



The Vitamin & Herb Stores

**Human Technology Research Synopsis**

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**Editors Top Five:**

1. **1.Mounting evidence shows red wine antioxidant kills cancer**
2. **JAMA editor-in-chief comments on Pfizer lawsuit**
3. **A ton of bitter melon produces sweet results for diabetes**
4. **REVIEW OF GROUP-BASED CANCER TRIALS REVEALS FLAWS IN STUDIES' DESIGN AND ANALYSIS**
5. **Green tea helps beat super bugs**

**In this issue:**

1. **UC Davis researchers discover how HIV turns food-poisoning into lethal infection**
2. **Free drug samples may burden patients' pockets**
3. **JAMA editor-in-chief comments on Pfizer lawsuit**
4. **Too much information? Study shows how ignorance can be influential**
5. **Study: Dramatic Rise in Hepatitis C-Related Deaths in the United States Middle-aged Patients are Hardest Hit**
6. **Hormone replacement therapy increases breast cancer recurrence**
7. **REVIEW OF GROUP-BASED CANCER TRIALS REVEALS FLAWS IN STUDIES' DESIGN AND ANALYSIS**
8. **Are Organic Crops as Productive as Conventional?**
9. **Mounting evidence shows red wine antioxidant kills cancer**
10. **A link between antidepressants and type 2 diabetes**
11. **FDA deadlines may compromise drug safety by rushing approval**
12. **Apple pectin, apple juice extracts shown to have anticarcinogenic effects on colon**
13. **Dental chair a possible source of neurotoxic mercury waste**
14. **Infant formula must contain DHA omega-3 and AA omega-6, say international experts**
15. **U of T research finds glycine could be key to REM Sleep Behavior Disorder**

- 16. A ton of bitter melon produces sweet results for diabetes**
- 17. Folate scores a win in animal studies: Brief, high doses of B vitamin blunt damage from heart attack**
- 18. Family study bolsters link between pesticides and Parkinson's**
- 19. Study shows why synthetic estrogens wreak havoc on reproductive system**
- 20. Hormone that controls hunger and appetite also linked to reduced fertility**
- 21. No laughing matter -- bacteria are releasing a serious greenhouse gas**
- 22. Green tea helps beat super bugs**
- 23. Most people believe smallpox not an extinct disease**
- 24. Are blood thinners post-op killers?**
- 25. Congress: Vytorin Makers Held Bad News**

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## UC Davis researchers discover how HIV turns food-poisoning into lethal infection

(SACRAMENTO, Calif.) — **Nearly half of all HIV-positive African adults who become infected with Salmonella die from what otherwise would be a seven-day bout of diarrhea.** Now, UC Davis School of Medicine scientists have discovered how salmonella becomes lethal for AIDS patients. Their findings also implicate a mechanism by which HIV evades the powerful drugs used to treat AIDS.

“We have found the defect in the immune response that allows Salmonella to cross the mucosal barrier of the gut, enter the bloodstream and infect other organs,” said Andreas Bäumlér, a UC Davis professor of medical microbiology and immunology and co-author of the study.

The results of the study, which will be published online by Nature Medicine March 23, revealed that viral infection of the intestine results in the depletion of a type of white blood cell, called Th-17, in the gut mucosa. This T helper lymphocyte produces IL-17, a cytokine or chemical messenger that plays a crucial role in the inflammatory response, recruiting other immune system cells to the site of infection.

This kind of interruption in the gut’s immune response could be allowing HIV to maintain reservoirs that evade drug treatments, said Satya Dandekar, professor and chair of the department of medical microbiology and immunology.

“It’s like putting out the fire, but leaving the embers smoldering,” Dandekar said.

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The rise in patients with acquired immune deficiency syndrome (AIDS) in sub-Saharan Africa has led to a dramatic increase in the frequency of non-typhoidal Salmonella serotypes (NTS), the strains of the bacteria that cause acute food-borne disease world wide. Normally, this infection is limited to the intestine, causing gastroenteritis. In AIDS patients, however, the infection spreads to the bloodstream and causes what is called NTS bacteremia.

While at a conference, Bäumlér was surprised to learn from epidemiologist and physician Melita Gordon of the University of Liverpool that Salmonella was quickly becoming one of the leading causes of death in parts of Africa. (Gordon is a co-author on the current paper.) Bäumlér returned to Davis and approached Dandekar about collaborating.

Dandekar had been studying the role of gut-associated lymphoid tissue in HIV. In a 2006 study, she found that HIV continued to replicate in the gut mucosa and suppress immune

function in patients being treated with antiretroviral therapy — even when T-cell counts from blood samples from the same individuals indicated antiretroviral treatment was working.

“We think the real battle between an individual’s immune system and HIV is happening in the gut mucosa where there is massive destruction of immune cells,” Dandekar said. Gut-associated lymphoid tissue, she pointed out, accounts for 70 percent of the body’s immune system.

In HIV-infected patients, there is a gradual loss of CD4+ T cells over time. These cells, also called T helper cells, organize the immune system’s attack on disease-causing invaders, like Salmonella. Unlike the steady decline of T cells in peripheral blood, there is a very rapid loss of CD4+ T cells in the gut mucosa, Dandekar said.

“We wanted to know whether the loss of the CD4+ T-cells in the gut contributed to the inactivation of the immune system one sees in HIV-infected patients,” she said.

Both Bäumlér and Dandekar said the timing was perfect for their collaboration. Together, they developed a novel technique that allowed them to study early intestinal responses to Salmonella infection in rhesus macaques infected with simian immunodeficiency virus (SIV), an established model for HIV infection.

“We found that animals that had no SIV infection were able to generate immediate responses to bacterial exposure, producing Th17 cells in large amounts,” Dandekar said. The SIV-infected animals, however, had either a significantly lower response or lacked did not produce measurable amounts of the cytokine.

“This muted Th17 response led to dissemination of Salmonella from the gut to the peripheral blood,” Dandekar said.

The team of researchers also used mice that lacked the IL-17 receptor, an arm of the mucosal immune response, to confirm that IL-17 deficiency leads to increased systemic dissemination of Salmonella.

“We believe IL-17 deficiency causes defects in the mucosal barrier of the gut,” Dandekar said.

Both Bäumlér and Dandekar agreed that the results of their collaboration have exciting implications for both HIV and Salmonella research and, more importantly, get scientists closer to finding treatments for HIV and the deadly form of Salmonella.

In terms of HIV, the results suggest that Th17 may make a good biomarker for monitoring HIV infection and testing the efficacy of vaccines and other therapies. They also suggest that efforts to enhance Th17 function may improve existing antiretroviral treatments.

“We are interested in looking at different molecules and compounds to see if we can boost mucosal immune defenses in the gut,” she said.

Dandekar is also interested in looking at Th17 function in those who respond well to treatment and in long-term non-progressors, those individuals who carry HIV for years without going onto develop AIDS.

“Now we know these cells are playing a big role, but we need to better understand how they are contributing to immune inactivation and inflammation,” Dandekar said.

In terms of Salmonella, Bäumlér’s next step is to discover the mechanisms by which non-immunocompromised patients are able to rid themselves of the infections.

“We now know which cytokines orchestrate the mucosal barrier function, but we still don’t know what kills these bacteria,” he said.

**Public release date: 24-Mar-2008**

### **Free drug samples may burden patients' pockets**

Following free drug sample receipt, patients who receive these samples have significantly higher out-of-pocket prescription costs than those who don't, according to the first study to look at the out-of-pocket cost associated with free-sample use, published in the March 24, 2008, issue of Medical Care.

**Patients who never received samples had estimated out-of-pocket prescription costs of \$178 over six months. Patients who received samples spent an estimated \$166 for a six-month period prior to getting free samples, \$244 for the six months in which they received samples and \$212 for the six-month period following sample receipt.**

"Our findings suggest that physicians should use caution in assuming that the use of free samples ultimately reduces patients' out-of-pocket prescription cost," said study author G. Caleb Alexander, MD, assistant professor of medicine at the University of Chicago Medical Center.

There has been widespread debate about the advantages and disadvantages of free samples. In 2006, the New York Times published a letter to the editor from Ken Johnson, senior vice president of the Pharmaceutical Research and Manufacturers of America. He argued that "many uninsured and low-income patients benefit from these free samples, which often serve as a safety net."

"Samples may be particularly valuable in providing patients economic relief when they are used short-term and not followed-up with long-term prescription for the same medicine," says Alexander. "However, all too often, physicians and patients end up

continuing the medicines initially begun as samples, even though older, less expensive alternatives may exist."

Previous surveys have found that free samples can lead to overuse of newer drugs over their older counterparts, but these prior studies have usually examined just one clinical setting and have not examined the costs associated with sample receipt.

"We believe our study is one of the first to look at the economic consequences of sample receipt," Alexander said.

His team used the Medical Expenditure Panel Survey, conducted by the Agency for Healthcare Research and Quality, to examine the characteristics of those receiving samples, as well the relationship between sample receipt and out-of-pocket prescription costs.

They followed 5,709 patients from the national survey for up to two years. The mean age of patients was 48 years, 84 percent were white and 76 percent had private insurance. Fourteen percent of patients received at least one sample, with a total of 2,343 samples dispensed during the analysis period.

The authors found that there were important differences in the characteristics of patients who received samples and those who did not. The odds of sample receipt were lower among those who were older and also among those who had Medicaid as their source of insurance coverage.

The study was not designed to identify the exact reason that sample users have higher prescription costs after sample receipt. However, the authors hypothesize two main possibilities for this surprising finding.

First, those who received samples may have been more seriously ill than those who did not. But underlying health status, say the authors, explains only a part of the difference in out-of-pocket costs.

**Equally important, they suggest, is that patients who receive free samples may end up paying for a prescription for the medicine initially begun as a free samples. The medicines that are given as free samples are often the newest and the most expensive.**

"Regardless of the degree to which these different mechanisms account for our findings," Alexander said, "patients and physicians should consider complementary ways to reduce patients' burden from out-of-pocket prescription costs, such as using more generic medicines, stopping non-essential treatments, and using three-month rather than one-month supplies."

For policy-makers and researchers, their findings provide an opportunity to consider the complexity of issues raised by sample use.

"Further research is needed to examine patient-physician communication about samples," suggests Alexander, "as well as how physicians decide who needs samples and how samples are distributed across different types of physician practices."

They are also continuing studies that look the economic consequences of other common prescribing decisions that physicians and patients face.

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## **JAMA editor-in-chief comments on Pfizer lawsuit**

**In an editorial published early online today, JAMA Editor-in-Chief Catherine D. DeAngelis, M.D., M.P.H., and JAMA Editorial Counsel Joseph P. Thornton, J.D., write about a recent court ruling regarding litigation involving JAMA and the Archives of Internal Medicine (AIM) "that significantly threatened the integrity of our peer review process."**

**Attorneys for the pharmaceutical company Pfizer, Inc. had issued subpoenas last year to obtain confidential information from the journals concerning studies published on the pain relief medications called COX-2 inhibitors – (cyclooxygenase 2 inhibitors) celecoxib and valdecoxib.**

"... the subpoenas sought all documents regarding the decision to accept or reject manuscripts, copies of rejected manuscripts, the identities of peer reviewers and the manuscripts they reviewed, and the comments by and among peer reviewers and editor regarding manuscripts, revisions, and publication decisions. For months, JAMA and AIM consistently argued that the sanctity of the confidential peer review process should not be violated."

"In a ruling issued March 14, 2008, the Court agreed with JAMA and AIM that information kept confidential from Pfizer, the general public, and the medical community at large was irrelevant to the pending claims."

"... JAMA and our Archives journals have historically and deliberately kept unpublished manuscripts and peer review comments confidential. This promise to reviewers and authors allows the peer review process to work in an unrestrained environment."

"The subpoenas attempted to invade the peer review process, and we are delighted that Magistrate Judge Keys said so when he ruled they could not be enforced against us."

**Public release date: 24-Mar-2008**

## **Too much information? Study shows how ignorance can be influential**

In the current issue of The RAND Journal of Economics, USC researchers provide a challenge to the classic economic model of information manipulation, in which knowing more than anybody else is the key to influence.

Instead, economists Isabelle Brocas and Juan D. Carrillo present a situation – commonly observed in real life – in which all parties have access to the same information, but one party still manages to control public opinion.

For example, a pharmaceutical company such as Merck may be obliged to make public the findings of all studies related to a new drug. Preliminary trials may indicate no short-term side effects, and the company may elect not to perform follow-up trials before releasing the drug on the market.

“Optimally, you want to provide enough information so the other party reaches a certain level of confidence, but stop once you reach that level,” Brocas explained. “Otherwise, it may be the case that more information causes the confidence level to go down.”

The study, “Influence Through Ignorance,” is the first to thoroughly examine situations in which power comes from controlling the flow of public information, as opposed to the possession of private information.

As Brocas and Carrillo explain, there are secrets – facts that are deliberately withheld – and there are facts that are not known to anybody.

“It’s not necessary to have extra information,” Brocas said. “You can induce people to do what you want just by stopping the flow of information or continuing it. That’s enough.”

Notably, the party manipulating the flow of information must deliberately choose to remain uninformed as well – which can backfire.

**In Merck’s case, a study released five years after the drug was introduced on the market showed that taking Vioxx significantly increased the risk of heart attacks. Merck funded the study, which had been intended to see if the painkiller was also effective against colon polyps.**

Now, embroiled in a \$4.85 billion settlement, the company claims that Vioxx poses no statistically significant long-term risk to the heart once it is no longer taken. This claim is disputed: Merck stopped monitoring patients after only a year, discontinuing the study once the drug was taken off the market.

Similarly, the researchers explain, the head of a council may terminate discussion and introduction of new evidence about, say, whether to continue searching for weapons of mass destruction. Calling for a vote when sentiment seems biased in a certain direction effectively curtails how much all members, including the chairperson, know about the

issue at stake.

“Overall, the ability of to control the flow of news and remain publicly ignorant gives the leader some power, which is used to influence the actions of the follower,” the researchers wrote. “Our result suggests that the chairperson, the President and media can bias the decision of the committee, electorate and public by strategically restricting the flow of information.”

Brocas and Carrillo are in the midst of a follow-up to the study that gauges how well individuals intuitively understand the “influence through ignorance” phenomenon: “We’re interested in whether people understand their ability to manipulate information and if they do it optimally,” Brocas said.

The paper also provide implications for several important variants, such as how public opinion is affected when there is more than one source of information available to everyone and it is not excessively costly to obtain.

Competition, supported by media diversity and public sources of research funding, not only induces outlets to release more information but also causes the “influence through ignorance” effect to diminish – and under certain circumstances to vanish – the researchers found.

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## **Study: Dramatic Rise in Hepatitis C-Related Deaths in the United States Middle-aged Patients are Hardest Hit**

**Hepatitis C-related deaths in the United States increased by 123 percent from 1995 through 2004, the most recent year for which data are available.** Mortality rates peaked in 2002, then declined slightly overall, while continuing to rise among people 55 to 64 years old. These findings appear in the April issue of *Hepatology*, a journal of the American Association for the Study of Liver Diseases (AASLD). The article is also available online at Wiley Interscience ([www.interscience.wiley.com](http://www.interscience.wiley.com)).

Hepatitis C virus (HCV) is the most common blood-borne infection in the United States, affecting about 1.3 percent of the population. Up to one-in-five sufferers develop liver cirrhosis, and up to one-in-20 develop liver cancer. HCV is the top reason for liver transplantation, and the 16th leading cause of premature death in the country. Recent evidence has suggested that disease burden and mortality from chronic HCV infection

may increase in the coming years, as the number of persons with longstanding infections continues to rise.

To update estimates of trends and demographics of hepatitis C-related mortality in the U.S., a team of researchers led by Matthew Wise of UCLA and including researchers from the CDC and the Los Angeles County Department of Public Health analyzed mortality rates derived from U.S. Census and multiple-cause-of-death data from 1995-2004. They included 56,409 HCV related deaths, including those for which the disease was the underlying cause; those for which chronic liver disease was the underlying cause and hepatitis C was a contributing cause; and those for which HIV was the underlying cause and chronic liver disease and hepatitis C were contributing causes.

During the study period, HCV-related mortality rates increased from 1.09 deaths per 100,000 persons in 1995 to 2.57 per 100,000 in 2002, before declining slightly to 2.44 per 100,000 in 2004. Average annual increases were smaller during 2000-2004 than 1995-1999. The most dramatic age-specific increases were observed among 45 to 54 year olds who had an increase of 376 percent, and 55 to 64 year olds who had an increase of 188 percent. For the latter group, rates rose for the entire duration of the study.

“The highest mortality rates were observed among males, persons aged 45-54 and 55-64 years, Hispanics, non-Hispanic blacks and non-Hispanic Native American/Alaska Natives,” the authors report. They suggest that demographic differences are related to prevalence among the various populations.

The observed increases likely reflect both true increases in mortality and the growing use of serologic tests for HCV, the authors say. “As such, true increases in hepatitis C-related mortality during 1995-1999 were likely more gradual than the observed trends, and differences in mortality patterns between the time periods are difficult to interpret.” While the study was limited by possible inaccuracies in death certificate data, the authors believe that this more likely lead to an underestimate of the true number of hepatitis C-related deaths.

“In summary, substantial increases in overall hepatitis-C-related mortality rates have occurred since 1995,” the authors conclude. “The relatively young age of persons dying from hepatitis C-related liver disease has made hepatitis C-related disease a leading infectious cause of years of potential life lost as well as an important cause of premature mortality overall.” They point out the ongoing need for measures to prevent progression of liver disease among those infected with HCV, and the need for ongoing analysis of mortality trends.

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## **Hormone replacement therapy increases breast cancer recurrence**

Hormone replacement therapy (HRT) for peri- and postmenopausal symptoms increases disease recurrence in breast cancer survivors, according to an article published online March 25 in the Journal of the National Cancer Institute.

Previous studies have shown that HRT increases breast cancer incidence in healthy women, but its impact on breast cancer survivors has remained obscure. Observational studies and one small randomized trial had suggested that HRT had no effect or even might reduce recurrence. However, two-year follow-up data from the randomized HABITS (Hormonal Replacement After Breast Cancer —Is It Safe?) trial indicated that survivors who took HRT were more likely to suffer disease recurrence than those who did not take HRT.

In the current analysis, Lars Holmberg, M.D., Ph.D., currently at King's College London and his mostly Scandinavian colleagues examined the breast cancer rates for women in the HABITS trial after a median follow-up of four years.

**At the time of this analysis, 39 (17.6 percent) of the 221 women in the HRT treatment arm had developed breast cancer recurrence or a new breast cancer malignancy, compared with 17 (7.7 percent) of 221 women in the control arm. The estimated 5-year cumulative rate for disease recurrence was 22.2 percent for the HRT arm and 9.5 percent in the control arm, for an absolute increase in risk of 14.2 percent.**

“The results of the HABITS trial indicate a substantial risk for a new breast cancer event among breast cancer survivors using [HRT]. The risk elevation is in line with the evidence from observational studies and randomized trials that [HRT] increases the risk of breast cancer in healthy women,” the authors write.

In an accompanying editorial, Kathy I. Pritchard, M.D., of the Sunnybrook Odette Cancer Center in Toronto discusses the results of the HABITS trial and the Women's Health Initiative trial (which showed increased breast cancer risk among healthy women) in the context of the much less worrisome findings from observational studies. Observational studies, she writes, can be misleading because they have inherent biases, such as the types of patients selected for participation in the study. Although a randomized study from Stockholm found no increased risk of breast cancer recurrence among breast cancer survivors taking HRT, there may be key differences between this trial and the HABITS study, including the dosing schedule, the duration of treatment, and the type of hormones used—synthetic versus natural compounds. Those differences leave open several questions.

Despite these issues, the data are clear. “Although randomized data concerning use of HRT for symptomatic intervention in breast cancer survivors are still sparse, it seems that

the harmful side effects of HRT have finally been clearly demonstrated,” Pritchard writes.

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## **REVIEW OF GROUP-BASED CANCER TRIALS REVEALS FLAWS IN STUDIES’ DESIGN AND ANALYSIS**

COLUMBUS, Ohio – A new study reviewing 75 group-randomized cancer trials over a five-year stretch shows that fewer than half of those studies used appropriate statistical methods to analyze the results. The review suggests that some trials may have reported that interventions to prevent disease or reduce cancer risks were effective when in fact they might not have been.

**More than a third of the trials contained statistical analyses that the reviewers considered inappropriate to assess the effects of an intervention being studied. And 88 percent of those studies reported statistically significant intervention effects that, because of analysis flaws, could be misleading to scientists and policymakers, the review authors say.**

David Murray

**“We cannot say any specific studies are wrong. We can say that the analysis used in many of the papers suggests that some of them probably were overstating the significance of their findings,”** said David Murray, lead author of the review study and professor and chair of epidemiology in the College of Public Health at Ohio State University.

**“If researchers use the wrong methods, and claim an approach was effective, other people will start using that approach. And if it really wasn’t effective, then they’re wasting time, money and resources and going down a path that they shouldn’t be going down.”**

Murray and colleagues call for investigators to collaborate with statisticians familiar with group-randomized study methods and for funding agencies and journal editors to ensure that such studies show evidence of proper design planning and data analysis.

The review appears online in the Journal of the National Cancer Institute.

In group-randomized trials, researchers randomly assign identifiable groups to specific conditions and observe outcomes for members of those groups to assess the effects of an intervention under study.

These trials are used to investigate interventions that operate at a group level, manipulate the social or physical environment, or cannot be delivered to individuals in the same way a pill or surgical procedure can. For example, a group-randomized trial might study the use of mass media to promote cancer screenings and then assess how many screenings result among groups that receive different kinds of messages.

In analyzing the outcomes of such trials, researchers should take into account any similarities among group members or any common influences affecting the members of the same group, Murray said. But too often, this review found that the common ground among group members was not factored into the final statistical analysis.

What can result is called a Type 1 error, when a difference between outcomes in groups is found that doesn't really exist.

"In science, generally, we allow for being wrong 5 percent of the time. If you use the wrong analysis methods with this kind of study, you might be wrong half the time. We're not going to advance science if we're wrong half the time," said Murray, also a member of the Cancer Control Program in Ohio State's Comprehensive Cancer Center.

The review identified 75 articles published in 41 journals that reported intervention results based on group-randomized trials related to cancer or cancer risk factors from 2002 to 2006. Thirty-four of the articles, or 45 percent, reported the use of appropriate methods used to analyze the results. Twenty-six articles, or 35 percent, reported only inappropriate methods were used in the statistical analysis. Eight percent of the articles used a combination of appropriate and inappropriate methods, and nine articles had insufficient information to even judge whether the analytic methods were appropriate or not.

"Am I surprised by these findings? No, because we have done reviews in other areas and have seen similar patterns," Murray said. "It's not worse in cancer than anywhere else, but it's also not better. What we're trying to do is simply raise the awareness of the research community that you need to attend to these special problems that we have with this kind of design."

The use of inappropriate analysis methods is not considered willful or in any way designed to skew results of a trial, Murray noted.

"I've seen creative reasons people give in their papers for using the methods they use, but I've never seen anybody say it was done to get a more significant effect. But that's what can happen if you use the wrong methods and that's the danger," he said. "What we want to know from a trial is what really happened. If an intervention doesn't work, we need to know that, too, so we can try something else."

The review also is not an indictment of the study design. Murray is a proponent of such trials and was the first U.S. expert to author a textbook on the subject (Design and

Analysis of Group-Randomized Trials, Oxford University Press, 1998).

He also is a co-investigator on three group-randomized trials in progress at Ohio State. Two trials use specific clinics as the assigned groups. One is analyzing the effectiveness of having specially trained guides help cancer patients negotiate the health-care system. The second is investigating the effectiveness of aggressive physician promotion of colorectal cancer screening for patients with cancer risk factors. A third trial will use Appalachian counties as groups to compare the effectiveness of a media campaign to promote colorectal cancer screenings.

“We’re not trying to discourage people from using this design. It remains the best design available if you have an intervention that can’t be studied at the individual level,” Murray said.

This review study was supported by grants from the National Cancer Institute and the American Cancer Society.

Murray conducted the review with Sherri Pals of the Centers for Disease Control and Prevention; Jonathan Blitstein of RTI International in Research Triangle Park, N.C.; Catherine Alfano of the Division of Health Behavior and Health Promotion in Ohio State’s College of Public Health; and Jennifer Lehman of Ohio State’s Department of Family Medicine.

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## **Are Organic Crops as Productive as Conventional?**

MADISON, WI, March 24, 2008 -- **Can organic cropping systems be as productive as conventional systems? The answer is an unqualified, “Yes” for alfalfa or wheat and a qualified “Yes most of the time” for corn and soybeans according to research reported by scientists at the University of Wisconsin-Madison and agricultural consulting firm AGSTAT in the March-April 2008 issue of Agronomy Journal.**

The researchers primarily based their answer on results from the Wisconsin Integrated Cropping Systems Trials, conducted for 13 years (1990-2002) at Arlington, WI and 8 years (1990-1997) at Elkhorn, WI. These trials compared six cropping systems (three cash grain and three forage based crops) ranging from diverse, organic systems to less diverse, conventional systems. The cash grain systems were 1) conventional continuous corn, 2) conventional corn-soybean, and 3) organic corn-soybean-wheat where the wheat included a leguminous cover crop. The three forage based systems were 1) conventional corn-alfalfa-alfalfa-alfalfa, 2) organic corn-oats-alfalfa-alfalfa, and 3) rotationally grazed pasture.

**In this research they found that: organic forage crops yielded as much or more dry matter as their conventional counterparts with quality sufficient to produce as much milk as the conventional systems; and organic grain crops: corn, soybean, and**

**winter wheat produced 90% as well as their conventionally managed counterparts. In spite of some climatic differences and a large difference in soil drainage between the two sites, the relatively small difference in the way the cropping systems performed suggested that these results are widely applicable across prairie-derived soils in the U.S. upper Midwest. The researchers also compared their results to other data analysis done on this topic in the U.S. Midwest.**

Although researchers found that diverse, low-input/organic cropping systems were as productive as conventional systems most of the time, there is a need for further research, according to the study's author Dr. Joshua L. Posner, University of Wisconsin.

“There continues to be improvements in weed control for organic systems that may close the gap in productivity of corn and soybeans in wet seasons,” Posner says. “On the other hand, technological advances may accelerate productivity gains in conventional systems that would outstrip the gains in organic systems even in favorable years.”

The true question of whether organic cropping systems are as productive as conventional systems is a dynamic question and one that requires continual reevaluation.

Ralph's Note - So why does organic have to be so expensive?

**Public release date: 25-Mar-2008**

## **Mounting evidence shows red wine antioxidant kills cancer**

### **Researchers pinpoint how resveratrol induces pancreatic cancer cell death**

Rochester researchers showed for the first time that a natural antioxidant found in grape skins and red wine can help destroy pancreatic cancer cells by reaching to the cell's core energy source, or mitochondria, and crippling its function. The study is published in the March edition of the journal, *Advances in Experimental Medicine and Biology*.

The study also showed that when the pancreatic cancer cells were doubly assaulted -- pre-treated with the antioxidant, resveratrol, and irradiated -- the combination induced a type of cell death called apoptosis, an important goal of cancer therapy.

The research has many implications for patients, said lead author Paul Okunieff, M.D., chief of Radiation Oncology at the James P. Wilmot Cancer Center at the University of Rochester Medical Center.

Although red wine consumption during chemotherapy or radiation treatment has not been well studied, it is not "contraindicated," Okunieff said. In other words, if a patient already drinks red wine moderately, most physicians would not tell the patient to give it up during treatment. Perhaps a better choice, Okunieff said, would be to drink as much red

or purple grape juice as desired.

Yet despite widespread interest in antioxidants, some physicians are concerned antioxidants might end up protecting tumors. Okunieff's study showed there is little evidence to support that fear. In fact, the research suggests resveratrol not only reaches its intended target, injuring the nexus of malignant cells, but at the same time protects normal tissue from the harmful effects of radiation.

"Antioxidant research is very active and very seductive right now," Okunieff said. "The challenge lies in finding the right concentration and how it works inside the cell. In this case, we've discovered an important part of that equation. Resveratrol seems to have a therapeutic gain by making tumor cells more sensitive to radiation and making normal tissue less sensitive."

Resveratrol is known for its ability to protect plants from bacteria and fungi. Purified versions have been described in scientific journals as potential anti-cancer, anti-inflammatory and anti-atherogenic agents, and for their ability to modulate cell growth. Other well-known antioxidants derived from natural sources include caffeine, melatonin, flavonoids, polyphenols, and vitamins C and E.

A flurry of antioxidant studies in recent years has not proven how and why they work at the cellular level. At the suggestion of a young scientist in his lab, Okunieff began studying resveratrol as a tumor sensitizer. That's when they discovered its link to the mitochondria.

The discovery is critical because, like the cell nucleus, the mitochondria contains its own DNA and has the ability to continuously supply the cell with energy when functioning properly. Stopping the energy flow theoretically stops the cancer.

Researchers divided pancreatic cancer cells into two groups: cells treated without resveratrol, or with resveratrol, at a relatively high dose of 50 mg/ml, in combination with ionizing radiation. (The resveratrol concentration in red wine can be as high as 30 mg/ml, the study said, and higher doses are expected to be safe as long as a physician is monitoring.)

They evaluated the mitochondria function of the cells treated with resveratrol, and also measured apoptosis (cell death), the level of reactive oxygen species in the cells, and how the cell membranes responded to the antioxidant.

Laboratory experiments showed that resveratrol:

Reduced the function of proteins in the pancreatic cancer cell membranes that are responsible for pumping chemotherapy out of the cell, making the cells chemo-sensitive.

Triggered the production of reactive oxygen species (ROS), which are substances

circulating in the human body that have been implicated in a number of diseases: when ROS is increased, cells burn out and die.

Caused apoptosis, which is likely the result of increased ROS.

Depolarized the mitochondrial membranes, which indicates a decrease in the cell's potential to function. Radiation alone does not injure the mitochondrial membrane as much.

The team also wanted to investigate why pancreatic cancer cells seem to be particularly resistant to chemotherapy. The pancreas, a gland located deep in the abdomen, produces insulin and regulates sugar, and pumps or channels powerful digestive enzymes into the duodenum. This natural pumping process, however, ends up ridding the needed chemotherapy from cells in the pancreas. But just as resveratrol interferes with the cancer cells' energy source, it also may decrease the power available to pump chemotherapy out of the cell.

"While additional studies are needed," Okunieff said, "this research indicates that resveratrol has a promising future as part of the treatment for cancer."

In the same journal, Okunieff and his group also reviewed why resveratrol protects normal tissue, and found that antioxidants can be designed to take advantage of certain biochemical properties or cellular targets, making them more effective.

**Public release date: 25-Mar-2008**

## **A link between antidepressants and type 2 diabetes**

While analyzing data from Saskatchewan health databases, Lauren Brown, researcher with the U of A's School of Public Health, found people with a history of depression had a 30 per cent increased risk of type 2 Diabetes.

Brown then studied the medical history of 2,400 people who were diagnosed with depression and were taking antidepressants to determine whether there was a clear correlation between that disease and type 2 Diabetes.

Brown divided the group into four categories: those who took antidepressants that were considered older therapies, patients who were using newer treatments, those using a combination of both an old and new treatments and people who were switching medications.

What she found was the risk of diabetes almost doubled for the patients who were using two types of therapies at the same time, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Brown says people are usually prescribed multiple medications "if they have severe depression or if they are having a problem finding the

right therapy.”

Brown believes these results, and results of previous studies demonstrating an increased risk of type 2 diabetes in people with depression, emphasize the need for regular screening for type 2 diabetes in people with depression, particularly those taking more than one antidepressant. She also encourages diabetes and depression organizations to educate their members about this link.

**Public release date: 26-Mar-2008**

## **FDA deadlines may compromise drug safety by rushing approval**

### **Fast-tracked medications more likely to face later regulatory action to remedy safety concerns**

CAMBRIDGE, Mass. – Many medications are approved by the U.S. Food and Drug Administration on the brink of congressionally mandated deadlines, and those drugs are more likely to face later regulatory intervention than those approved with greater deliberation, researchers at Harvard University have found. Drugs fast-tracked by the FDA are more likely to eventually be withdrawn from global markets for safety reasons, undergo manufacturing revisions, or face labeling changes, according to Daniel Carpenter, professor of government in Harvard’s Faculty of Arts and Sciences. The research will be published in the Mar. 27 issue of the *New England Journal of Medicine*.

Carpenter’s co-authors were Jerry Avorn, Professor of Medicine at Harvard Medical School/chief, Division of Pharmacoepidemiology at Brigham and Women’s Hospital and Evan James Zucker, a student at Harvard Medical School.

“We found that while these deadlines speed up the approval process, many drugs are approved right up against the deadline, which might lead to unintended consequences with regard to drug safety,” says Carpenter. “This suggests that drug safety might improve under an FDA approval protocol that is more flexible and less driven by deadline pressures and more by stable growth in FDA resources.”

The deadlines imposed on the FDA’s drug-approval process were first enacted as part of the Prescription Drug User Fee Act (PDUFA) of 1992, which mandated that the FDA must act on 90 percent of all drug candidates within 12 months of submission or face funding cuts. The timeline was tightened to 10 months as part of the 1997 Food and Drug Administration Modernization Act, a timeline extended by Congress in 2002 as part of bioterrorism legislation and renewed again in 2007.

Some observers have suggested that these deadlines lead to the rushed approval of medications, a theory Carpenter tested by examining data on the timing of FDA approvals dating back to 1950. He found that the enactment of PDUFA in 1992 appeared to introduce a temporal discontinuity into FDA review cycles, with disproportionate

approvals coming in the two months immediately before deadlines. Compared to drugs approved at a more measured pace in the months following the deadline, those approved right before the review clock expired were far more likely to require later regulatory intervention.

**“Drugs rushed to approval just before the deadline are two to three times more likely to eventually be pulled off shelves due to safety concerns, two to seven times more likely to receive added label warnings known as ‘black box revisions,’ twice as likely to experience changes in manufacture, and two to seven times more likely to be voluntarily discontinued by manufacturers due to weak clinical demand,”** says Carpenter.

In previous work, Carpenter developed a mathematical model to understand how government agencies “learn” and how deadlines affect organizational behavior. This model predicts the pattern of outcomes described in the New England Journal study.

**Fifty years ago, the FDA approved most new medications within a few months of receiving applications from manufacturers. Over time, the process slowed as new review protocols were added in the wake of pharmaceutical missteps such as thalidomide, which led to the births of thousands of deformed babies in the late 1950s and early 1960s.**

“Because of similarly high-profile regulatory mistakes in recent years, we will likely see greater congressional scrutiny in coming decades as these FDA deadlines come up for renewal every five years,” Carpenter says. “While we are not arguing that these deadlines should be abandoned, our research indicates that mechanisms other than strict deadlines may better balance the need for expeditious yet rigorous drug approval.”

**Public release date: 26-Mar-2008**

## **Apple pectin, apple juice extracts shown to have anticarcinogenic effects on colon**

WASHINGTON - The apples and apple juice you consume may have positive effects in one of the most unlikely places in the body – in the colon. New research has demonstrated that both apple pectin and polyphenol-rich apple juice components actually enhance biological mechanisms that produce anticarcinogenic compounds during the fermentation process.

Using human fecal matter as the test substance, German researchers Dr. Dieter Schrenk, M.D. and his colleagues hypothesized that the compound butyrate could be increased in the presence of apple pectin and apple juice extracts.

Butyrate has been suggested to be a chemopreventative metabolite that might prevent the occurrence of colorectal cancer, which is very common in Western industrialized countries. It is a short chain fatty acid which is seen as a major factor contributing to healthy colon mucosa. The research notes, “Butyrate not only serves as a major nutrient

for the colon epithelia but is also thought to play an important role in the protective effect of natural fiber against colorectal cancer.”

So how do apple pectin and apple juice extracts play a role in increasing amounts of butyrate? The laboratory tests performed by Schrenk found that by the increased production of butyrate via the addition of apple components, histone deacetylases (HDAC) were inhibited. With slowed production of HDAC, there would be significantly less growth of precancerous and tumor cells.

The research, published in the April 2008 issue of *Nutrition*, notes, “apples are a major source of natural fiber and of low molecular weight plant polyphenols in the Western diet.” The researchers conclude, “Pectin-rich apple products can thus be expected to exert anticarcinogenic effects in the colon.”

**Public release date: 26-Mar-2008**

## **Dental chair a possible source of neurotoxic mercury waste**

Mercury is a large component of dental fillings, but it is not believed to pose immediate health risks in that form. When exposed to sulfate-reducing bacteria, however, mercury undergoes a chemical change and becomes methylated, making it a potent, ingestible neurotoxin.

While the major source of neurotoxic mercury comes from coal-fired electric power plants, researchers at the University of Illinois at Chicago and at Urbana-Champaign say mercury entering drain water from dental clinics and offices is also a source.

"We found the highest levels of methyl mercury ever reported in any environmental water sample," said Karl Rockne, associate professor of environmental engineering at UIC and corresponding author of the study that appeared online March 12 in the journal *Environmental Science and Technology*.

Working with James Drummond, UIC professor of restorative dentistry, Rockne gathered waste water samples in collection tanks generated from both a single-chair dentist's office and a 12-chair dental clinic to check for methyl mercury.

Water collected was allowed to settle. Clear layers above the settled particles were then analyzed for presence of methyl mercury. Fine, slow-settling particles of mercury get into the waste water mostly after dentists use high-speed drills to remove old amalgam fillings. The numerous fine particles the drilling produces provide an ample source of exposed mercury surfaces, making them prime targets for sulfur-reducing bacteria that commonly live in anaerobic conditions and are known to methylate mercury.

"It appears to be produced partially, if not fully in the waste water, and it's being

produced very rapidly," said Rockne, adding that it was significant this was happening before the particles were getting into sewers, where sulfur-reducing bacteria thrive.

The finding raised the question whether the culprit bacteria were living in the mouths of dental patients. "We don't have the answer," Rockne said.

**Based on their sample studies, the researchers estimate that 2-5 kilograms, or up to 11 pounds, of methyl mercury could be entering the public water supply of the United States each year from dental waste water. While this may not seem like much, methyl mercury is highly toxic in minute amounts.**

When in waterways, methyl mercury tends to get biomagnified up the food chain, moving from algae and phytoplankton to fish and, ultimately, to humans.

While surprised by the level of contaminants found in the study, Rockne says follow-up research is necessary -- then, possibly, some basic engineering.

"Amalgam separators are a good first step, but maybe something else is necessary downstream to prevent further methylation and prevent further soluble mercury from getting through the system," he said.

"We have to take more steps to prevent the problem from occurring in the first place," he said. "We're dealing with a pipe -- a control point. As an engineer, I see this as a problem that is tractable -- something we can definitely do something about."

*Ralph's Note- Toxic in minute amounts, but it is safe in your mouth?*

**Public release date: 26-Mar-2008**

### **Infant formula must contain DHA omega-3 and AA omega-6, say international experts**

New recommendations published by international experts in the Journal of Perinatal Medicine state that infant formula should include DHA omega-3 and AA omega-6 to guarantee a correct eye and brain development.

These recommendations for DHA and AA intake have been developed by a panel of child health experts from 11 countries with endorsement from organizations such as The World Association of Perinatal Medicine, Child Health Foundation and the Early Nutrition Foundation.

The expert team emphasizes that breastfeeding is the preferred method of feeding, as DHA and AA are available in breast milk. However, when the mother is unable or

chooses not to breastfeed, infant formula should include DHA at the recommended levels of between 0.2% and 0.5% of fatty acids and the amount of AA should be at least equal to the DHA level. The experts also note that the addition of at least 0.2% DHA plus AA is necessary to achieve functional developmental benefits.

“Over the past decade, many research studies have highlighted the importance of DHA omega-3 and AA omega-6 in infant development -said Cristina Campoy, of the Department of Paediatrics of the University of Granada (CIBM)-. It is therefore vital that pregnant and nursing mothers consume adequate amounts of DHA in their own diet, and, if using an infant formula, should provide their infants with a formula containing DHA and AA at recommended levels”.

DHA omega-3 and AA omega-6

**Docosaheptaenoic acid, or DHA, is a long-chain polyunsaturated omega-3 fatty acid, or ‘good’ fat, found throughout the body. It is a major structural fat in the brain and retina of the eye accounting for up to 97 percent of the omega-3 fats in the brain and up to 93 percent of the omega-3 fats in the retina. It is also a key component of the heart.**

Studies have shown that DHA omega-3 is important for infant brain, eye and nervous system development and has been shown to support long-term heart health. It is important throughout pregnancy, but particularly in the third trimester when significant brain growth occurs.

**Arachidonic acid, AA, is a long-chain omega-6 fatty acid, another ‘good’ fat. It is the principal omega-6 in the brain, representing about 48 percent of the omega-6 fats.** Like DHA, AA omega-6 is important for proper brain development in infants. It is also a precursor to a group of hormone-like substances called eicosanoids that play a role in immunity, blood clotting and other vital functions in the body.

Infants whose mothers supplement with DHA during pregnancy and nursing or who are fed formula milk supplemented with DHA and AA have significantly enhanced levels of these nutrients available to them. Major infant brain growth occurs during pregnancy and throughout the first two years of life. During these times, infants have the greatest need for DHA omega-3 and AA omega-6.

DHA and AA in the diet

The main dietary source of DHA is oily fish. AA is found in foods such as meat, eggs and milk. While most women typically consume enough AA in their diets, those who consume a typical Western diet are at risk for low stores of DHA. This may be because oily fish is not a staple of the typical Western diet. Additionally, expert bodies have advised pregnant and nursing women to limit their fish consumption due to the potentially high levels of toxins such as mercury.

The amount of essential fatty acids provided to infants through maternal intake during pregnancy and/or breastfeeding and through supplemented formula milks is important. Babies cannot make these essential fats themselves, which is why it is vital that they are made available via the mother's diet during pregnancy and breastfeeding or through supplemented infant formula.

#### About the recommendations

The Recommendations and Guidelines for Perinatal Medicine were developed by a team of 19 experts from 11 countries who reviewed the current research and recommendations on DHA and AA and evaluated the body of research exploring how DHA & AA affect infant brain and eye development. The expert team, which included experts from Italy, France, Germany, Spain and the UK concluded that both DHA and AA should be added to infant formula in order to provide formula-fed infants these important nutrients at a comparable rate to their breastfed counterparts. The guidelines also recommend that pregnant or breastfeeding women should include enough DHA in their diets to support the brain and eye development of their babies. The Recommendations and Guidelines for Perinatal Medicine were supported by the The World Association of Perinatal Medicine ([www.wapm.info](http://www.wapm.info)), the Early Nutrition Academy ([www.metabolic-programming.org](http://www.metabolic-programming.org)), and the Child Health Foundation ([www.kindergesundheit.de](http://www.kindergesundheit.de)).

#### Summary of the recommendations

The authors emphasize the importance of a balanced diet for breastfeeding women, including a regular supply of DHA

Pregnant women should aim for a DHA intake of at least 200mg a day (equivalent to two portions of oily sea fish per week)

If breast milk is not available to the baby, current evidence supports the addition of DHA and AA to infant formula

The DHA added should make between 0.2% and 0.5% of fatty acids [noting that 0.2% is the minimum level necessary to see functional developmental benefits]

Infant formula should be supplemented with AA in amounts at least equal to the amount of DHA

EPA, another omega-3 fatty acid, should be less than the amount of DHA

Dietary supply of DHA and AA should continue during the second six months of life, but experts do not have enough information to recommend exact amounts

**Public release date: 27-Mar-2008**

## **U of T research finds glycine could be key to REM Sleep Behavior Disorder**

TORONTO, ON. – There is new promise on the horizon for those who suffer from REM Sleep Behaviour Disorder (RBD) according to researchers at the University of Toronto.

RBD, a neurological disorder that causes violent twitches and muscle contractions during rapid eye-movement (REM) sleep, can lead to serious injuries. John Peever, Assistant Professor at the University of Toronto, discovered that an inhibitory brain chemical called glycine is responsible for actively suppressing muscle twitches in REM sleep. **Deficiency in glycine levels in the brain cells that control muscles (motoneurons) was found to cause the violent muscle contractions that mimic the primary symptom of RBD.**

“This study shows the mechanism that suppresses muscles twitches in REM sleep and this will lead to better treatments and potential cures for this disorder,” says Peever. “Treating REM sleep disorder may have much broader implications, since within five to eight years of being diagnosed with this disorder, 60-80% of individuals eventually develop Parkinson’s disease.”

**Public release date: 26-Mar-2008**

### **A ton of bitter melon produces sweet results for diabetes**

Scientists have uncovered the therapeutic properties of bitter melon, a vegetable and traditional Chinese medicine, that make it a powerful treatment for Type 2 diabetes. Teams from the Garvan Institute of Medical Research and the Shanghai Institute of Materia Medica pulped roughly a tonne of fresh bitter melon and extracted four very promising bioactive components. **These four compounds all appear to activate the enzyme AMPK, a protein well known for regulating fuel metabolism and enabling glucose uptake. The results are published online today in the international journal Chemistry & Biology.**

“We can now understand at a molecular level why bitter melon works as a treatment for diabetes,” said Professor David James, Director of the Diabetes and Obesity Program at Garvan. “By isolating the compounds we believe to be therapeutic, we can investigate how they work together in our cells.”

People with Type 2 diabetes have an impaired ability to convert the sugar in their blood into energy in their muscles. This is partly because they don’t produce enough insulin, and partly because their fat and muscle cells don’t use insulin effectively, a phenomenon known as ‘insulin resistance’.

Exercise activates AMPK in muscle, which in turn mediates the movement of glucose transporters to the cell surface, a very important step in the uptake of glucose from the circulation into tissues in the body. This is a major reason that exercise is recommended as part of the normal treatment program for someone with Type 2 diabetes. The four compounds isolated in bitter melon perform a very similar action to that of exercise, in that they activate AMPK.

Garvan scientists involved in the project, Drs Jiming Ye and Nigel Turner, both stress

that while there are well known diabetes drugs on the market that also activate AMPK, they can have side effects.

“The advantage of bitter melon is that there are no known side effects,” said Dr Ye. “Practitioners of Chinese medicine have used it for hundreds of years to good effect.” Garvan has a formal collaborative arrangement with the Shanghai Institute of Materia Medica. In addition to continuing to work together on the therapeutic potential of bitter melon, we will be exploring other Chinese medicines.

Professor Yang Ye, from the Shanghai Institute and a specialist in natural products chemistry, isolated the different fractions from bitter melon and identified the compounds of interest.

“Bitter melon was described as “bitter in taste, non-toxic, expelling evil heat, relieving fatigue and illuminating” in the famous Compendium of Materia Medica by Li Shizhen (1518-1593), one of the greatest physicians, pharmacologists and naturalists in China’s history,” said Professor Ye. “It is interesting, now that we have the technology, to analyse why it has been so effective.”

“Some of the compounds we have identified are completely novel. We have elucidated the molecular structures of these compounds and will be working with our colleagues at Garvan to decipher their actions at a molecular level. We assume it’s working through a novel pathway inside cells, and finding that pathway is going to be very interesting.”

**Public release date: 26-Mar-2008**

### **Folate scores a win in animal studies: Brief, high doses of B vitamin blunt damage from heart attack**

Long known for its role in preventing anemia in expectant mothers and spinal birth defects in newborns, the B vitamin folate, found in leafy green vegetables, beans and nuts has now been shown to blunt the damaging effects of heart attack when given in short-term, high doses to test animals.

In a new study, an international team of heart experts at Johns Hopkins and elsewhere report that rats fed 10 milligrams daily of folate, also known as folic acid or vitamin B9, for a week prior to heart attack had smaller infarcts than rats who took no supplements. On average, researchers say, the amount of muscle tissue exposed to damage and scarred by the arterial blockage was shrunk to less than a tenth.

The team’s findings, set for publication in the April 8 edition of the journal *Circulation*, come just weeks after other international studies in humans suggested that low-dose folic acid supplements may prevent dementia in the elderly and premature births.

“We want to emphasize that it is premature for people to begin taking high doses of folic

acid,” says senior study investigator David Kass, M.D., a professor at The Johns Hopkins University School of Medicine and its Heart Institute.

“But if human studies prove equally effective, then high-dose folate could be given to high-risk groups to guard against possible heart attack or to people while they are having one,” says Kass.

The more likely and most practical advantage to ingesting supplements, he says, lies in folic acid’s potential to act as a short-term buffer for people who may be having a heart attack and who rush to their local emergency room complaining of chest pain.

Clinical trials are expected in the near future, although Kass says a major challenge in testing is that a high dose of folic acid for humans comparable to that given the rats would require an average-size adult to swallow more than 200 one-milligram pills per day, “an impractical and unrealistic regimen, even if the body excretes the excess.”

In addition, he cautions, “we do not yet know if folate is safe to consume in this high a dose, or how much or how little of it is needed to be effective,” citing 25 milligrams per day as the highest dose previously tested safe to consume in adults as.

Kass says that such large amount of folate may also yield unpredictable side effects. Some studies have linked the nutrient supplement to increased rates of colon and prostate cancer.

Each year, an estimated 565,000 first-time heart attacks occur in the United States, with an additional 300,000 recurrent heart attacks.

Results from the new study, conducted in rats - dozens were fed supplements and dozens more did not receive any - showed that overall pumping function during heart attack remained strong in vitamin B9-fortified animals.

**The amount of blood pumped by the treated hearts during a 30-minute window when blood flow to the heart was restricted to simulate a heart attack stayed near normal for rodents, at an average ejection fraction of 73 percent. Meanwhile, it fell in the untreated group to 27 percent.**

**Similarly, the muscle wall at the front of the heart kept contracting during heartbeats, thickening by 37 percent in the supplement-fed group, but the muscle could barely compress, thickening by 5 percent, in the untreated group. (Sixty percent would be the normal amount of thickening in a healthy rat heart.)**

**Moreover, researchers found that an injection of folic acid into the bloodstream of rats that had never before taken supplements, within the first 10 minutes of a heart attack, was almost equally as effective as preventive therapy in reversing muscle damage, and in lowering infarct size by a factor of 10.**

“Folic acid is already well known to be safe to consume in high doses in the short term, and it is very inexpensive, costing pennies per milligram, so its prospects look promising,” says Kass.

Researchers plan further tests to determine precisely why folate protects the heart, and to determine how effective it is in not-as-high doses. But they point out that it has long been known for its role in the normal workings of the cell’s principal energy source, the mitochondria, whose function is essential to maintaining healthy blood vessels.

It was this evidence that led to the latest study, which, says lead investigator An Moens, M.D., suggests that folate acts as an energy reserve in the heart, “providing much needed energy for muscle contraction, in the form of ATP, at the same time the heart is being starved for oxygen-carrying blood by a blocked artery.”

According to Moens, a postdoctoral cardiology research fellow at Johns Hopkins, study results showed that high-energy phosphate levels went down 43 percent in the blood of treated rats, but levels dropped by one-third more (by 66 percent) in untreated rats.

“With more fuel, the heart kept pumping even though its blood flow was reduced,” says Moens, now a cardiologist at the University of Antwerp in Belgium. “The smaller heart attacks seemed related to this better energy balance in the heart produced by the folate.”

In the study, heart function was monitored by more than two dozen key tests, such as echocardiogram and magnetic resonance imaging, as well as by blood analysis before, during and after the heart attack, when blood flow was allowed to resume in the coronary artery that had been blocked.

Among the team’s other findings that backed up the protective effects of folate on the heart were mild, slight dips in systolic blood pressure during heart attack in treated rats, while pressure fell in untreated animals by 25 percent. Similarly, blood flow was stable in the treated group, but dropped by 40 percent in untreated animals. Post-heart attack buildup of dangerous chemicals, known as reactive oxygen species, was halved in treated rats. And fatal arrhythmias, unstable heartbeats that can immediately follow a heart attack, also went down from 36.7 percent to 8.3 percent in the supplement-fed group.

“In future, we might just pop in an I.V., and give people high-dose folate while they are waiting for their catheterization or CT scans to search for blockages,” says Moens.

**Public release date: 27-Mar-2008**

## **Family study bolsters link between pesticides and Parkinson's**

For the first time, the association between Parkinson’s disease and exposure to pesticides has been shown in patients with the neurological disorder compared with their unaffected relatives, according to a study in the online open access journal BMC Neurology.

Parkinson's disease is a common neurological disorder affecting about 1 million people in the USA. The disorder typically develops in later life resulting in symptoms such as tremors and muscle rigidity

Although variations in several genes have been identified that contribute to the disease, these rare genetic defects account for a small proportion of the overall prevalence of the disorder.

The majority of Parkinson's disease cases are thought to be due to an interaction between genetic and environmental factors.

**“Previous studies have shown that individuals with Parkinson's disease are over twice as likely to report being exposed to pesticides as unaffected individuals” says the study's lead author, Dana Hancock, “but few studies have looked at this association in people from the same family or have assessed associations between specific classes of pesticides and Parkinson's disease.”**

The study of related individuals who share environmental and genetic backgrounds that might contribute to Parkinson's disease enables researchers to identify specific differences in exposures between individuals with and without the disease. The research team from Duke University Medical Center (Durham, NC) and the University of Miami Miller School of Medicine Morris K. Udall Parkinson Disease Research Center of Excellence (Miami, FL, USA) recruited 319 patients and over 200 relatives. They used telephone interviews to obtain histories of pesticide exposure, living or working on a farm, and well-water drinking.

The authors detected an association between pesticide use and Parkinson's disease. Among these, the strongest were between the disorder and use of herbicides and insecticides, such as organochlorides and organophosphates. No association was found between Parkinson's disease and well-water drinking or living or working on a farm, which are two commonly used proxies for pesticide exposures.

Many studies have supported pesticides as a risk factor for PD, but “biological evidence is presently insufficient to conclude that pesticide exposure causes PD”, says Hancock. “Further investigation of these specific pesticides and others may lead to identification of pertinent biological pathways influencing PD development.” In addition future genetic studies of Parkinson's disease should consider the influence of pesticides, since exposure to pesticides may provide a trigger for the disease in genetically predisposed individuals.

**Public release date: 28-Mar-2008**

## **Study shows why synthetic estrogens wreak havoc on reproductive system**

Researchers at Yale School of Medicine now have a clearer understanding of why synthetic estrogens such as those found in many widely-used plastics have a detrimental

effect on a developing fetus, cause fertility problems, as well as vaginal and breast cancers.

Preliminary results of the study will be presented at the 2008 Society for Gynecologic Investigation (SGI) Annual Scientific Meeting held March 26-29 in San Diego, California. The study was led by Hugh S. Taylor, M.D., professor in the Department of Obstetrics, Gynecology & Reproductive Science and section chief of Reproductive Endocrinology and Infertility at Yale School of Medicine.

Past research shows that exposure to the synthetic estrogen diethylstilbestrol (DES) alters the expression of HOXA10, a gene necessary for uterine development, and increases the risk of cancer and pregnancy complications in female offspring.

**The team sought to understand why a developing female fetus exposed to DES might develop uterine cancer and other problems years after exposure. Even though DES is no longer on the market, the authors chose to study its effects to gain insight into how similar synthetic estrogens might work.**

The team studied DNA from the offspring of 30 pregnant mice injected with DES. They found changes in certain regions of the HOXA10 gene. These alterations continued beyond the time of development and persisted into adulthood, indicating that exposure to DES and similar substances results in lasting genetic memory, known as “imprinting.”

“We found that HOXA 10 protein expression was shifted to the bottom portion of the uterus in the female offspring,” said Taylor. “We also found increased amounts of the enzyme responsible for changes in the DNA. Rather than just changing how much of the protein is there, DES is actually changing the structure of the HOXA 10 gene.

“These findings bring us closer to understanding the way in which DES interacts with the developing reproductive system,” said Taylor.

**Pregnant women are frequently exposed to other similar substances with estrogen-like properties, such as Bisphenol-A (BPA). BPA is found in common household plastics and has recently been linked to long-term fertility problems. Like DES, these other substances may also impact female reproductive tract development and the future fertility of female fetuses**

**Public release date: 28-Mar-2008**

**Hormone that controls hunger and appetite also linked to reduced fertility**

Researchers at Yale School of Medicine have found that in-utero exposure to the hormone ghrelin, a molecule that controls appetite and hunger and nutrition, can result in decreased fertility and fewer offspring.

Results from this research will be presented in an abstract at the 2008 Society for Gynecologic Investigation (SGI) Annual Scientific Meeting held March 26-29 in San Diego, California.

Ghrelin, the so-called “hunger hormone,” is produced in the stomach and brain, induces food intake, and operates through a brain region that controls cravings for food and other energy sources. Ghrelin decreases the HOXA 10 gene that is involved in developmental programming of the uterus. The HOXA 10 gene determines how the uterus will develop in adulthood.

**“When you’re obese, ghrelin levels are lower, and based on these preliminary findings, they may result in lower fertility,”** said lead author on the abstract, **Hugh S. Taylor, M.D., professor in the Department of Obstetrics, Gynecology & Reproductive Sciences and section chief of Reproductive Endocrinology and Infertility at Yale School of Medicine.**

The researchers bred mice designed to be deficient in ghrelin production. These mice had offspring with decreased fertility and that produced smaller litter sizes. These offspring also had lower expression of the HOXA 10 gene, which is important for proper development of the uterus in the embryo. In the adult uterus, it maintains the ability of the uterus to provide an optimal environment for proper development of the embryo.

“Obesity may have an effect on pregnancy in the next generation,” said Taylor, adding that the findings underscore the importance of nutrition, energy utilization and appropriate ghrelin levels on normal uterine development. Taylor and his team will next study the effects of lower ghrelin levels on humans.

**Public release date: 30-Mar-2008**

## **No laughing matter -- bacteria are releasing a serious greenhouse gas**

Unlike carbon dioxide and methane, laughing gas has been largely ignored by world leaders as a worrying greenhouse gas. But nitrous oxide must be taken more seriously, says Professor David Richardson from the University of East Anglia in Norwich, UK, speaking today (Monday 31 March 2008) at the Society for General Microbiology’s 162nd meeting being held this week at the Edinburgh International Conference Centre.

**“It only makes up 9% of total greenhouse gas emissions, but it’s got 300 times more global warming potential than carbon dioxide”, says Prof Richardson. “It can survive in the atmosphere for 150 years, and it’s recognised in the Kyoto protocol as one of the key gases we need to limit”.**

The potent gas is mainly coming from waste treatment plants and agriculture. Its release is increasing at the rate of 50 parts per billion or 0.25% every year. This means that it can be better controlled with suitable management strategies, but only if the importance of nitrous oxide (N<sub>2</sub>O) is widely recognised first.

“When faced with a shortage of oxygen, many species of bacteria can switch from using oxygen to using nitrates instead”, says Prof Richardson. “Nitrates can support their respiration, the equivalent of our breathing, and bacteria can get energy through processes called denitrification and ammonification. When they do this nitrous oxide is released into the environment”.

Municipal sewage treatment plants, landfill sites and marshy areas polluted with too much agricultural fertiliser are all places teeming with so many bacteria that there is a shortage of oxygen for all of them to survive using normal respiration alone. This means they need to use other respiratory strategies, which release nitrous oxide.

The researchers are using a combination of laboratory based studies, fieldwork and computer modelling to understand better the key environmental variables that make different micro-organisms release nitrous oxide.

“We are finding new biological routes for nitrous oxide emission that no-one ever suspected before. This could make a big impact on our environment”, says Prof Richardson. “Global warming affects everyone, and understanding the biology of nitrous oxide emissions will be an important step in mitigating their impact. We urgently need to start developing better strategies to improve management of these emissions in the agricultural and waste treatment sectors”.

***Ralph's Note - While Pseudo Science based politicians , have us barking up the wrong tree. True environmental hazards biologically and chemical are taking place now. The true crime being, that many of these issues can be fixed a whole lot easier. Than the one's some of the leaders are trying to sell us on now.***

**Public release date: 30-Mar-2008**

## **Green tea helps beat superbugs**

Green tea can help beat superbugs according to Egyptian scientists speaking today (Monday 31 March 2008) at the Society for General Microbiology's 162nd meeting being held this week at the Edinburgh International Conference Centre.

The pharmacy researchers have shown that drinking green tea helps the action of important antibiotics in their fight against resistant superbugs, making them up to three times more effective.

Green tea is a very common beverage in Egypt, and it is quite likely that patients will drink green tea while taking antibiotics. The medical researchers wanted to find out if green tea would interfere with the action of the antibiotics, have no effect, or increase the medicines' effects.

“We tested green tea in combination with antibiotics against 28 disease causing micro-

organisms belonging to two different classes,” says Dr Mervat Kassem from the Faculty of Pharmacy at Alexandria University in Egypt. “In every single case green tea enhanced the bacteria-killing activity of the antibiotics. **For example the killing effect of chloramphenicol was 99.99% better when taken with green tea than when taken on its own in some circumstances.**”

**Green tea also made 20% of drug-resistant bacteria susceptible to one of the cephalosporin antibiotics. These are important antibiotics that new drug resistant strains of bacteria have evolved to resist.**

The results surprised the researchers, showing that in almost every case and for all types of antibiotics tested, drinking green tea at the same time as taking the medicines seemed to reduce the bacteria’s drug resistance, even in superbug strains, and increase the action of the antibiotics. In some cases, even a low concentration of green tea was effective.

“Our results show that we should consider more seriously the natural products we consume in our everyday life,” says Dr Kassem. “In the future, we will be looking at other natural herb products such as marjoram and thyme to see whether they also contain active compounds which can help in the battle against drug resistant bacteria”.

**Public release date: 30-Mar-2008**

## **Most people believe smallpox not an extinct disease**

The vast majority of Scottish people interviewed in the streets of Edinburgh are unaware of one of the greatest achievements of medical science – the eradication of smallpox from the world over 40 years ago. **A poll sponsored by the Society for General Microbiology (SGM), in conjunction with the Edinburgh International Science Festival, has revealed that 87% of 200 individuals questioned did not know that the horrendous, killer disease is now extinct.**

But there’s good news too. The study, conducted by Scotinform, showed that many people are conscious of the wide range of activities of microorganisms. Three quarters of interviewees knew that microbes are used to make medicines, while 65% knew that bacteria can live inside active volcanoes and 54% knew that they can attack North Sea oil platforms. **About 44% were even aware of the role of microbes in chocolate making (where they promote the fermentation of the cacao beans).**

“Overall, these results are reassuring,” says Dr Bernard Dixon, who will present a report of the research during a session of the SGM’s Spring Meeting at the Edinburgh International Conference Centre on Monday 31 March. “However, there are a few worries. For example, while 80% of people knew that microbes were invisible forms of life such as bacteria and viruses, this did not apply at the lowest age range. **Nearly 40% of 16-24 year olds did not know what microbes are.**

“Particularly disquieting overall was the level of ignorance of smallpox eradication. This

disease killed 300-500 million victims during the 20th century. As recently as 1967, 15 million people contracted the appalling, disfiguring infection and 2 million of them died. However, thanks to a World Health Organization campaign, based on vaccination, smallpox was declared extinct in 1979.”

“Scientists are often reluctant to trumpet achievements of this sort, so they themselves may be partly to blame for the level of ignorance revealed by the survey in Edinburgh (which would almost certainly have produced the same result in London or elsewhere in Britain),” says Dr Dixon. “But smallpox elimination is not just a piece of history. When people today reject immunisation against other killer diseases such as measles, they are often unaware of the huge impact vaccines have made in protecting us not only against smallpox but also against diphtheria, poliomyelitis and other fearful conditions.”

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## **Are blood thinners post-op killers?**

New study shows that the use of powerful anticoagulants to prevent pulmonary embolism may actually lead to more deaths after surgery

Current US guidelines for the prescription of potent anticoagulants by surgeons who perform joint replacement operations could be doing patients more harm than good, according to Dr. Nigel Sharrock and his team from the Hospital for Special Surgery in New York. They argue for a revision of the American College of Chest Physicians’ guidelines, in light of their review showing that the use of powerful anticoagulants to prevent pulmonary embolism may actually lead to more deaths among patients who take these drugs. The paper<sup>1</sup> was published in the March issue of Springer’s journal *Clinical Orthopaedics and Related Research*.

Anticoagulants are routinely prescribed before and after total hip and knee replacement operations to reduce the risk of thrombosis, and death from pulmonary embolism in particular, as recommended by the Chest Physicians Consensus Statement. During the last decades, deaths from pulmonary embolism have fallen significantly due to a combination of advancements in anesthesia, better surgical techniques and care pre- and post-surgery, as well as a better understanding of how thrombosis develops as a result of surgery. In light of these developments, Sharrock and his team looked at whether the prescription of potent anticoagulants by surgeons who perform joint replacement operations is still warranted, as these drugs also have side effects.

The authors reviewed 20 studies among a total of just over 28,000 patients undergoing joint replacement surgery who were prescribed medication to reduce the risk of thrombosis. They compared the total number of deaths and cases of non-fatal pulmonary embolism between three frequently used prevention protocols worldwide. Patients in group A received potent anticoagulants such as low molecular weight heparin; those in group B received local spinal or epidural anesthesia, pneumatic compression and aspirin; patients in group C were prescribed slow-acting oral anticoagulants such as warfarin.

The lowest number of deaths occurred in patients in group B. Patients in groups A and C were more than twice as likely to have died as those in group B. There was no difference in the number of deaths between groups A and C. **Patients in group A were also at 60-70% greater risk of non-fatal pulmonary embolism than those in group B, indicating that pulmonary embolism occurs despite the use of powerful anticoagulants.**

Sharrock and colleagues conclude that “the American College of Chest Physicians should reconsider their guidelines to reflect the fact that pulmonary embolism occurs despite the use of potent anticoagulants and may, in fact, expose patients to increased mortality after surgery.” In their view, the current recommendations often result in physicians feeling compelled to prescribe these anticoagulants to avoid potential litigation when, in reality, these drugs could be doing more harm than good.

**Public Release: 31-Mar-2008**

## **Congress: Vytorin Makers Held Bad News**

### **Congress Releases Evidence Merck, Schering-Plough, Delayed Releasing Bad Vytorin Results**

TRENTON, N.J. (AP) -- A congressional committee, investigating whether the makers of cholesterol drug Vytorin withheld data that would hurt sales, released new evidence supporting such suspicions Monday.

The Senate Finance Committee said even the researcher who led a crucial study of the drug accused Vytorin makers Merck & Co. and partner Schering-Plough Corp. of withholding negative results to boost sales.

A letter from the committee's ranking Republican, Sen. Chuck Grassley of Iowa, **states that delaying the results affected medical decisions and put financial burdens on patients and the federal government, which has paid hundreds of millions of dollars for Vytorin since the study ended nearly 2 years ago.**

Spokespeople for both drug makers said the letter is just one in a series from Grassley's committee and that their companies are cooperating fully.

The letter comes as shares of Merck and Schering-Plough tanked after top cardiologists urged doctors to go back to older, well-proven treatments for high cholesterol. The doctors spoke at a major heart specialists' conference after hearing full results Sunday of the Vytorin study, called ENHANCE, that showed it worked no better than an inexpensive generic.

"This is the last thing that Schering and Merck need, especially in a political year," said

analyst Steve Brozak of WBB Securities Ltd. "This can become brutal."

**For months, the Senate Finance Committee and the House Energy and Commerce Committee have been investigating how Merck and Schering-Plough handled data from a study comparing Vytorin with Merck's older cholesterol drug, Zocor. Vytorin, which costs \$100 a month or more, combines Zocor -- available as a generic for about one-third as much -- and Schering-Plough's cholesterol drug Zetia.**

Between the two committees, congressional staffers have been probing everything from who knew what when to whether executives of Merck and Schering-Plough sold large amounts of stock based on insider knowledge.

The two New Jersey companies released partial results of the study on Jan. 14 -- under pressure from the congressional investigators.

On Sunday, the full results showed Vytorin was no better than Zocor alone at limiting plaque buildup in arteries, even though it sharply lowered bad cholesterol and blood fats called triglycerides.

"I am troubled to learn that after careful analysis of the ENHANCE results, medical experts are now calling Vytorin the cholesterol fighter of last resort," Grassley wrote Monday in a letter to the chief executives of Merck and Schering-Plough.

**The letter cites testy e-mails to Schering-Plough executives from ENHANCE's lead researcher, Dr. John Kastelein. In one last July, he states that if it is true the study results wouldn't be presented at an upcoming medical conference, "our collaboration is over... this starts smelling like extending the publication for no other (than) political reasons."**

**The next day, Grassley stated, Kastelein wrote, "you will be seen as a company that tries to hide something and I will be perceived as being in bed with you!"**

Merck spokeswoman Mary Elizabeth Blake said those excerpts "do not reflect the legitimate scientific discussion that was going on between Dr. Kastelein and the company."

She said the companies' executives did not know the ENHANCE study results until the beginning of this year, shortly before they released the partial results in a press release, and that difficulties in interpreting the complex data caused the delay.

Schering-Plough spokeswoman Rosemarie Yancosek said her company did not deliberately delay the results to boost sales.

**The House committee has cited evidence from an Internet site where pharmaceutical sales reps posted comments in March 2007 indicating they knew "the study is a bust."**

**The two drug makers once heavily advertised Vytorin and Zetia, which brought their joint venture \$5.1 billion in 2007 sales. Since then, their stocks have dipped to 12-year lows, and they've been hit with numerous lawsuits.**

**Grassley wrote that the companies budgeted at least \$3.5 million to entertain doctors to persuade them to prescribe Vytorin.** He demanded more information about how much they spent marketing Vytorin after the study ended.

**Grassley also wrote Monday to the head of the American College of Cardiology, stating he is concerned about "the appearance of influence" because Merck has funded the group's conference booths, expo fees and other items totaling more than \$568,000 already this year. After the partial results were released Jan. 14, the specialists' group said patients should not panic and should not stop taking Vytorin based just on that study.**

Analyst Brozak said normally the companies would be looking like takeover candidates, but "I do not know what company, at what price, would want to acquire these companies, given how little they have in their pipelines ... and given how much scrutiny they will receive."

On Monday, Merck's shares fell \$6.56, or 14.7 percent, to \$37.95 and Schering-Plough's dropped \$5.06, or 26 percent, to \$14.41.

Standard & Poor's Ratings Services put long-term ratings for Schering-Plough on credit watch, with negative implications, but left Merck's ratings unchanged because it has a more diverse line of medicines.

Some analysts downgraded their ratings for Schering-Plough. However, Natixis Bleichroeder Inc.'s Jon LeCroy wrote: "we think investors are overreacting and note that Schering-Plough still offers tremendous value."

Merck, based in Whitehouse Station, N.J., is the world's No. 8 drug maker; much-smaller Schering-Plough is based in Kenilworth, N.J.

**Ralph's Note- Remember some Doctors, and medical professionals are truly hero's. They stood up for something, against incredible pressure. Even though some doctors were duped, it is their responsibility to inform their patients of better options.**

**The drug companies responsible for this cover up, should loose their insurance protection. In addition to becoming criminally liable to all those who became injured on a drug. That had no therapeutic value.**

