nearly twice the risk of all-cause mortality (26.3 percent vs. 11.2 percent).**

"It is also important to note that the population of men in whom the use of neoadjuvant HT may be detrimental was limited to 5 percent (256 of 5,077) in this community-based study cohort. This latter point may explain why there has been a survival benefit observed in the major randomized trials comparing HT plus external beam radiation therapy to external beam radiation therapy alone," the authors write.

"The clinical significance of this finding is that for men with favorable-risk prostate cancer and a history of congestive heart failure or myocardial infarction who require neoadjuvant HT solely to eliminate pubic arch interference, alternative strategies such as active surveillance or treatment with external beam radiation therapy or prostatectomy should be considered. However, for men with unfavorable–risk prostate cancer who require HT in addition to radiation therapy to take advantage of its survival benefit, appropriate medical evaluation prior to initiation should facilitate clinicians in balancing the relative risks against the benefits of HT use."

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**More obesity blues**

UCLA and Pittsburgh researchers report that obese people are at greater risk for developing Alzheimer's. Obesity is on a rampage, with the World Health Organization pegging the numbers at more than 300 million worldwide, with a billion more overweight. With obesity comes the increased risk for cardiovascular disease, Type II diabetes, and hypertension.

Now comes more discouraging news. In the current online edition of the journal *Human Brain Mapping*, Paul Thompson, senior author and a UCLA professor of neurology, and lead author Cyrus A. Raji, a medical student at the University of Pittsburgh School of Medicine, and colleagues compared the brains of people who were obese, overweight, and of normal weight, to see if they had differences in brain structure; that is, did their brains look equally healthy.

**They found that obese people had 8 percent less brain tissue than people with normal weight, while overweight people had 4 percent less tissue.** According to Thompson, who is also a member of UCLA's Laboratory of Neuro Imaging, this is the first time anyone has established a link between being overweight and having what he describes as "severe brain degeneration."

"That's a big loss of tissue and it depletes your cognitive reserves, putting you at much greater risk of Alzheimer's and other diseases that attack the brain," said Thompson. "But you can greatly reduce your risk for Alzheimer's, if you can eat healthily and keep your weight under control."

The researchers used brain images from an earlier study called the Cardiovascular Health Study Cognition Study. Scans were selected of 94 elderly people in their 70s who were healthy not cognitively impaired—five years after the scan was taken. To define the weight categories, they used the Body Mass Index (BMI), the most widely used measurement for obesity. Normal weight people were defined as having a BMI between 18.5-25; overweight people between 25-30, and obese people greater than 30. The researchers then converted the scans into detailed three-dimensional images using tensor-based morphometry, a neuroimaging method that offers high resolution mapping of anatomical differences in the brain.

In looking at both grey matter and white matter of the brain, they found that the people defined as obese had lost brain tissue in the frontal and temporal lobes, areas of the brain critical for planning and memory, and in the anterior cingulate gyrus (attention and executive functions), hippocampus (long term memory) and basal ganglia (movement). Overweight people showed brain loss in the basal ganglia, the corona radiata, white matter comprised of axons, and the parietal lobe (sensory lobe).

"The brains of obese people looked 16 years older than the brains of those who were lean, and in overweight people looked eight years older," says Thompson.

"It seems that along with increased risk for health problems such as type 2 diabetes and heart disease, obesity is bad for your brain: we have linked it to shrinkage of brain areas that are also targeted by Alzheimer's," said Pittsburgh's Raji. "But that could mean exercising, eating right and keeping weight under control can maintain brain health with aging and potentially lower the risk for Alzheimer's and other dementias."

**Public release date: 25-Aug-2009**

## **Unlocking the body's defenses against cancer**

Scientists have discovered a way of allowing healthy cells to take charge of cancerous cells and stop them developing into tumours in what could provide a new approach to treating early-stage cancers.

University of Manchester researchers found that a special type of the chemicals known as '**kinase inhibitors**' **opened up communication channels on the surface of cells that enabled healthy cells to 'talk' to the cancer cells.**

"When we added the chemicals to a mixture of healthy and cancerous cells in a flask the diseased cells

stopped multiplying and began acting like normal cells again," said Dr Ian Hampson, who carried out the research with wife Dr Lynne Hampson.

"Further tests revealed that the chemicals helped the cancer cells form connections with surrounding healthy cells that allowed these normal cells to take charge of the mechanism by which cancer cells divide and grow out of control."

Cell division occurs naturally and continuously in human organs and tissue as part of the body's normal repair processes to combat wear and tear but in cancer the cells divide in an uncontrolled way.

Dr Hampson says the findings, published in the British Journal of Cancer, are all the more exciting because the chemicals, which were developed with colleagues at the University of Salford, appear to be relatively non-toxic and the positive effect on the cancer cells persists even when the chemicals are withdrawn.

"When the chemicals were added to a culture containing just cancer cells they had little effect," said Dr Hampson, who is based in Manchester's School of Cancer and Imaging Sciences. "It was only when we added the chemicals to a mixture of cancer cells and normal cells – similar to how you would find them in the body – that growth was suppressed.

"Intriguingly, the connections that allowed the healthy cells to communicate with the cancer cells stayed open even when the kinase inhibitors were removed indicating that a potential drug based on these chemicals could be given as a short course of treatment.

**"Furthermore, the chemicals are non-poisonous and do not actually kill cells like conventional cancer therapies, such as chemotherapy and radiotherapy, so if we were able to develop a drug it is likely to have far fewer side-effects."**

The team say the next stage of their research will be to find out exactly how the chemicals are able to increase the number of connections between cancer and normal cells. Once this is known, it should be possible to produce a drug based on these chemicals that could hopefully be used in humans.

Dr Lynne Hampson added: "We are currently applying for funding to carry out further research into the biochemistry of how these chemicals cause the effect we have observed. We also intend to investigate the use of different types of cell cultures to assess the potency and range of activity of these agents."

The research was funded by the Association for International Cancer Research, The Humane Research Trust, The Caring Cancer Research Trust, Kidscan and the Cancer Prevention Research Trust.

Ralph's Note: This is where health care dollars should be invested. In promising no harm technologies, that break away from the poison makes the dose philosophy.

**Public release date: 26-Aug-2009**

## **Discovery of natural odors could help develop mosquito repellents**

Applications of research by UC Riverside entomologists include prevention of West Nile virus and other mosquito-borne diseases

RIVERSIDE, Calif. – Entomologists at the University of California, Riverside working on fruit flies in the lab have discovered a novel class of compounds that could pave the way for developing inexpensive and safe mosquito repellents for combating West Nile virus and other deadly tropical diseases.

When fruit flies undergo stress, they emit carbon dioxide (CO<sub>2</sub>) that serves as a warning to other fruit flies

that danger or predators could be nearby. The fruit flies are able to detect the CO<sub>2</sub> and escape because their antennae are equipped with specialized neurons that are sensitive to the gas.

But fruits and other important food sources for fruit flies also emit CO<sub>2</sub> as a by-product of respiration and ripening. If the innate response of the fruit fly is to avoid CO<sub>2</sub>, how then does it find its way to these foods?

Anandasankar Ray, an assistant professor in the Department of Entomology, and Stephanie Turner, his graduate student, now provide an answer to the paradox.

They have identified a new class of odorants – chemical compounds with smells – present in ripening fruit that prevent the CO<sub>2</sub>-sensitive neurons in the antennae from functioning. In particular two odors, hexanol and 2,3- butanedione, are strong inhibitors of the CO<sub>2</sub>-sensitive neurons in the fruit fly.

The research has strong implications for control of deadly diseases transmitted by Culex mosquitoes such as West Nile virus disease and filariasis, an infectious tropical disease affecting the lymphatic system. Since 1999, nearly 29,000 people in the United States have been reported with West Nile virus disease. Lymphatic filariasis has affected more than 120 million people in the world.

**"CO<sub>2</sub> emitted in human breath is the main attractant for the Culex mosquito to find people, aiding the transmission of these deadly diseases,"** Ray said. **"In our experiments we identified hexanol, and a related odor, butanal, as strong inhibitors of CO<sub>2</sub>-sensitive neurons in Culex mosquitoes.** These compounds can now be used to guide research in developing novel repellents and masking agents that are economical and environmentally safe methods to block mosquitoes' ability to detect CO<sub>2</sub> in our breath, thereby dramatically reducing mosquito-human contact."

Study results appear Aug. 26 in the advance online publication of Nature.

A video, "Combating West Nile Virus and other Tropical Diseases," is available here.

"This is a beautiful study that breaks new ground in the field of olfaction," said John Carlson, the Eugene Higgins Professor of Molecular, Cellular and Developmental Biology at Yale University, who was not involved in the research. "It shows that certain odorants can strongly inhibit the response of receptors that detect CO<sub>2</sub>. The results suggest some very interesting new strategies for the control of certain insect pests."

Besides showing that inhibitory odors can play an important role in modifying insect behavior, the research paper also illustrates how some of these odors have a long-term effect. Ray and Turner found, for example, that some odors silenced the CO<sub>2</sub> neuron in the fruit fly well beyond the period of application.

"To our surprise, we found that exposure to a long-term CO<sub>2</sub> response inhibitor can exert a profound and specific effect on the behavior of the insect, even after the inhibitor is no longer in the environment," Ray said. "This means this odorant could potentially be used to keep mosquitoes at bay for longer periods of time, benefiting people in areas where mosquito-transmitted diseases are prevalent."

Ray received his doctoral degree in molecular, cellular and developmental biology from Yale University in 2005. He joined UC Riverside in 2007. His awards include Yale University's John Spangler Nicholas Prize and the Polak Young Investigator Award from the Association of Chemoreception Sciences.

Originally from India, Ray contracted malaria during childhood. When his wife caught dengue fever on a trip to India a few years ago, he decided to intensify his research on mosquito-borne diseases.

Stephanie Turner, the first author of the research paper, received her bachelor's degree in biochemistry from UC Santa Cruz, where she performed research as an undergraduate. She worked for two years in biotechnology before joining the Cell, Molecular and Developmental Biology Graduate Program at UCR.

The research related to this project was conceived, initiated and carried out at UCR over the past one year, and was supported by UCR startup funds. Ray has plans to launch a startup company in the near future to

take his basic science research on the odorants from the lab to applications that directly benefit people.

Ray and Turner already have begun work in the lab on mosquitoes that cause malaria and dengue fever. They also are setting up collaborations with a number of scientists from around the globe to do research on various mosquito species and tsetse flies.

The UCR Office of Technology Commercialization has filed a patent application on the discovery.

**Public release date: 26-Aug-2009**

## **Bird flu leaves the nest -- adapting to a new host**

Hamburg, Germany – Current research suggests that viral polymerase may provide a new therapeutic target for host-adapted avian influenza. The related report by Gabriel et al, "Spread of Infection and Lymphocyte Depletion in Mice Depends on Polymerase of Influenza Virus" appears in the September 2009 issue of the American Journal of Pathology.

Highly pathogenic avian influenza, commonly known as bird flu, is a strain of the influenza virus that has adapted to infect birds. Although bird-specific flu strains rarely cross species, further adaptation can lead to lethal infection in humans.

To determine which genetic changes may lead to host adaptation, Gülsah Gabriel (currently at the Heinrich-Pette-Institute for Experimental Virology and Immunology the University of Hamburg) and Hans-Dieter Klenk at the Institute of Virology at the Philipps University of Marburg examined two strains of avian influenza, an unadapted avian strain and an avian strain adapted to infect mice by mutations that increase the efficiency of the viral polymerase. They found that whereas the avian strain only infected the lungs, the mouse-adapted strain caused suppression of the immune system, which resulted in infection in multiple organs. In addition, while the avian strain caused only mild symptoms in mice, the mouse-adapted strain led to severe illness including pneumonia and infection of the brain, followed by death. The viral polymerase may therefore provide an important target in preventing systemic flu in humans.

Gabriel et al suggest that "reduction of high virus loads by targeting the viral polymerase may play an important role in the treatment of human influenza with systemic virus spread." In future studies, Dr. Gabriel and colleagues will aim to develop drugs interfering with virus polymerase activity.

Ralph's Note: Remember this one, and give it one or two years.....

**Public release date: 26-Aug-2009**

## **Heat forms potentially harmful substance in high-fructose corn syrup**

Researchers have established the conditions that foster formation of potentially dangerous levels of a toxic substance in the high-fructose corn syrup (HFCS) often fed to honey bees. Their study, which appears in the current issue of ACS' bi-weekly Journal of Agricultural and Food Chemistry, could also help keep the substance out of soft drinks and dozens of other human foods that contain HFCS. **The substance, hydroxymethylfurfural (HMF), forms mainly from heating fructose.**

In the new study, Blaise LeBlanc and Gillian Eggleston and colleagues note HFCS's ubiquitous usage as a sweetener in beverages and processed foods. Some commercial beekeepers also feed it to bees to increase reproduction and honey production. When exposed to warm temperatures, HFCS can form HMF and kill honeybees. Some researchers believe that HMF may be a factor in Colony Collapse Disorder, a mysterious disease that has killed at least one-third of the honeybee population in the United States.

The scientists measured levels of HMF in HFCS products from different manufacturers over a period of 35 days at different temperatures. As temperatures rose, levels of HMF increased steadily. **Levels jumped dramatically at about 120 degrees Fahrenheit.** "The data are important for commercial beekeepers, for manufacturers of HFCS, and for purposes of food storage. Because HFCS is incorporated as a sweetener in many processed foods, the data from this study are important for human health as well," the report states. It adds that **studies have linked HMF to DNA damage in humans. In addition, HMF breaks down in the body to other substances potentially more harmful than HMF.**

Ralph's Note: Remember 120 degrees Fahrenheit when preparing food for anyone. Or I guess don't drink soda on a Hot summer day?

**Public release date: 26-Aug-2009**

## **Nuisance or nutrient? Kudzu shows promise as a dietary supplement**

Kudzu, the nuisance vine that has overgrown almost 10 million acres in the southeastern United States, may sprout into a dietary supplement. Scientists in Alabama and Iowa are reporting the first evidence that root extracts from kudzu show promise as a dietary supplement for a high-risk condition — the metabolic syndrome — that affects almost 50 million people in the United States alone. Their study appears in the current issue of ACS' Journal of Agricultural and Food Chemistry, a bi-weekly publication.

J. Michael Wyss and colleagues note in the new study that people with metabolic syndrome have obesity, high blood pressure, high blood cholesterol, and problems with their body's ability to use insulin. Those disorders mean a high risk for heart attacks, strokes, and other diseases. Scientists have been seeking natural substances that can treat the metabolic syndrome. The new study evaluated kudzu root extracts, which contain healthful substances called isoflavones. People in China and Japan long have used kudzu supplements as a health food.

**The study found that a kudzu root extract had beneficial effects lab rats used as a model for research on the metabolic syndrome. After two months of taking the extract, the rats had lower cholesterol, blood pressure, blood sugar, and insulin levels that a control group not given the extract.** Kudzu root "may provide a dietary supplement that significantly decreases the risk and severity of stroke and cardiovascular disease in at-risk individuals," the article notes.

**Public release date: 26-Aug-2009**

## **People vary widely in ability to eliminate arsenic from the body**

Large variations exist in peoples' ability to eliminate arsenic from the body, according to a new study that questions existing standards for evaluating the human health risks from the potentially toxic substance. The study found that some people eliminate more than 90 percent of the arsenic consumed in the diet. Others store arsenic in their bodies, where it can have harmful effects. The research, based on the first application of new methods for studying arsenic, is scheduled for the Sept. 21 issue of ACS's Chemical Research in Toxicology, a monthly journal.

In the study, Kevin Francesconi and colleagues point out that drinking water in many parts of the world, including some regions of the United States, contain amounts of arsenic that exceed the World Health Organization's maximum acceptable levels. Consumption of seafood, the article notes, is another major source of arsenic contamination. **Health effects from chronic arsenic exposure include skin and internal cancers, cardiovascular disease, and possibly diabetes, it adds.**

The scientists describe monitoring arsenic excretion in the urine of human volunteers. **They found that ability to eliminate arsenic from the body varied greatly, with some participants excreting up to 95 percent of the ingested arsenic but others eliminating as little as four percent.** "This observed individual variability in handling [arsenic] exposure has considerable implications for the risk assessment of arsenic ingestion," the paper states. It adds that further study is needed to assess potential risks to humans consuming seafood products. "The data presented here suggest that the long held view that seafood arsenic is harmless because it is present mainly as organoarsenic compounds needs to be reassessed."

Ralph's Note: Keep in mind earlier one of the studies showed that higher arsenic levels were associated with a greater susceptibility to swine flu.

**Public release date: 27-Aug-2009**

## **Immune defect is key to skin aging**

Scientists funded by the Biotechnology and Biological Sciences Research Council (BBSRC) have discovered why older people may be so vulnerable to cancer and infections in the skin. The team from UCL has shown in human volunteers that defective immunity in the skin is caused by an inability to mobilise essential defences that would otherwise recognise threats and clear them before irreparable damage is done. This discovery could be important for preventing, managing or treating many age-related skin health problems. The study will be published in 31 August edition of the Journal of Experimental Medicine.

"Older people are very prone to having infections generally and our studies in the skin of such subjects identifies one reason for this." said Professor Arne Akbar from UCL, who led the study.

He continued: "It's actually incredibly difficult to get to the root of exactly which mechanisms cause the diseases that show up as a factor of old age. We wanted to uncover the workings of skin health in order to see why older people don't deal well with skin infections and are prone to skin cancers also."

It has been known for some time that older people have compromised immunity and therefore defend themselves less well against infection and disease than younger people. In the past, the reduction in skin health was put down to potential defects in the white blood cells called T-cells that would usually help to identify and clear infection. However, when experiments were carried out with healthy young individuals under the age of 40 years and older individuals over the age of 70 years in this study, it was shown that in fact there is nothing wrong with the T-cells in the older group; instead it is the inability of their skin tissue to attract T-cells where and when they are needed that is the source of reduced immunity.

Professor Akbar added: "Knowing this now raises the question of whether the same defect also occurs in other tissues during ageing. Is it possible that, for example, lung tissues also fail to give out the right message to T-cells to bring them into the tissue to do their job? This may explain, in part, the higher rates of lung cancer, chest infections and pneumonia in older people, perhaps."

**"We also, obviously, would like to know if it is possible to reverse the skin defect in older people. We've done some experiments that show that, at least in the test tube, it is possible to make older skin express the missing signals that attract T cells. This indicates that, in principle, the defect is entirely reversible.** Once we get to the bottom of exactly which part of the signal to T-cells has gone wrong we might then be in a position to intervene to boost skin immunity in older people."

BBSRC Deputy Chief Executive, Steve Visscher said: "We are living longer and longer in the UK, but we need to ensure that a long life is also a healthy one. What Professor Akbar and his team have identified is a normal part of the ageing process that contributes to disease and therefore reduced quality of life in older

people. The more knowledge we have about healthy ageing, the better we get at preventing, managing and treating diseases that are simply a factor of an ageing body."

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## **Healthy food obsession sparks rise in new eating disorder**

Fixation with healthy eating can be sign of serious psychological disorder

Eating disorder charities are reporting a rise in the number of people suffering from a **serious psychological condition** characterised by an obsession with healthy eating.

The condition, orthorexia nervosa, affects equal numbers of men and women, but sufferers tend to be aged over 30, middle-class and well-educated.

The condition was named by a Californian doctor, Steven Bratman, in 1997, and is described as a "fixation on righteous eating". Until a few years ago, there were so few sufferers that doctors usually included them under the catch-all label of "Ednos" – eating disorders not otherwise recognised. Now, experts say, orthorexics take up such a significant proportion of the Ednos group that they should be treated separately.

"I am definitely seeing significantly more orthorexics than just a few years ago," said Ursula Philpot, chair of the British Dietetic Association's mental health group. "Other eating disorders focus on quantity of food but orthorexics can be overweight or look normal. They are solely concerned with the quality of the food they put in their bodies, refining and restricting their diets according to their personal understanding of which foods are truly 'pure'."

**Orthorexics commonly have rigid rules around eating. Refusing to touch sugar, salt, caffeine, alcohol, wheat, gluten, yeast, soya, corn and dairy foods is just the start of their diet restrictions. Any foods that have come into contact with pesticides, herbicides or contain artificial additives are also out.**

**The obsession about which foods are "good" and which are "bad" means orthorexics can end up malnourished.** Their dietary restrictions commonly cause sufferers to feel proud of their "virtuous" behaviour even if it means that eating becomes so stressful their personal relationships can come under pressure and they become socially isolated.

"The issues underlying orthorexia are often the same as anorexia and the two conditions can overlap but orthorexia is very definitely a distinct disorder," said Philpot. "Those most susceptible are middle-class, well-educated people who read about food scares in the papers, research them on the internet, and have the time and money to source what they believe to be purer alternatives."

Deanne Jade, founder of the National Centre for Eating Disorders, said: "There is a fine

line between people who think they are taking care of themselves by manipulating their diet and those who have orthorexia. I see people around me who have no idea they have this disorder. I see it in my practice and I see it among my friends and colleagues."

Jade believes the condition is on the increase because "modern society has lost its way with food". She said: "It's everywhere, from the people who think it's normal if their friends stop eating entire food groups, to the trainers in the gym who [promote] certain foods to enhance performance, to the proliferation of nutritionists, dieticians and naturopaths [who believe in curing problems through entirely natural methods such as sunlight and massage].

"And just look in the bookshops – all the diets that advise eating according to your blood type or metabolic rate. This is all grist for the mill to those looking for proof to confirm or encourage their anxieties around food."

**Ralph's Note: First we are too skinny, in the sun too much, drink too much water, exercise too much, and now eat too healthy. I think I am beginning to see a pattern emerge in a bizarre new culture war. In addition after reading Dr. Steven Bratman's view of orthorexia, the article has taken him totally out of context.**

**Public release date: 27-Aug-2009**

## **Natural compounds, chemotherapeutic drugs may become partners in cancer therapy**

**CORVALLIS, Ore. – Research in the Linus Pauling Institute at Oregon State University suggests that some natural food compounds, which previously have been studied for their ability to prevent cancer, may be able to play a more significant role in treating it – working side-by-side with the conventional drugs that are now used in chemotherapy.**

A new study just published in the International Journal of Cancer examined **the activity of chlorophyllin and found that, on a dose-by-dose basis, it was 10 times more potent at causing death of colon cancer cells than hydroxyurea, a chemotherapeutic drug commonly used in cancer treatment.**

**Beyond that, chlorophyllin kills cancer cells by blocking the same phase of cellular division that hydroxyurea does, but by a different mechanism.** This suggests that it – and possibly other "cocktails" of natural products – might be developed to have a synergistic effect with conventional cancer drugs, helping them to work better or require less toxic dosages, researchers said.

"We conclude that chlorophyllin has the potential to be effective in the clinical setting, when used alone or in combination with currently available cancer therapeutic agents," the researchers wrote in their study.

The concept of combining conventional or new cancer drugs with natural compounds that have been shown to have anti-cancer properties is very promising, said Rod Dashwood, professor and director of the Cancer Chemoprotection Program in the Linus Pauling Institute.

"Most chemotherapeutic approaches to cancer try to target cancer cells specifically and do something that

slows or stops their cell growth process,” Dashwood said. “We’re now identifying such mechanisms of action for natural compounds, including dietary agents. With further research we may be able to make the two approaches work together to enhance the effectiveness of cancer therapies.”

**Chlorophyllin is a water-soluble derivative of chlorophyll** – the green pigment found in most plants and many food products that makes possible the process of photosynthesis and plant growth from the sun’s energy. Chlorophyllin is inexpensive, and animal studies plus human clinical data suggest that it can be ingested at relatively high levels without toxicity.

In the new study, researchers found that pharmacologic doses of chlorophyllin caused colon cancer cells to spend more time than normal in their “synthesis phase” in which DNA is duplicated. Timing is critical to the various phases of cell growth, researchers said, and this disruption started a process that ultimately led to cell death, the study found.

In particular, the presence of high levels of chlorophyllin caused a major reduction in the level of ribonucleotide reductase, an enzyme critical to DNA synthesis, researchers found. This is also the mechanism of action of hydroxyurea, one drug already being used for cancer chemotherapy.

“In cancer research right now there’s interest in approaches that can reduce ribonucleotide reductase,” Dashwood said. “At the doses used in our experiments, chlorophyllin almost completely stops the activity of this enzyme.”

Further research is needed both in laboratory and animal studies, with combinations of chlorophyllin and existing cancer drugs, before it would be appropriate for human trials, Dashwood said. Chlorophyllin, in general, is poorly absorbed from the human gastrointestinal tract, so it’s unclear what levels might be needed for therapeutic purposes or how well they would work.

Other dietary agents also might have similar potential. Work just published by LPI researchers in the journals *Carcinogenesis* and *Cancer Prevention Research* explored the role of organic selenium compounds in killing human prostate and colon cancer cells. Colorectal and prostate cancers are consistently among the leading causes of cancer mortality in the United States, and will account respectively for 18 percent and 9 percent of all cancer deaths in 2009, according to estimates from the American Cancer Society.

In the recent studies, a form of organic selenium found naturally in garlic and Brazil nuts was converted in cancer cells to metabolites that acted as “HDAC inhibitors” – a promising field of research in which silenced tumor suppressor genes are re-activated, triggering cancer cell death.

“Whether it’s HDAC inhibition leading to one manner of cancer cell growth arrest, or loss of ribonucleotide reductase activity leading to another, as seen with chlorophyllin, there’s significant promise in the use of natural products for combined cancer therapies,” Dashwood said. “These are areas that merit continued research.”

**September 1, 2009**

## **Daily aspirin does more harm than good: study**

LONDON (AFP) – Healthy people taking a daily dose of aspirin to prevent heart attacks may be doing themselves more harm than good, according to a new study by British scientists.

Researchers found that the risks of bleeding from taking aspirin were such that its routine use in healthy people “cannot be supported” -- although they did not dispute its use in patients with a history of vascular problems.

The results of the Aspirin for Asymptomatic Atherosclerosis (AAA) study add to a long-running debate about whether the potential dangers of taking aspirin could outweigh the benefits from reducing the risk of clots.

"We know that patients with symptoms of artery disease, such as angina, heart attack or stroke, can reduce their risk of further problems by taking a small dose of aspirin each day," said Professor Peter Weissberg, medical director of the British Heart Foundation which helped fund the research.

"The findings of this study agree with our current advice that people who do not have symptomatic or diagnosed artery or heart disease should not take aspirin, because the risks of bleeding may outweigh the benefits."

The study was led by Professor Gerry Fowkes from the Wolfson Unit for Prevention of Peripheral Vascular Diseases in Edinburgh, Scotland, and presented at the European Society of Cardiology Congress in Barcelona Sunday.

It involved 3,350 men and women aged 50 to 75 years who tests revealed may have a condition where the arteries in their legs were furred up -- but who had no symptoms of heart disease or history of heart attack.

They were given either a daily 100 mg dose of aspirin or a placebo (a dummy pill) and monitored over eight years.

**While there was no difference in the number of heart attacks, strokes and other cardiovascular events suffered, major bleeding occurred in two percent of the aspirin group compared to just 1.2 percent of the placebo group.**

**September 1, 2009**

## **H1N1 Pandemic Virus Does Not Mutate Into 'Superbug' in UMd. Lab Study**

**COLLEGE PARK, Md. - A laboratory study by University of Maryland researchers suggests that some of the worst fears about a virulent H1N1 pandemic flu season may not be realized this year, but does demonstrate the heightened communicability of the virus.**

Using ferrets exposed to three different viruses, the Maryland researchers found no evidence that the H1N1 pandemic variety, responsible for the so-called swine flu, combines in a lab setting with other flu strains to form a more virulent 'superbug.' Rather, the pandemic virus prevailed and out-competed the other strains, reproducing in the ferrets, on average, twice as much.

The researchers believe their study is the first to examine how the pandemic virus interacts with other flu viruses. The findings are newly published in an online scientific journal designed to fast-track science research and quickly share results with other investigators, PLOS Currents.

"The H1N1 pandemic virus has a clear biological advantage over the two main seasonal flu strains and all the makings of a virus fully adapted to humans," says virologist Daniel Perez, the lead researcher and program director of the University of Maryland-based Prevention and Control of Avian Influenza Coordinated Agricultural Project.

"I'm not surprised to find that the pandemic virus is more infectious, simply because it's new, so hosts haven't had a chance to build immunity yet. Meanwhile, the older strains encounter resistance from hosts' immunity to them," Perez adds.

Some of the animals who were infected with both the new virus and one of the more familiar seasonal viruses (H3N2) developed not only respiratory symptoms, but intestinal illness as well. Perez and his team call for additional research to see whether this kind of co-infection and multiple symptoms may account for some of the deaths attributed to the new virus.

Among other research findings, the pandemic virus successfully established infections deeper in the ferret's respiratory system, including the lungs. The H1 and H3 seasonal viruses remained in the nasal passages.

"Our findings underscore the need for vaccinating against the pandemic flu virus this season," Perez concludes. "The findings of this study are preliminary, but the far greater communicability of the pandemic virus serves as a clearly blinking warning light."

Perez and his team used samples of the H1N1 pandemic variety from last April's initial outbreak of the so-called swine flu.

The research is funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health.

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**These reports are done with the appreciation of all the Doctors, Scientist, and other Medical Researchers who sacrificed their time and effort. In order to give people the ability to empower themselves. Without the base aspirations for fame, or fortune. Just honorable people, doing honorable things.**