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Human Technology Research Synopsis

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Public release date: 13-Nov-2008

Many doctors plan to quit or cut back: survey

WASHINGTON (Reuters) – Primary care doctors in the United States feel overworked and nearly half plan to either cut back on how many patients they see or quit medicine entirely, according to a survey released on Tuesday.

And 60 percent of 12,000 general practice physicians found they would not recommend medicine as a career.

"The whole thing has spun out of control. I plan to retire early even though I still love seeing patients. The process has just become too burdensome," the Physicians' Foundation, which conducted the survey, quoted one of the doctors as saying.

The survey adds to building evidence that not enough internal medicine or family practice doctors are trained or practicing in the United States, although there are plenty of specialist physicians.

Health care reform is near the top of the list of priorities for both Congress and president-elect Barack Obama, and doctor's groups are lobbying for action to reduce their workload and hold the line on payments for treating Medicare, Medicaid and other patients with federal or state health insurance.

The Physicians' Foundation, founded in 2003 as part of a settlement in an anti-racketeering lawsuit among physicians, medical societies, and insurer Aetna, Inc., mailed surveys to 270,000 primary care doctors and 50,000 practicing specialists.

The 12,000 answers are considered representative of doctors as a whole, the group said, with a margin of error of about 1 percent. **It found that 78 percent of those who answered believe there is a shortage of primary care doctors.**

More than 90 percent said the time they devote to non-clinical paperwork has increased in the last three years and 63 percent said this has caused them to spend less time with each patient.

Eleven percent said they plan to retire and 13 percent said they plan to seek a job that removes them from active patient care. Twenty percent said they will cut back on patients seen and 10 percent plan to move to part-time work.

Seventy six percent of physicians said they are working at "full capacity" or "overextended and overworked".

Many of the health plans proposed by members of Congress, insurers and employers's groups, as well as Obama's, suggest that electronic medical records would go a long way to saving time and reducing costs.

Ralph's Note - The incredible responsibility they have mixed with a huge workload, is breaking these people. With little to read up on new breakthroughs, an just general information as a whole. It is probably the sing le greatest reason for what I call Assembly Line Medicine. Imagine if your doctor had 20% more time to read and research better treatments for you. Instead of trying to figure out how to get medicare to pay your bills. Bring back the age of House calls.

Public release date: 13-Nov-2008

Obese kids' artery plaque similar to middle-aged adults

Study highlights:

- The plaque buildup in the neck arteries of obese children or those with high cholesterol is similar to levels in middle-aged adults.
- Using ultrasound images, researchers equated the "vascular age" to be 45 years old in these children.
- Obese children who have high triglycerides are the most likely to have prematurely aging arteries; these children should be treated as high risk for cardiovascular disease, researchers concluded.

NEW ORLEANS, La., Nov. 11, 2008 – The neck arteries of obese children and teens look more like those of 45-year-olds, according to research presented at the American Heart Association's Scientific Sessions 2008.

"There's a saying that 'you're as old as your arteries,' meaning that the state of your arteries is more important than your actual age in the evolution of heart disease and stroke," said Geetha Raghuvver, M.D., M.P.H., associate professor of pediatrics at the University of Missouri Kansas City School of Medicine and cardiologist at Children's Mercy Hospital. "We found that the state of the arteries in these children is more typical of a 45-year-old than of someone their own age."

Researchers used ultrasound to measure the thickness of the inner walls of the neck (carotid) arteries that supply blood to the brain. Increasing carotid artery intima-media thickness (CIMT) indicates the fatty buildup of plaque within arteries feeding the heart muscle and the brain, which can lead to heart attack or stroke.

Investigators calculated CIMT in 34 boys and 36 girls who were "at-risk," (average age 13, 89 percent white) and found:

- These children had abnormal levels of one or more types of cholesterol – elevated levels of low-density lipoprotein (LDL), which is known as "bad cholesterol;" low levels of high-density lipoprotein (HDL), which is the "good cholesterol;" or high triglyceride levels.
- Forty (57 percent) had a body mass index (BMI, a calculation of weight for height) above the 95th percentile.

Their average CIMT was 0.45 millimeters (mm), with a maximum of 0.75 mm.

The children's "vascular age" — the age at which the level of thickening would be normal for their gender and race — was about 30 years older than their actual age, Raghuvver said.

The children were deemed at high risk for future heart disease because of obesity, abnormal cholesterol, and/or a family history of early heart disease.

On average, these children had:

- total cholesterol levels of 223.4 milligrams per deciliter (mg/dL) (less than 170 is considered acceptable by American Heart Association recommendations);
- LDL cholesterol levels of 149.8 mg/dL (less than 110 is considered acceptable); and
- triglycerides levels of 151.9 mg/dL (below 150 is considered acceptable).

Researchers found that having a higher BMI and higher systolic blood pressure had the most impact on CIMT.

Of the various risk factors, the children with triglycerides over 100 mg/dL were most likely to have an advanced vascular age. Thirty-eight children with high triglycerides had a CIMT above the 25th percentile for 45-year-olds, while only five in the group were below the 25th percentile. Children with lower triglycerides were evenly divided between those who scored below (13) or above (14) the 25th percentile on the charts for 45-year-olds.

“Vascular age was advanced the furthest in the children with obesity and high triglyceride levels, so the combination of obesity and high triglycerides should be a red flag to the doctor that a child is at high risk of heart disease,” Raghuvver said.

Further studies are needed to determine whether artery build-up will decrease if children lose weight, exercise, or are treated for abnormal lipids. Some studies have shown that CIMT can be reduced when children at extremely high risk are treated with cholesterol-lowering statin medications, and that exercise can improve blood vessel function in children with a high BMI.

“I’m optimistic that something can be done,” Raghuvver said. “In children, the buildup in the vessels is not hardened and calcified. We can improve the vessel walls and blood flow in adults through treatment, and I’m sure we can help children even more.”

Other risk factors for high CIMT in children are high blood pressure, exposure to secondhand smoke and insulin resistance – which is frequently seen in obese children.

Co-authors are: Joseph Le, medical student; Menees Spencer, medical student; David McCrary, M.D.; Danna Zhang, M.S.; and Chen Jie, Ph.D. Individual author disclosures are available on the abstract. The Sarah Morrison Medical Student Research Grant from the University of Missouri, Kansas City, funded the research.

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Evolution's new wrinkle: Proteins with cruise control provide new perspective

A team of Princeton University scientists has discovered that chains of proteins found in most living organisms act like adaptive machines, **possessing the ability to control their own evolution.**

The research, which appears to **offer evidence of a hidden mechanism guiding the way biological organisms respond to the forces of natural selection,** provides a new perspective on evolution, the scientists said.

The researchers -- Raj Chakrabarti, Herschel Rabitz, Stacey Springs and George McLendon -- made the discovery while carrying out experiments on proteins constituting

the electron transport chain (ETC), a biochemical network essential for metabolism. A mathematical analysis of the experiments showed that the proteins themselves acted to correct any imbalance imposed on them through artificial mutations and restored the chain to working order.

"The discovery answers an age-old question that has puzzled biologists since the time of Darwin: How can organisms be so exquisitely complex, if evolution is completely random, operating like a 'blind watchmaker'?" said Chakrabarti, an associate research scholar in the Department of Chemistry at Princeton. "Our new theory extends Darwin's model, demonstrating how organisms can subtly direct aspects of their own evolution to create order out of randomness."

The work also confirms an idea first floated in an 1858 essay by Alfred Wallace, who along with Charles Darwin co-discovered the theory of evolution. Wallace had suspected that certain systems undergoing natural selection can adjust their evolutionary course in a manner "exactly like that of the centrifugal governor of the steam engine, which checks and corrects any irregularities almost before they become evident." In Wallace's time, the steam engine operating with a centrifugal governor was one of the only examples of what is now referred to as feedback control. Examples abound, however, in modern technology, including cruise control in autos and thermostats in homes and offices.

The research, published in a recent edition of *Physical Review Letters*, provides corroborating data, Rabitz said, for Wallace's idea. "What we have found is that certain kinds of biological structures exist that are able to steer the process of evolution toward improved fitness," said Rabitz, the Charles Phelps Smyth '16 Professor of Chemistry. "The data just jumps off the page and implies we all have this wonderful piece of machinery inside that's responding optimally to evolutionary pressure."

The authors sought to identify the underlying cause for this self-correcting behavior in the observed protein chains. Standard evolutionary theory offered no clues. Applying the concepts of control theory, a body of knowledge that deals with the behavior of dynamical systems, the researchers concluded that this self-correcting behavior could only be possible if, during the early stages of evolution, the proteins had developed a self-regulating mechanism, analogous to a car's cruise control or a home's thermostat, allowing them to fine-tune and control their subsequent evolution. The scientists are working on formulating a new general theory based on this finding they are calling "evolutionary control."

The work is likely to provoke a considerable amount of thinking, according to Charles Smith, a historian of science at Western Kentucky University. "Systems thinking in evolutionary studies perhaps began with Alfred Wallace's likening of the action of natural selection to the governor on a steam engine -- that is, as a mechanism for removing the unfit and thereby keeping populations 'up to snuff' as environmental actors," Smith said. "Wallace never really came to grips with the positive feedback part of the cycle, however, and it is instructive that through optimal control theory Chakrabarti et al. can now suggest a coupling of causalities at the molecular level that extends Wallace's

systems-oriented approach to this arena."

Evolution, the central theory of modern biology, is regarded as a gradual change in the genetic makeup of a population over time. It is a continuing process of change, forced by what Wallace and Darwin, his more famous colleague, called "natural selection." In this process, species evolve because of random mutations and selection by environmental stresses. Unlike Darwin, Wallace conjectured that species themselves may develop the capacity to respond optimally to evolutionary stresses. Until this work, evidence for the conjecture was lacking.

The experiments, conducted in Princeton's Frick Laboratory, focused on a complex of proteins located in the mitochondria, the powerhouses of the cell. A chain of proteins, forming a type of bucket brigade, ferries high-energy electrons across the mitochondrial membrane. This metabolic process creates ATP, the energy currency of life.

Various researchers working over the past decade, including some at Princeton like George McClendon, now at Duke University, and Stacey Springs, now at the Massachusetts Institute of Technology, fleshed out the workings of these proteins, finding that they were often turned on to the "maximum" position, operating at full tilt, or at the lowest possible energy level.

Chakrabarti and Rabitz analyzed these observations of the proteins' behavior from a mathematical standpoint, concluding that it would be statistically impossible for this self-correcting behavior to be random, and demonstrating that the observed result is precisely that predicted by the equations of control theory. By operating only at extremes, referred to in control theory as "bang-bang extremization," the proteins were exhibiting behavior consistent with a system managing itself optimally under evolution.

"In this paper, we present what is ostensibly the first quantitative experimental evidence, since Wallace's original proposal, that nature employs evolutionary control strategies to maximize the fitness of biological networks," Chakrabarti said. "Control theory offers a direct explanation for an otherwise perplexing observation and indicates that evolution is operating according to principles that every engineer knows."

The scientists do not know how the cellular machinery guiding this process may have originated, but they emphatically said it does not buttress the case for intelligent design, a controversial notion that posits the existence of a creator responsible for complexity in nature.

Chakrabarti said that one of the aims of modern evolutionary theory is to identify principles of self-organization that can accelerate the generation of complex biological structures. "Such principles are fully consistent with the principles of natural selection. Biological change is always driven by random mutation and selection, but at certain pivotal junctures in evolutionary history, **such random processes can create structures capable of steering subsequent evolution toward greater sophistication and complexity.**"

The researchers are continuing their analysis, looking for parallel situations in other biological systems.

The research was funded by the National Science Foundation.

Ralph's Note - Evolution without the need to Adapt to external stressors, hmm. Or do we Evolve in anticipation of future unknown needs. In either case it raises some interesting questions.

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Mandatory HPV Vaccination Is Unwarranted and Unwise

Washington, D.C. – November 12, 2008 – The HPV vaccine, sold as Gardasil in the U.S., is intended to prevent four strains of the human papillomavirus, the most common sexually transmitted infection in the world. The vaccine also prevents against cervical cancer. While the vaccine represents a significant public health advance, a new article in the *Journal of Law, Medicine & Ethics* suggests that it is premature for states to currently mandate the HPV vaccine as a condition for school attendance.

Gail Javitt, J.D., M.P.H., Deena Berkowitz, M.D., M.P.H., and Lawrence O. Gostin, J.D., LL.D., review the scientific evidence supporting Gardasil's approval and the legislative actions in the states that followed and raise several concerns about state mandates for HPV vaccination.

To begin with, they assert that Gardasil is relatively new and long-term safety and effectiveness in the general population is unknown. Outcomes of those voluntarily vaccinated should be followed for several years before mandates are imposed.

Additionally, they argue that the HPV vaccine does not represent a public health necessity of the type that has justified previous vaccine mandates, so Constitutional concerns are raised. It is possible that state mandates could lead to a public backlash that will undermine both HPV vaccination efforts and existing vaccination programs.

Finally, they note that the economic consequences of mandating HPV are significant and could have a negative impact on financial support for other vaccines as well as other public health programs. Such consequences should be evaluated before the vaccine is mandated.

“HPV will not be the last disease that state legislatures will attempt to prevent

through mandatory vaccination," the authors conclude. "This is a good time to reevaluate the criteria that should be used to mandate vaccination of children as a condition of school attendance."

Public release date: 13-Nov-2008

Plastic surgeons warn of malnutrition in body contouring patients

ARLINGTON HEIGHTS, Ill. – Identifying malnutrition before surgery in massive weight loss patients seeking body contouring will significantly decrease surgical complications, accelerate wound healing, improve scar quality and boost patient energy levels, according to a study in the December issue of *Plastic and Reconstructive Surgery*®, the official medical journal of the American Society of Plastic Surgeons (ASPS). Optimizing nutrition with the addition of supplements, such as powder drinks and multi-vitamin tablets formulated for massive weight loss patients, is vital to successful body contouring surgery, the study reveals.

"Body contouring procedures for massive weight loss patients are major operations with large incisions in many areas that demand a lot of the body during the healing process," said ASPS Member Surgeon and study co-author Dennis Hurwitz, MD. "By carefully monitoring nutritional deficiencies preoperatively and supplementing the patient with the necessary nutrients, minerals and vitamins, I have seen a significant decrease in complications and improved postoperative healing. In my practice, I won't do body contouring procedures on this patient population without a preoperative regimen of nutritional supplements."

The study was performed in two parts; First, medical literature regarding nutrition's effect on healing from the 1940s to the present was reviewed. The authors then compared healing and wound problems in 75 of their massive weight loss body contouring patients from 2001 to 2005 who did not receive supplementation, with 37 patients from 2006 to present, who participated in a uniquely designed nutritional supplement program prior to surgery. The study also noted the role of each nutrient in wound healing and immune response.

The study found that complications and wound problems occurred in 66 percent of the 75 patients who did not receive supplementation before 2006. In the 37 patients on the nutritional supplement regimen after 2006, major complication rates were reduced to 19 percent. The study found specifically that improving nutritional deficiencies in massive weight loss patients improved the healing process, wound tension, and scar quality, in addition to increasing patients' energy levels.

Because of reduced calorie intake for massive weight loss patients, they are highly susceptible to malnutrition, the study observed. At one year after bariatric surgery, most

patients' food intake remains at about 1,000 calories per day, not even close to meeting standard recommendations regarding calories and protein intake. The study also noted the role various nutrients play in wound healing: Protein, vitamins A, B complex, C, arginine, glutamine, iron, zinc and selenium promote wound healing, collagen production and immune response; Vitamin B complex has also been associated with reducing the risk of deep vein thrombosis.

According to the ASPS, nearly 67,000 body contouring procedures after massive weight loss were performed in 2007.

Public release date: 13-Nov-2008

Soluble fiber, antispasmodics and peppermint oil should be used to treat IBS

Effect of fiber, antispasmodics and peppermint oil in irritable bowel syndrome:
Systematic review and meta-analysis

Fibre, antispasmodics and peppermint oil are all effective therapies for irritable bowel syndrome (IBS) and should become first-line treatments, according to a study on bmj.com today.

National guidelines on the management of IBS should be updated in light of this evidence, say the authors.

IBS is characterised by abdominal pain and an irregular bowel habit, and affects between 5% and 20% of the population. Because the exact cause of IBS is unknown it is difficult to treat. A wide range of therapies are currently used including fibre supplements, probiotics, antidepressants, hypnotherapy and laxatives.

Because of a lack of suitable drug treatments, international and national guidelines promote the use of complementary and alternative treatments, including the recently published National Institute of Health and Clinical Excellence (NICE) guidelines on the management of IBS.

Fibre, antispasmodics and peppermint oil are used to treat IBS, but evidence of their effectiveness is unclear because of conflicting conclusions and errors in previous studies.

In an attempt to resolve this uncertainty, Dr Alex Ford and colleagues performed a systematic review and meta-analysis of randomised trials comparing fibre, antispasmodics and peppermint oil with placebo or no treatment in more than 2500 adult patients with IBS..

Fibre, antispasmodics and peppermint oil were all found to be effective treatments for IBS. The number needed to treat to prevent IBS symptoms in one patient was 11 for fibre, 5 for antispasmodics, and 2.5 for peppermint oil. None of the treatments had serious adverse effects.

The researchers analysed 12 studies which compared fibre with placebo or no treatment involving 591 patients. Interestingly, insoluble fibre such as bran was not beneficial, only isphaghula husk (soluble fibre) significantly reduced symptoms.

They identified 22 studies comparing various antispasmodics with placebo in 1778 patients. Hyoscine was the most successful at preventing symptoms of IBS. The authors suggest that hyoscine, which is extracted from the cork wood tree, be used as the first-line antispasmodic therapy in primary care.

Peppermint oil seemed to be the most effective treatment of the three, based on four trials involving 392 patients.

These treatments have been overlooked because of the introduction of newer more expensive drugs which were withdrawn due to lack of efficacy and safety concerns, say the authors. All three treatments have been shown to be potentially effective therapies for IBS and current national and international guidelines need to be revised to include this new evidence, they add.

The results of this study should "reawaken interest in the pharmacotherapy of irritable bowel syndrome and stimulate further research", says Professor Roger Jones from King's College London.

However, he cautions that this new evidence must not detract from the need to make a holistic diagnosis and integrated approach to the treatment of IBS which takes account of the physical, psychological, and social factors involved.

Public release date: 13-Nov-2008

Arsenic linked to cardiovascular disease at EPA-regulated drinking water standards

University of Pittsburgh mouse study published in Journal of Clinical Investigations
PITTSBURGH, Nov. 13 – When mice are exposed to arsenic at federally-approved levels for drinking water, pores in liver blood vessels close, potentially leading to cardiovascular disease, say University of Pittsburgh researchers in the Dec. 1 issue of the Journal of Clinical Investigation, available online Nov. 13. The study, while preliminary, also reveals how an enzyme linked to hypertension and atherosclerosis alters cells, and may call into question current Environmental Protection Agency standards that are based solely on risks for cancer.

In the study, Aaron Barchowsky, Ph.D., associate professor of environmental and occupational health at the University of Pittsburgh Graduate School of Public Health, and his research team looked at specialized cells in the liver called sinusoidal endothelial cells, which are tasked with removing wastes from blood and enabling nutrients to regulate metabolism. After exposing mice to 10 to 100 parts per billion (ppb) of arsenic

over a two-week period, the cells were less able to remove damaged proteins from the blood and lost their characteristic pores or "windows," severely compromising the cells' ability to effectively exchange nutrients and waste. Dr. Barchowsky notes that despite their small size, mice are usually less sensitive to the effects of arsenic than people

The current EPA standard for arsenic in public water systems is 10 ppb, reduced from 50 ppb in 2006. The standard applies only to drinking water sources that serve more than 20 people.

"These results are important since this type of cellular dysfunction, over time, can impair the body's ability to clear fats and waste proteins that build up in blood vessels and can lead to cardiovascular diseases such as hypertension and atherosclerosis," said Dr. Barchowsky

According to Dr. Barchowsky, arsenic increased the activity of an enzyme called NADPH oxidase and the levels of oxidants it produces, compromising sinusoidal cell functions. Mice that lacked the enzyme did not have changes in liver blood vessels when exposed to arsenic and their cells were able to continue to function effectively.

"Our findings raise some concerns about whether current EPA-developed standards can effectively protect against cardiovascular risks posed by arsenic in drinking water," said Dr. Barchowsky. "We are especially concerned about water from individual wells in small, rural and semi-rural communities that are exempt from the EPA requirement and often contain levels of arsenic that exceed the EPA limit.

Next phases of the research will focus on further understanding how arsenic increases the production of oxidants by NADPH oxidase and determining effective preventative measures to lessen the impact of arsenic and other environmental exposures on the function of the endothelial cells. Additional studies will investigate the relationship between arsenic's effects on liver blood vessels and metabolism and disease-related changes in other blood vessels in the body.

Arsenic is a naturally occurring mineral primarily found in groundwater. Drinking high levels of arsenic over many years has been linked to increased risks for lung, bladder and skin cancers, as well as heart disease, diabetes and neurological damage.

Public release date: 16-Nov-2008

Calcium may only protect against colorectal cancer in presence of magnesium

High magnesium intake has been associated with low risk of colorectal cancer. Americans have similar average magnesium intake as East Asian populations. If that were all that were involved, observers might expect both groups to have similar risk for colorectal cancer.

However, the United States has seen a much higher colorectal cancer incidence rate than East Asian populations. Furthermore, when East Asians immigrated to the United States, their incidence rates for colorectal cancer increased. This led researchers at Vanderbilt University to suspect there was something else at work.

Calcium supplementation has been shown to inhibit colorectal carcinogenesis although high calcium may simultaneously be preventing the body from absorbing magnesium. United States patients have a higher calcium intake and higher colorectal cancer incidence. "If calcium levels were involved alone, you'd expect the opposite direction. There may be something about these two factors combined – the ratio of one to the other – that might be at play", said Qi Dai, M.D., Ph.D., assistant professor of medicine at Vanderbilt University.

Dai and colleagues examined this hypothesis in a large clinical trial and found indeed that supplementation of calcium only reduced the risk of adenoma recurrence if the ratio of calcium to magnesium was low and remained low during treatment. "The risk of colorectal cancer adenoma recurrence was reduced by 32 percent among those with baseline calcium to magnesium ratio below the median in comparison to no reduction for those above the median," said Qi.

The implications for prevention of adenoma recurrence or reduced risk of primary colorectal cancer is that designing a personalized diet/supplementation regimen that takes the ratio of both nutrients into account may be better than supplementing with one or the other alone.

About one in eighteen individuals will develop colorectal cancer in their lifetime and 40 percent will die within five years of diagnosis, mainly due to diagnosis at a late stage. The understanding of how dietary factors affect colorectal cancer may lead to the prevention of cancer recurrence and possibly prevention of the initial cancer.

Public release date: 17-Nov-2008

Study helps clarify role of vitamin D in cancer therapy

A colon cancer cell isn't a lost cause. Vitamin D can tame the rogue cell by adjusting everything from its gene expression to its cytoskeleton. In the Nov. 17 issue of the *Journal of Cell Biology*, Ordóñez-Morán et al. show that one pathway governs the vitamin's diverse effects. The results help clarify the actions of a molecule that is undergoing clinical trials as a cancer therapy.

Vitamin D stymies colon cancer cells in two ways. It switches on genes such as the one that encodes E-cadherin, a component of the adherens junctions that anchor cells in epithelial layers. The vitamin also induces effects on the cytoskeleton that are required for gene regulation and short-circuiting the Wnt/b-catenin pathway, which is overactive in most colon tumors. The net result is to curb division and prod colon cancer cells to differentiate into epithelial cells that settle down instead of spreading.

To delve into the mechanism, the team dosed colon cancer cells with calcitriol, the metabolically active version of vitamin D. Calcitriol triggered a surge of calcium into the cells and the subsequent switching on of RhoA–RhoGTPases, which have been implicated in the cytoskeletal changes induced by vitamin D. The activated RhoA in turn switched on one of its targets, the rho-associated coiled kinase (ROCK), which then roused two other kinases. Each step in this nongenomic pathway was necessary to spur the genomic responses, the researchers showed. The team also nailed down the contribution of the vitamin D receptor (VDR). The receptor was crucial at the beginning of the pathway, where it permitted the calcium influx, and at the end, where it activated and repressed genes.

The study is the first to show that vitamin D's genomic and nongenomic effects integrate to regulate cell physiology. One question the researchers now want to pursue is whether VDR from different locations—the nucleus, the cytosol, and possibly the cell membrane—has different functions in the pathway.

Public release date: 17-Nov-2008

What cures you may also ail you: Antibiotics, your gut and you

We are always being told by marketers of healthy yogurts that the human gut contains a bustling community of different bacteria, both good and bad, and that this balance is vital to keeping you healthy. But if you target the disease-causing bacteria with medicine, what might be the collateral damage to their health-associated cousins that call the human body home?

A new study by Les Dethlefsen et al, to be published this week in the online open-access journal PLoS Biology, looks into the changes that happen in the human gut when it is exposed to the widely used antibiotic, ciprofloxacin. Ciprofloxacin is prescribed for a number of conditions, including common afflictions such as urinary tract infections. It was previously believed to cause only modest harm to the abundant beneficial bacteria of the human body.

To investigate ciprofloxacin's effect on health-associated bacteria a team of researchers, led by Dr. David Relman of Stanford University, catalogued types of bacteria present in the faeces of volunteers who were undergoing a course of treatment of ciprofloxacin. The DNA-analysis technique, massively-parallel pyrosequencing, was central to their approach, which is outlined in a companion paper scheduled for publication in PLoS Genetics on Friday the 21st of November. With this technique, the researchers examined the diversity and abundance of bacteria present in human faeces, identifying over 5,600 different bacterial species and strains. The dramatically increased detection power of this approach allowed the team to track carefully the changes in the gut's bacterial community both during and after the course of treatment.

The study found that while the patients were undergoing treatment the overall abundance of approximately 30% of the species and strains was significantly affected. The effects varied greatly between individuals, with two of the subjects showing a strong reduction in diversity. The effects didn't stop there. Once the course of treatment had been halted, it took up to four weeks for most strains of gut bacteria to return to their pre-treatment levels. Even six months later, some types of bacteria had not managed to return to pre-treatment abundance levels. During this time of population upheaval none of the patients in the study reported signs of gut-related problems.

The bacteria present in the human gut are responsible for various aspects of host nutrition, metabolism and immune responses. This study reveals aspects of resiliency in the indigenous microbiota when subjected to perturbation, but underlines the concern that antibiotic treatment, especially when prolonged or repeated, may have long-lasting effects on overall wellbeing that could go un-noticed.

Public release date: 17-Nov-2008

Indigo ointment may help treat patients with psoriasis

An ointment made from indigo naturalis, a dark blue plant-based powder used in traditional Chinese medicine, appears effective in treating plaque-type psoriasis, according to a report in the November issue of Archives of Dermatology, one of the JAMA/Archives journals.

Psoriasis is a chronic skin disease for which no cure exists, only therapies that bring it into remission, according to background information in the article. "Traditional Chinese medicine is one of the most frequently chosen alternative therapies in China and Taiwan, and psoriasis has been treated for centuries with topical and oral herbal preparations," the authors write. "Indigo naturalis is one of the Chinese herbal remedies that has been reported to exhibit potential antipsoriatic efficacy. However, long-term systemic use has been occasionally associated with irritation of the gastrointestinal tract and adverse hepatic [liver] effects."

Yin-Ku Lin, M.D., of Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, and colleagues conducted a randomized trial of an ointment containing indigo naturalis in 42 patients with treatment-resistant psoriasis. Participants enrolled in the study between May 2004 and April 2005 and applied the indigo naturalis ointment to a psoriatic plaque on one side of their body (usually on the arm, elbow, leg or knee) and then a non-medicated ointment to a parallel plaque on the other side of their body. The researchers assessed and photographed patients' skin plaques at the beginning of the study and again after two, four, six, eight, 10 and 12 weeks.

After 12 weeks of treatment, the plaques treated with indigo naturalis ointment showed significant improvement in scaling, erythema (redness) and induration (hardening) when compared with the plaques treated with non-medicated ointment. "Weighting the sum of scaling, erythema and induration scores by the lesion area and comparing between the start and end of the study, **the indigo naturalis ointment–treated lesions showed an 81 percent improvement**, whereas the vehicle [non-medicated] ointment–treated lesions showed a 26 percent improvement," the authors write.

Of the 34 patients who completed the study, none experienced worsening psoriasis in the areas treated with indigo naturalis, while the treated plaques were completely or nearly completely cleared for 25 of them (74 percent). None experienced serious adverse effects. Four patients reported itching after applying the indigo naturalis ointment, but only for a couple of days at the start of treatment.

"In conclusion, we present a randomized controlled trial showing the use of topical indigo naturalis ointment for the treatment of chronic plaque psoriasis to be both safe and effective," the authors write. "Future research for a more potent extraction from this crude herb that can provide better absorption and convenience would help improve patient compliance with the treatment regimen. However, much more research will be necessary to clarify the pharmacology of indigo naturalis."

Public release date: 18-Nov-2008

Broccoli may lower lung cancer risk in smokers

WASHINGTON, D.C. - The cancer preventive properties of broccoli and other cruciferous vegetables appear to work specifically in smokers, according to data presented at the American Association for Cancer Research's Seventh Annual International Conference on Frontiers in Cancer Prevention Research.

Cruciferous vegetables have been shown to be protective in numerous studies, but this is the first comprehensive study that showed a protective benefit in smokers, specifically in former smokers, according to lead author Li Tang, Ph.D., a post-doctoral fellow at Roswell Park Cancer Institute.

"Broccoli is not a therapeutic drug, but for smokers who believe they cannot quit nor do anything about their risk, this is something positive," Tang said. "People who quit smoking will definitely benefit more from intake of cruciferous vegetables."

Li and colleagues conducted a hospital-based, case-controlled study with lung cancer cases and controls matched on smoking status. The study included all commonly consumed cruciferous vegetables, and also considered raw versus cooked form. Researchers performed statistical calculations to take into account smoking status, duration and intensity.

Among smokers, the protective effect of cruciferous vegetable intake ranged from a 20 percent reduction in risk to a 55 percent reduction in risk depending on the type of vegetable consumed and the duration and intensity of smoking.

For example, among current smokers, only the consumption of raw cruciferous vegetables was associated with risk reduction of lung cancer. No significant results were found for consumption of vegetables in general and fruits.

Researchers further divided their findings by four subtypes of lung cancer and found the strongest risk reduction among patients with squamous or small-cell carcinoma. These two subtypes are more strongly associated with heavy smoking.

"These findings are not strong enough to make a public health recommendation yet," said Li. "However, strong biological evidence supports this observation. These findings, along with others, indicate cruciferous vegetables may play a more important role in cancer prevention among people exposed to cigarette-smoking. "

Public release date: 18-Nov-2008

Exercise increases brain growth factor and receptors, prevents stem cell

drop in middle age

BETHESDA, Md. (Nov. 18, 2008) - A new study confirms that exercise can reverse the age-related decline in the production of neural stem cells in the hippocampus of the mouse brain, and suggests that this happens because exercise restores a brain chemical which promotes the production and maturation of new stem cells.

Neural stem cells and progenitor cells differentiate into a variety of mature nerve cells which have different functions, a process called neurogenesis. There is evidence that when fewer new stem or progenitor cells are produced in the hippocampus, it can result in impairment of the learning and memory functions. The hippocampus plays an important role in memory and learning.

The study, "Exercise enhances the proliferation of neural stem cells and neurite growth and survival of neuronal progenitor cells in dentate gyrus of middle-aged mice," was carried out by Chih-Wei Wu, Ya-Ting Chang, Lung Yu, Hsiun-ing Chen, Chauying J. Jen, Shih-Ying Wu, Chen-Peng Lo, Yu-Min Kuo, all of the National Cheng Kung University Medical College in Taiwan. The study appears in the November issue of the *Journal of Applied Physiology*, published by The American Physiological Society.

Rise in corticosterone or fall in nerve growth factor?

The researchers built on earlier studies that found that the production of stem cells in the area of the hippocampus known as the dentate gyrus drops off dramatically by the time mice are middle age and that exercise can slow that trend. In the current study, the researchers wanted to track these changes in mice over time, and find out why they happen.

One hypothesis the researchers investigated is that the age-related decline in neurogenesis is tied to a rise in corticosterone in middle age. Elevation of corticosterone has been associated with a drop in the production of new stem cells in the hippocampus.

The second hypothesis is that nerve growth factors -- which encourage new neural cell growth but which decrease with age -- account for the drop in neurogenesis. Specifically, the study looked at whether a decrease in brain-derived neurotrophic growth factor leads to a decline in new neural stem cells.

Variables studied

The researchers trained young (3 months), adult (7 months), early middle-aged (9 months), middle-aged (13 months) and old (24 months) mice to run a treadmill for up to one hour a day.

The study tracked neurogenesis, age, exercise, serum corticosterone levels and brain-derived neurotrophic factor (BDNF) and its receptor TrkB levels in the hippocampus. The researchers focused on middle age as a critical stage for the decline of neurogenesis

in the mice.

As expected, the study found that neurogenesis drops off sharply in middle-aged mice. For example, the number of neural progenitor and mitotic (dividing) cells in the hippocampus of middle-aged mice was only 5% of that observed in the young mice.

The researchers also found that exercise significantly slows down the loss of new nerve cells in the middle-aged mice. They found that production of neural stem cells improved by approximately 200% compared to the middle-aged mice that did not exercise. In addition, the survival of new nerve cells increased by 170% and growth by 190% compared to the sedentary middle-aged mice. Exercise also significantly enhanced stem cell production and maturation in the young mice. In fact, exercise produced a stronger effect in younger mice compared to the older mice.

How does this happen?

Based on these results, it appears that nerve growth factor has more to do with these findings than the corticosterone:

The middle-aged exercisers had more brain-derived neurotrophic factor and its receptor, TrkB, compared to the middle-aged mice that did not exercise. This suggests that exercise promotes the production of brain-derived neurotrophic factor which, in turn, promotes differentiation and survival of new brain cells in the hippocampus. Exercise did not change the basal level of serum corticosterone in middle-aged mice. This suggests that the reduction of neurogenesis during aging is not due to the drop in corticosterone levels

Public release date: 18-Nov-2008

Garlic chemical tablet treats diabetes I and II

drug based on a chemical found in garlic can treat diabetes types I and II when taken as a tablet, a study in the new Royal Society of Chemistry journal Metallomics says.

When Hiromu Sakurai and colleagues from the Suzuka University of Medical Science, Japan, gave the drug orally to type I diabetic mice, they found it reduced blood glucose levels.

The drug is based on vanadium and allaxin, a compound found in garlic, and its action described in an Advance Article from Metallomics available free online from today. The first issue of the new journal will be published in 2009.

In previous work they had discovered the vanadium-allaxin compound treated both diabetes types when injected, but this new study shows the drug has promise as an oral treatment for the disease.

Type I diabetes (insulin dependent) is currently treated with daily injections of insulin, while type II (non-insulin dependent) is treated with drugs bearing undesirable side-effects - the authors note neither treatment is ideal.

The researchers aim to test the drug in humans in future work.

Public release date: 18-Nov-2008

Fake TV News: Widespread and Undisclosed

Although the number of media formats and outlets has exploded in recent years, television remains the dominant news source in the United States. More than three-quarters of U.S. adults rely on local TV news, and more than 70 percent turn to network TV or cable news on a daily or near-daily basis, according to a January 2006 Harris Poll. The quality and integrity of television reporting thus significantly impacts the public's ability to evaluate everything from consumer products to medical services to government policies.

To reach this audience—and to add a veneer of credibility to clients' messages—the public relations industry uses video news releases (VNRs). VNRs are pre-packaged "news" segments and additional footage created by broadcast PR firms, or by publicists within corporations or government agencies. VNRs are designed to be seamlessly integrated into newscasts, and are freely provided to TV stations. Although the accompanying information sent to TV stations identifies the clients behind the VNRs, nothing in the material for broadcast does. **Without strong disclosure requirements and the attention and action of TV station personnel, viewers cannot know when the news segment they're watching was bought and paid for by the very subjects of that "report."**

From an ad for the broadcast PR firm D S Simon Productions In recent years, the U.S. Congress, the Federal Communications Commission, journalism professors, reporters and members of the general public have expressed concern about VNRs. In response, public relations executives and broadcaster groups have vigorously defended the status quo, claiming there is no problem with current practices. In June 2005, the president of the Radio-Television News Directors Association (RTNDA), Barbara Cochran, told a reporter that VNRs were "kind of like the Loch Ness Monster. Everyone talks about it, but not many people have actually seen it."

To inform this debate, the Center for Media and Democracy (CMD) conducted a ten-month study of selected VNRs and their use by television stations, tracking 36 VNRs issued by three broadcast PR firms. Key findings include:

VNR use is widespread. CMD found 69 TV stations that aired at least one VNR from June 2005 to March 2006—a significant number, given that CMD was only able to track a small percentage of the VNRs streaming into newsrooms during that time. Collectively, these **69 stations broadcast to 52.7 percent of the U.S. population**, according to Nielsen Media figures. Syndicated and network-distributed segments sometimes included VNRs, further broadening their reach.

VNRs are aired in TV markets of all sizes. TV stations often use VNRs to limit the costs associated with producing, filming and editing their own reports. However, VNR usage is not limited to small-town stations with shoestring budgets. Nearly two-thirds of the VNRs that CMD tracked were aired by stations in a Top 50 Nielsen market area, such as Detroit, Pittsburgh or Cincinnati. Thirteen VNRs were broadcast in the ten largest markets, including New York, Los Angeles, Chicago, Philadelphia and Boston. TV stations don't disclose VNRs to viewers. Of the 87 VNR broadcasts that CMD documented, not once did the TV station disclose the client(s) behind the VNR to the news audience. Only one station, WHSV-3 in Harrisonburg, VA, provided partial disclosure, identifying the broadcast PR firm that created the VNR, but not the client, DaimlerChrysler. WHSV-3 aired soundbites from a Chrysler representative and directed viewers to websites associated with Chrysler, without disclosing the company's role in the "report."

TV stations disguise VNRs as their own reporting. In every VNR broadcast that CMD documented, the TV station altered the VNR's appearance. Newsrooms added station-branded graphics and overlays, to make VNRs indistinguishable from reports that genuinely originated from their station. A station reporter or anchor re-voiced the VNR in more than 60 percent of the VNR broadcasts, sometimes repeating the publicist's original narration word-for-word.

TV stations don't supplement VNR footage or verify VNR claims. While TV stations often edit VNRs for length, in only seven of the 87 VNR broadcasts documented by CMD did stations add any independently-gathered footage or information to the segment. In all other cases, the entire aired "report" was derived from a VNR and its accompanying script. In 31 of the 87 VNR broadcasts, the entire aired "report" was the entire pre-

packaged VNR. Three stations (WCPO-9 in Cincinnati, OH; WSYR-9 in Syracuse, NY; and WYTV-33 in Youngstown, OH) removed safety warnings from a VNR touting a newly-approved prescription skin cream. WSYR-9 also aired a VNR heralding a "major health breakthrough" for arthritis sufferers—**a supplement that a widely-reported government study had found to be little better than a placebo.**

The vast majority of VNRs are produced for corporate clients. Of the hundreds of VNRs that CMD reviewed for potential tracking, only a few came from government agencies or non-profit organizations. Corporations have consistently been the dominant purveyors of VNRs, though the increased scrutiny of government-funded VNRs in recent years may have decreased their use by TV newsrooms. Of the VNRs that CMD tracked, 47 of the 49 clients behind them were corporations that stood to benefit financially from the favorable "news" coverage.

Satellite media tours may accompany VNRs. Broadcast PR firms sometimes produce both VNRs and satellite media tours (SMTs) for clients. SMTs are actual interviews with TV stations, but their focus and scope are determined by the clients. In effect, SMTs are live recitations of VNR scripts. CMD identified 10 different TV stations that aired SMTs for 17 different clients with related VNRs. In only one instance was there partial disclosure to viewers. An anchor at WLTX-19 in Columbia, SC, said after the segment, "This interview ... was provided by vendors at the consumer trade show," but did not name the four corporate clients behind the SMT.

In sum, television newscasts—the most popular news source in the United States—frequently air VNRs without disclosure to viewers, without conducting their own reporting, and even without fact checking the claims made in the VNRs. VNRs are overwhelmingly produced for corporations, as part of larger public relations campaigns to sell products, burnish their image, or promote policies or actions beneficial to the corporation.

Public release date: 20-Nov-2008

Red, red wine: How it fights Alzheimer's Researchers discover how compounds found in wine thwart disease in mice

Red, red wine: How it fights Alzheimer's

Researchers discover how compounds found in wine thwart disease in mice
Scientists call it the "French paradox" — a society that, despite consuming food high in cholesterol and saturated fats, has long had low death rates from heart disease. Research has suggested it is the red wine consumed with all that fatty food that may be beneficial — and not only for cardiovascular health but in warding off certain tumors and even Alzheimer's disease.

Now, Alzheimer's researchers at UCLA, in collaboration with Mt. Sinai School of Medicine in New York, have discovered how red wine may reduce the incidence of the

disease. Reporting in the Nov. 21 issue of the Journal of Biological Chemistry, David Teplow, a UCLA professor of neurology, and colleagues show how naturally occurring compounds in red wine called polyphenols block the formation of proteins that build the toxic plaques thought to destroy brain cells, and further, how they reduce the toxicity of existing plaques, thus reducing cognitive deterioration.

Polyphenols comprise a chemical class with more than 8,000 members, many of which are found in high concentrations in wine, tea, nuts, berries, cocoa and various plants. Past research has suggested that such polyphenols may inhibit or prevent the buildup of toxic fibers composed primarily of two proteins — A β 40 and A β 42 — that deposit in the brain and form the plaques which have long been associated with Alzheimer's. Until now, however, no one understood the mechanics of how polyphenols worked.

Teplow's lab has been studying how amyloid beta (A β) is involved in causing Alzheimer's. In this work, researchers monitored how A β 40 and A β 42 proteins folded up and stuck to each other to produce aggregates that killed nerve cells in mice. They then treated the proteins with a polyphenol compound extracted from grape seeds. They discovered that polyphenols carried a one-two punch: They blocked the formation of the toxic aggregates of A β and also decreased toxicity when they were combined with A β before it was added to brain cells.

"What we found is pretty straightforward," Teplow said. "If the A β proteins can't assemble, toxic aggregates can't form, and thus there is no toxicity. Our work in the laboratory, and Mt. Sinai's Dr. Giulio Pasinetti's work in mice, suggest that administration of the compound to Alzheimer's patients might block the development of these toxic aggregates, prevent disease development and also ameliorate existing disease."

Human clinical trials are next.

"No disease-modifying treatments of Alzheimer's now exist, and initial clinical trials of a number of different candidate drugs have been disappointing," Teplow said. "So we believe that this is an important next step."

Public release date: 20-Nov-2008

Roche ordered to pay \$13M to users of acne drug

ATLANTIC CITY, N.J. – **A jury has ordered drugmaker Roche to pay nearly \$13 million to three patients who claim they developed a chronic bowel disorder because of the company's acne drug Accutane.**

Roche's U.S. subsidiary Hoffman-La Roche said it would appeal the verdict.

The money, handed down in New Jersey State Superior Court on Thursday, will be split among the three Florida residents, their attorneys said in a statement. **All three began using Accutane a**

decade ago to treat teenage acne. One of the group is expected to soon have his colon surgically removed while the others will require long-term drug therapy, the attorneys said.

The award is the latest stemming from a wave of lawsuits that accuse Roche of downplaying a link between Accutane and inflammatory bowel disease, which afflicts about 1.4 million people in the U.S. and Canada.

Accutane's warning label notes that the drug is "associated with" chronic bowel problems, but the company has argued that there is no direct connection between its drug and the disease.

Lawyers representing the three patients presented internal Roche studies that they argue show the company knew Accutane caused damage to the intestinal tract that leads to inflammatory bowel disease.

"This is an important outcome and consistent with the recognition by the medical community that Accutane is a trigger for IBD," said David Buchanan, a partner with Seeger Weiss in New York who helped argue the plaintiffs' case.

Nutley, N.J.-based Hoffman-La Roche reiterated in a statement "there is no reliable scientific evidence that Accutane actually causes" inflammatory bowel disease. The company pointed out that the disease often occurs in patients 15 to 35 years old — roughly the same group of patients who take Accutane.

More than 13 million people worldwide have used the drug since it was approved in 1982, according to Roche.

Public release date: 23-Nov-2008

Melatonin may save eyesight in inflammatory disease

Buenos Aires, Argentina — Current research suggests that melatonin therapy may help treat uveitis, a common inflammatory eye disease. The related report by Sande et al., "Therapeutic Effect of Melatonin in Experimental Uveitis," appears in the December issue of *The American Journal of Pathology*.

People with uveitis develop sudden redness and pain in their eyes, and their vision rapidly deteriorates. Untreated, uveitis can lead to permanent vision loss, accounting for an estimated 10-15% of cases of blindness in the US. Uveitis has a wide variety of causes, including eye injury, cancer, infection, and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. There is currently no optimal treatment for uveitis. Corticoid steroid eye drops are often used; however, long-term corticoid use has many negative side effects, including the possible development of glaucoma.

Researchers lead by Dr. Ruth Rosenstein of The University of Buenos Aires and The National Research Council (CONICET) hypothesized that melatonin, which regulates sleep/wake cycles and reduces jet lag, may be able to prevent the ocular inflammation in uveitis. They found in an experimental model of uveitis that levels of two factors that

contribute to inflammation, TNF α and NF κ B, were reduced with melatonin treatment. Importantly, melatonin treatment also decreased the appearance of clinical symptoms of uveitis such as inflammation, blood vessel expansion and cataract, and protected the blood-ocular barrier integrity.

Taken together, the data from Sande et al suggest that "melatonin, which lacks adverse collateral effects even at high doses, could be a promising resource in the management of uveitis. Alone or combined with corticosteroid therapy, the anti-inflammatory effects of melatonin may benefit patients with chronic uveitis and decrease the rate and degree of corticosteroid-induced complications." Future studies will aim at understanding the mechanisms governing melatonin protection in the eye.

Public release date: 24-Nov-2008

14 drugs identified as most urgently needing study for off-label use, Stanford professor says

STANFORD, Calif. — Physicians and policy-makers know that drugs are frequently prescribed to treat certain diseases despite a lack of FDA approval — a practice known as off-label prescribing. Yet they say the problem is so big they don't know how to begin tackling it.

But a potential game plan now exists. In a paper to be published in the December issue of *Pharmacotherapy*, a group of researchers has developed a list of 14 widely prescribed medications most urgently in need of additional study to determine how effective and safe they are for their off-label uses. Antidepressants and antipsychotics are the most prominent classes of drugs on the list, which specifically targets drugs that have high levels of off-label use without good scientific backing.

"Off-label prescribing means that we're venturing into uncharted territory where we lack the usual level of evidence presented to the FDA that tells us these drugs are safe and effective," said Randall Stafford, MD, PhD, associate professor of medicine at the Stanford Prevention Research Center, who is the senior author of the study. "This list of priority drugs might be a start for confronting the problem of off-label use with limited evidence."

Stafford collaborated on the research with lead author Surrey Walton, PhD, assistant professor of pharmacy administration at the University of Illinois-Chicago, and other researchers at UIC and the University of Chicago.

At the top of the list was **quetiapine (brand name Seroquel)**, an antipsychotic approved by the U.S. Food and Drug Administration in 1997 for treating schizophrenia. Not only did this drug lead all others in its high rate of off-label uses with limited evidence (76 percent of all uses of the drug), it also had features that raised additional concerns, including its high cost at \$207 per prescription, heavy marketing and the presence of a "black-box" warning from the FDA, Stafford said.

Rounding out the top five were warfarin, escitalopram, risperidone and montelukast.

The most common off-label use for six of the 14 drugs on the list was for bipolar disorder. "Many of the drugs and the conditions on the list represent situations where inadequate response to treatment is common and where drug side-effects are frequent," Stafford said. "Not only are these areas where patients and physicians are naturally interested in trying off-label therapies, but areas targeted for expansion by the makers of these drugs.

"When the volume of off-label use of any drug reaches the magnitude that we're documenting, it suggests a role of the pharmaceutical industry in facilitating these types of uses," he added.

Although companies are largely prohibited from marketing off-label uses to physicians and consumers, they make use of exceptions or may market drugs illegally, Stafford said. Companies are allowed to share with physicians any published research that supports off-label uses. Several recent lawsuits have identified systematic plans on the part of some companies to market their products for off-label uses, he noted.

Previous studies have demonstrated the breadth of off-label prescribing. A 1985 study found that of the 100 most common uses of marketed drugs, 31 of those uses did not have approval from the FDA. And a study that Stafford led in 2006 showed that of the estimated 21 percent of off-label drug uses in 2001, 73 percent did not have strong scientific support.

To get a drug approved by the FDA, a pharmaceutical company must complete three rounds of testing in human subjects to demonstrate its safety and effectiveness in treating a specific condition. Once a drug is approved and on the market, though, physicians may choose to prescribe it for any condition. But this carries unknown risks because often the drug hasn't been rigorously tested on patients with that condition.

"Many patients and physicians assume that the FDA has scrutinized all of the different ways a drug can be used, but they've only examined those uses that have gone through the approval process," Stafford said.

And pharmaceutical companies aren't often interested in spending money to investigate additional conditions that the drug might treat. Stafford said the companies may consider it risky to invest in additional testing that could show undesired results, especially when a

drug is already widely used off-label.

To come up with a plan for determining which drugs were most in need of additional research for off-label use, Stafford and his colleagues convened a panel of nine experts from the FDA, the health-insurance industry, the pharmaceutical industry and academia. Based on the panel's input, the researchers identified three factors to help them prioritize the drugs that should appear on the list, including:

The volume of off-label drug use with inadequate evidence supporting that use (based on a large, ongoing national survey of physician prescribing patterns conducted by IMS Health, a private market-research company).

The safety of the drug (based on any safety warnings issued by the FDA).

A composite of the drug's cost, how long it had been on the market and the amount spent marketing the drug.

After collecting the information, the researchers computed the drug rankings in each category and then came up with an overall list of the 14 drugs most in need of additional study. "Despite examining the data in a variety of ways by providing more or less emphasis on certain factors, we still came up with a very consistent list of drugs," Stafford said.

He said that in addition to prompting the FDA and other government agencies to study the priority drugs on the list, he hopes the research spurs patients to ask their doctors why they are prescribing a particular drug. "A dialogue needs to occur more frequently between physicians and patients regarding the level of evidence that supports a particular use of a drug."

Stafford also noted the societal costs associated with off-label drug use. With the prescription drug benefit now available through Medicare, taxpayers are getting the bill for costly drugs that may not be proven for the conditions they're prescribed to treat.

Public release date: 24-Nov-2008

Stomach ulcer bug causes bad breath

Bacteria that cause stomach ulcers and cancer could also be giving us bad breath, according to research published in the December issue of the Journal of Medical Microbiology. For the first time, scientists have found *Helicobacter pylori* living in the mouths of people who are not showing signs of stomach disease.

The mouth is home to over 600 different species of bacteria, some of which can cause disease. *Helicobacter pylori* has recently been shown to cause stomach ulcers and is also responsible for a large proportion of gastric cancers. **Scientists estimate that between 20 and 80 % of people in the developed world and over 90 % of people in the**

developing world carry the bacterium.

"Recently, scientists discovered that *H. pylori* can live in the mouth," said Dr Nao Suzuki from Fukuoka Dental College in Fukuoka, Japan. "We wanted to determine whether the bacteria can cause bad breath, so we tested patients complaining of halitosis for the presence of *H. pylori*."

The researchers found the bacteria in the mouths of 21 out of 326 Japanese people with halitosis (6.4%). In these people, the concentration of a bad breath gas and the level of oral disease was significantly higher. In patients with periodontal (gum) disease, 16 of 102 people (15.7%) had *H. pylori* in their mouths.

"Halitosis is a common problem in humans, and bad breath is largely caused by periodonitis, tongue debris, poor oral hygiene and badly fitted fillings," said Dr. Suzuki. "Bacteria produce volatile compounds that smell unpleasant, including hydrogen sulphide, methyl mercaptan and dimethyl sulphide. Doctors often measure the levels of these compounds to diagnose the problem. Gastrointestinal diseases are also generally believed to cause halitosis."

Patients who were carrying *H. pylori* had more blood in their saliva and were also carrying *Prevotella intermedia*, which is one of the major periodontal bacteria.

"Although the presence of *H. pylori* in the mouth does not directly cause bad breath, it is associated with periodontal disease, which does cause bad breath," said Dr. Suzuki. "We now need to look into the relationship between *H. pylori* in the mouth and in the stomach. We hope to discover the role of the mouth in transmitting *H. pylori* stomach infections in the near future."

Public release date: 24-Nov-2008

Mineral oil contamination in humans: A health problem?

From a quantitative standpoint, mineral oil is probably the largest contaminant of our body. That this contaminant can be tolerated without health concerns in humans has not been proven convincingly. The current Editorial of the European Journal of Lipid Science and Technology reflects on this and concludes that this proof either has to be provided or we have to take measures to reduce our exposure – from all sources, including cosmetics, pharmaceuticals and the environmental contamination.

In the Ukraine recently around 100,000 tonnes of sunflower oil were contaminated with mineral oil at concentrations often above 1000 mg/kg. Much of the contaminated oil was withdrawn, but there are products on the market which were produced before this contamination was detected; and this autumn there are still several 10,000 tonnes of contaminated oil in the Ukraine and other parts of the world. To protect consumers, a broad analytical campaign was initiated throughout Europe. The European Commission decided to apply a legal limit of 50 mg/kg to the mineral paraffins in Ukrainian sunflower

oil and in September 2008 it organized a workshop together with the Official Food Control Authority of Zurich, Switzerland, to promote this campaign.

The editorial by Dr. Koni Grob from the Official Food Control Authority of the Canton of Zurich, Switzerland, titled "Does the Ukrainian sunflower oil contaminated with mineral oil wake up sleeping dogs?" discusses the situation. Dr. Koni Grob says that in many more foods more than 50 mg/kg mineral oil components from other sources will be found and the enforcement authorities will then be in difficulty to decide how to react. Certain edible oils, but also certain other foods, like canned fish, frequently contain more than 50 mg/kg mineral oil components, some products as much as 1000 mg/kg. Although known for some time, so far no measures were taken to stop this. He continued, our lab works for the safety of the consumers. Presently there is insufficient knowledge about potential negative effects of mineral oil on human health. We are heading for data regarding the material we are exposed to and which is accumulated in our bodies, in order to provide toxicological data for an improved safety evaluation."

It has been shown that the molecular mass of the mineral paraffins resorbed by our body is higher than assumed by the safety evaluation of the European Food Safety Authority (EFSA). Further, probably a majority of the mineral oil products are not "white paraffin oils": they easily contain 30 % aromatic components, a substantial portion being alkylated adding to the health risk. This unerringly questions the current official safety evaluation – which, admittedly, is a difficult task because of the complexity of the material. It can only be hoped that the mineral oil contamination of the Ukrainian sunflower oil and the inconsistencies regarding the effects of mineral oil on the human body will make the responsible industry, science and authorities more aware of this smouldering problem.

Public release date: 24-Nov-2008

Pregnancy study finds strong association between two antidepressants and heart anomalies

Three-country study looks at fluoxetine and paroxetine

Women who took the antidepressant fluoxetine during the first three months of pregnancy gave birth to four times as many babies with heart problems as women who did not and the levels were three times higher in women taking paroxetine.

Although some of the conditions were serious, others were not severe and resolved themselves without the need for medical intervention, according to a three-country study in the November issue of the British Journal of Clinical Pharmacology.

Researchers have advised women taking the drugs to continue unless they are advised to stop by their doctor or consultant. But they are being urged to give up smoking, as the study also found that more than ten cigarettes a day was associated with a five-fold increase in babies with major heart problems.

The team has also suggested that women on fluoxetine should be given a foetal echocardiogram in their second trimester to diagnose possible heart anomalies.

International researchers from Israel, Italy and Germany followed the pregnancies of 2,191 women - 410 who had taken paroxetine during pregnancy, 314 who had taken fluoxetine and 1,467 controls who hadn't taken either of the drugs.

"After we excluded genetic and cytogenic anomalies, we found a higher rate of major heart anomalies in the women who had been taking the antidepressants" says lead author Professor Asher Ornoy from the Israeli Teratology Information Service in Jerusalem, Israel.

"Further analysis showed a strong association between major heart anomalies and taking fluoxetine in the first trimester. Women who smoked more than 10 cigarettes a day also had more babies with heart anomalies."

Women taking paroxetine or smoking less than ten cigarettes a day also faced elevated risks, but not to the same extent.

The women had all contacted either the Israeli Teratology Information Service in Jerusalem, Israel, the Servizio di Informazione Teratologica in Padua, Italy, or the Pharmakovigilanz-und Beratungszentrum für Embryonaltoxikologie in Berlin, Germany.

All three belong to the European Network of Teratology Information Services, which comprises organisations that investigate, and provide counselling on, environmental exposure during pregnancy.

The women in the control group had contacted the services because of concerns about exposure to substances that are not known to cause birth defects and the women in the medication groups because of their use of paroxetine and fluoxetine.

When the researchers looked at the outcomes of all of the pregnancies they found that:

The prevalence of major heart anomalies was 2.8% in the fluoxetine group, 2% in the paroxetine group and 0.6% in the control group. There was no increase in other major congenital anomalies.

Previous pregnancy terminations were also higher in the fluoxetine and paroxetine groups than the control group (7.8%, 4.8% and 2.8%). All groups included some terminations because of diagnosed anomalies.

Birth weights were slightly lower in the fluoxetine and paroxetine groups than the control group (3200g, 3250g and 3300g).

Women taking fluoxetine and paroxetine were more likely to smoke than women in the control group (20.1%, 20.7% and 7.5%) and more likely to smoke more than ten cigarettes a day (12.3%, 14% and 4.4%).

Taking all the factors into account, the authors calculated that the overall risk posed by antidepressant use and cigarette consumption was as follows:

Women who took fluoxetine during pregnancy were 4.47 times more likely to have a baby with a heart anomaly and women who took paroxetine were 2.66 times more likely.

Those smoking more than ten cigarettes a day were 5.40 times more likely to have a baby with a heart anomaly and women smoking less than ten cigarettes a day were 2.75 times more likely.

"These findings clearly show a significant association between major heart anomalies and taking fluoxetine and smoking during pregnancy" says Professor Ornoy.

"There is an ongoing debate in the medical literature about the possible association between women taking one of these two drugs during pregnancy and having a baby with a heart anomaly and we are keen to see further research in this area.

"We should point out that there is no evidence of any increased risk posed by citalopram and sertraline, which belong to the same group of antidepressants."

The authors say that it is important that women are aware of these findings, especially if they smoke. However if they are taking fluoxetine, they should speak to their family doctor or consultant and should not stop taking their medication unless advised to do so.

"It's estimated that as many as one in seven women suffer from clinical depression during pregnancy and clinicians need to weigh up the individual risks of pregnant women taking, or not taking, drugs like fluoxetine" stresses Professor Ornoy.

"Many heart anomalies can now be treated, so it is important to bear that in mind when making a decision about whether or not to continue with one of these drugs during pregnancy. The health of the mother and the baby are both important.

"We hope that this study will provide both doctors and pregnant women on antidepressants with some of the information they need to help them make those difficult decisions."

Ralph's note - Where are all those studies now, saying these drugs were safe for pregnant woman to use.

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Potassium loss from blood pressure drugs may explain higher risk of adult diabetes

Johns Hopkins researchers have discovered that a drop in blood potassium levels caused by diuretics commonly prescribed for high blood pressure could be the reason why people on those drugs are at risk for developing type 2 diabetes. The drugs helpfully accelerate loss of fluids, but also deplete important chemicals, including potassium, so that those who take them are generally advised to eat bananas and other potassium-rich foods to counteract the effect.

"Previous studies have told us that when patients take diuretic thiazides, potassium levels drop and the risk of diabetes climbs to 50 percent," says lead researcher Tariq Shafi, M.D., M.H.S., of the Department of Nephrology at Johns Hopkins University School of Medicine. "Now, for the first time, we think we have concrete information connecting the dots."

Thiazides, such as chlorthalidone, are an inexpensive and highly effective way to treat high blood pressure and have been used widely for decades. However, their association with diabetes has forced many hypertension sufferers to use other medications that can be several times as expensive, says Shafi.

"This study shows us that as long as physicians monitor and regulate potassium levels, thiazides could be used safely, saving patients thousands of dollars a year," says Shafi. "It could be as simple as increasing the consumption of potassium-rich foods like bananas and oranges and/or reducing salt intake, both of which will keep potassium from dropping."

Researchers examined data from 3,790 nondiabetic participants in the Systolic Hypertension in Elderly Program (SHEP). SHEP is a randomized clinical trial conducted

between 1985 and 1991 designed to determine the risk versus benefit of giving a certain high blood pressure medication to people age 60 years or older.

Half of the subjects were treated with chlorthalidone and half with a fake drug. Of the 3,790 subjects, 1,603 were men and 724 were nonwhite. None had a history of diabetes. In the original study, potassium levels were monitored as a safety precaution to guard against irregular heartbeat, a condition that can result from low potassium.

The results, published online this month in the journal *Hypertension*, showed that for each 0.5 milliequivalent-per-liter (mEq/L) decrease in serum potassium, there was a 45 percent increased risk of diabetes. None of the people in the group receiving the fake drug developed low potassium levels. Shafi says these findings should encourage physicians to establish a potassium baseline by checking hypertensive patients' medical records to determine their potassium levels before prescribing thiazides.

"We would normally look at the number only after six weeks of treatment to make sure it was not low enough to cause heart problems. As a result, we might not be aware that it dropped significantly from where it was before treatment — putting the patient at risk for developing diabetes," says Shafi.

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Feed a cold, feed a fever: Research shows calorie cut makes it harder to fight flu

EAST LANSING, Mich. -- Dieters or those who consume fewer calories during flu season could have a harder time fighting off the flu virus, according to research by Michigan State University nutritional immunology professor Elizabeth Gardner.

In a study published in the November issue of the *Journal of Nutrition*, Gardner showed that mice with a calorie-restricted diet were more likely to die during the first few days of infection than mice with a normal diet. Caloric restriction is the practice of reducing the intake of calories to 40 percent of a normal diet, while maintaining adequate vitamins and minerals.

"If you are exposed to a new strain of influenza, to which your body has not made adequate antibodies to protect you from infection, your body must rely on cells that will kill the virus," Gardner said. "The natural killer cells are important in controlling the early stages of virus infection, because they act quickly once they encounter virus-infected cells. Our studies show that calorically restricted mice have increased susceptibility to influenza, and their bodies are not prepared to produce the amount of

natural killer cells needed to combat the stress of fighting an infection.”

In Gardner’s research, both regularly fed mice and calorically restricted mice exposed to the virus exhibited decreased food intake as they tried to fight off the infection. Yet the mice on calorically restricted diets took longer to recover and exhibited increased mortality, weight loss and other negative effects. Even though both sets of mice had a diet fortified with appropriate vitamins, the mice consuming normal amounts of food had their appetites back sooner and recovered faster.

“Our research shows that having a body ready to fight a virus will lead to a faster recovery and less-severe effects than if it is calorically restricted,” Gardner said. “Adults can calorically restrict their diet eight months out for the year, but during the four months of flu season they need to bump it up to be ready. You need the reserves so your body is ready for any additional stress, including fighting a virus.”

Calorically restricted diets in general have been shown to increase lifespan in everything from yeast to primates, according to Gardner. But the model used in Gardner’s research can be extended to more vulnerable groups including children and the elderly, who don’t eat as much but often take vitamin supplements.

Flu shots can’t guarantee protection, in any case, since they are formulated months in advance and only can target a small handful of the many flu virus strains that might infect the population.

“If the strain of flu a person is infected with is different from the strain included in the flu vaccination, then your body sees this as a primary infection and must produce the antibodies to fight it off. A calorically restricted body is not as well prepared to do this and cannot control early infection, which impedes recovery,” Gardner added.

Gardner, an associate professor in the Department of Food Science and Human Nutrition, now is investigating the mechanisms responsible for decreased immune function during caloric restriction. Her research in nutritional immunology will lead to a better understanding of how a diet affects the immune system and the best conditions for a body to quickly and successfully fight infections.

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Pain is in the eyes of the beholder

By manipulating the appearance of a chronically achy hand, researchers have found they could increase or decrease the pain and swelling in patients moving their symptomatic limbs. The findings—reported in the November 25th issue of *Current Biology*, a Cell Press publication—reveal a profound top-down effect of body image on body tissues, according to the researchers.

"The brain is capable of many wonderful things based on its perception of how the body

is doing and the risks to which the body seems to be exposed," said G. Lorimer Moseley, who is now at the Prince of Wales Medical Research Institute in Australia. (The work was done at the University of Oxford.)

In the study, the researchers asked ten right-handed patients with chronic pain and dysfunction in one arm to watch their own arm while they performed a standardized set of ten hand movements. The participants repeated the movements under four conditions: with no visual manipulation, while looking through binoculars with no magnification, while looking through binoculars that doubled the apparent size of their arm, and while looking through inverted binoculars that reduced the apparent size of their arm.

While the patients' pain was always worse after movement than it was before, the extent to which the pain worsened depended on what people saw. Specifically, the pain increased more when participants viewed a magnified image of their arm during the movements, and—perhaps more surprisingly—the pain became less when their arm was seen through inverted binoculars that minimized its size.

The degree of swelling too was less when people watched a "minified" image of their arm during movements than when they watched a magnified or normal image, the researchers reported.

They aren't yet sure how this phenomenon works at the level of neurons. However, the researchers said, a possible philosophical explanation comes from the notion that protective responses—including the experience of pain—are activated according to the brain's implicit perception of danger level. "If it looks bigger, it looks sorer and more swollen," Moseley said. "Therefore, the brain acts to protect it."

While he said the findings don't mean that pain is any less real, they may lead to a new therapeutic approach for reducing pain. His team is now testing visual manipulations as an analgesic strategy for use in clinical settings.

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Estrogen therapy could be dangerous for women with existing heart risk

ANN ARBOR, Mich.—Hormone therapy could accentuate certain pre-existing heart disease risk factors and a heart health evaluation should become the norm when considering estrogen replacement, new research suggests.

The research also showed that in women without existing atherosclerosis, hormone therapy use included some positive effects on lipids but also some negative effects related to heart health, said MaryFran Sowers, lead researcher and professor of epidemiology at the University of Michigan School of Public Health.

The U-M study came about, Sowers said, in trying to explain what's behind the so-called timing hypothesis. The timing hypothesis suggests that if a woman implements a

hormone therapy program within six years of her final menstrual period, this narrow window is enough to deter heart disease from developing with the onset of menopause. But the U-M findings suggest that explanation isn't quite so simple, Sowers said.

Even within the six-year window, there were negative aspects related to heart disease. While the positive outcomes on HDL and LDL cholesterol levels were observed, Sowers said, researchers also saw negative outcomes in terms of the inflammation process—which can be related to heart disease.

Sowers said the research shows it's critical for women considering hormone therapy to discuss their heart health with their doctor.

"If the woman walks into the doctor's office with a certain degree of (heart disease) burden already, then she and her health care provider may decide that hormone therapy adds too much to the burden," Sowers said. "If she doesn't have that burden, they may decide that hormone therapy is an acceptable burden.

"The woman should say to her health care provider, 'What kind of information do we need to gather in order to make an informed decision about whether or not hormone therapy should be pursued,'" Sowers said. "I understand there could be some heart disease risk, but that the risk may be based upon where I am now, and can you tell me where that is?"

Heart disease risk can be measured through lipid panels, which are standard, but also by measuring inflammation markers, Sowers said. Tests for inflammation markers exist but their measurement isn't standard when a woman is considering hormone therapy, Sowers said.

Hormone therapy has been controversial for years, and there was a time when there was an almost knee jerk reaction against it, Sowers said. This backlash occurred after the findings from the Women's Health Initiative study showed that some women on estrogen therapy had increased heart disease risk. The six-year timing hypothesis was an attempt to explain the findings in the WHI study, Sowers said.

The University of Michigan School of Public Health has been working to promote health and prevent disease since 1941, and is consistently ranked among the top five public health schools in the nation. Faculty and students in the school's five academic departments and dozens of collaborative centers and initiatives are forging new solutions to the complex health challenges of today, including chronic disease, health care quality and finance, emerging genetic technologies, climate change, socioeconomic inequalities and their impact on health, infectious disease, and the globalization of health. Whether making new discoveries in the lab or researching and educating in the field, our faculty, students, and alumni are deployed around the globe to promote and protect our

**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.**