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Human Technology Research Synopsis

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Public Release: 31-Mar-2009

Physical activity may strengthen children's ability to pay attention

CHAMPAIGN, Ill. — As school districts across the nation revamped curricula to meet requirements of the federal “No Child Left Behind” Act, opportunities for children to be physically active during the school day diminished significantly.

Future mandates, however, might be better served by taking into account findings from a University of Illinois study suggesting the academic benefits of physical education classes, recess periods and after-school exercise programs. The research, led by Charles Hillman, a professor of kinesiology and community health and the director of the Neurocognitive Kinesiology Laboratory at Illinois, suggests that physical activity may increase students’ cognitive control – or ability to pay attention – and also result in better performance on academic achievement tests.

“The goal of the study was to see if a single acute bout of moderate exercise – walking – was beneficial for cognitive function in a period of time afterward,” Hillman said. “This question has been asked before by our lab and others, in young adults and older adults, but it’s never been asked in children. That’s why it’s an important question.”

For each of three testing criteria, researchers noted a positive outcome linking physical activity, attention and academic achievement.

Study participants were 9-year-olds (eight girls, 12 boys) who performed a series of stimulus-discrimination tests known as flanker tasks, to assess their inhibitory control.

On one day, students were tested following a 20-minute resting period; on another day, after a 20-minute session walking on a treadmill. Students were shown congruent and incongruent stimuli on a screen and asked to push a button to respond to incongruencies. During the testing, students were outfitted with an electrode cap to measure electroencephalographic (EEG) activity.

“What we found is that following the acute bout of walking, children performed better on the flanker task,” Hillman said. “They had a higher rate of accuracy, especially when the task was more difficult. Along with that behavioral effect, we also found that there were changes in their event-related brain potentials (ERPs) – in these neuroelectric signals that are a covert measure of attentional resource allocation.”

One aspect of the neuroelectric activity of particular interest to researchers is a measure referred to as the P3 potential. Hillman said the amplitude of the potential relates to the allocation of attentional resources.

“What we found in this particular study is, following acute bouts of walking, children had a larger P3 amplitude, suggesting that they are better able to allocate attentional resources, and this effect is greater in the more difficult conditions of the flanker test, suggesting that when the environment is more noisy – visual noise in this case – kids are better able to gate out that noise and selectively attend to the correct stimulus and act upon it.”

In an effort to see how performance on such tests relates to actual classroom learning, researchers next administered an academic achievement test. The test measured performance in three areas: reading, spelling and math.

Again, the researchers noted better test results following exercise.

“And when we assessed it, the effect was largest in reading comprehension,” Hillman said. In fact, he said, “If you go by the guidelines set forth by the Wide Range Achievement Test, the increase in reading comprehension following exercise equated to approximately a full grade level.

“Thus, the exercise effect on achievement is not statistically significant, but a meaningful difference.”

Hillman said he’s not sure why the students’ performance on the spelling and math portions of the test didn’t show as much of an improvement as did reading comprehension, but suspects it may be related to design of the experiment. Students were tested on reading comprehension first, leading him to speculate that too much time may have elapsed between the physical activity and the testing period for those subjects.

“Future attempts will definitely look at the timing,” he said. Subsequent testing also will introduce other forms of physical-activity testing.

“Treadmills are great,” Hillman said. “But kids don’t walk on treadmills, so it’s not an externally valid form of exercise for most children. We currently have an ongoing project that is looking at treadmill walking at the same intensity relative to a Wii Fit game – which is a way in which kids really do exercise.”

Still, given the preliminary study’s positive outcomes on the flanker task, ERP data and academic testing, study co-author Darla Castelli believes these early findings could be used to inform useful curricular changes.

“Modifications are very easy to integrate,” Castelli said. For example, she recommends that schools make outside playground facilities accessible before and after school.

“If this is not feasible because of safety issues, then a school-wide assembly containing a brief bout of physical activity is a possible way to begin each day,” she said. “Some schools are using the Intranet or internal TV channels to broadcast physical activity sessions that can be completed in each classroom.”

Among Castelli’s other recommendations for school personnel interested in integrating physical activity into the curriculum:

- scheduling outdoor recess as a part of each school day;
- offering formal physical education 150 minutes per week at the elementary level, 225 minutes at the secondary level;
- encouraging classroom teachers to integrate physical activity into learning.

An example of how physical movement could be introduced into an actual lesson would be “when reading poetry (about nature or the change of seasons), students could act like falling leaves,” she said.

The U. of I. study appears in the current issue of the journal *Neuroscience*. Along with Castelli and Hillman, co-authors are U. of I. psychology professor Art Kramer and kinesiology and community health graduate student Mathew Pontifex and undergraduate Lauren Raine.

Public release date: 1-Apr-2009

How probiotics can prevent disease

Using probiotics successfully against a number of animal diseases has helped scientists from University College Cork, Ireland to understand some of the ways in which they work, which could lead to them using probiotics to prevent and even to treat human diseases.

Presenting the work at the Society for General Microbiology meeting in Harrogate today (Thursday 2 April), Dr Colin Hill described how his team had used three animal models of disease that have human counterparts – bovine mastitis, porcine salmonellosis (a gastrointestinal disease) and listeriosis in mice (an often fatal form of food poisoning) – to demonstrate the protective effects of probiotics.

"Rather than use commercially available probiotics, we made our own probiotic preparations containing safe bacteria such as *Lactobacillus* species newly isolated from human volunteers" said Dr Hill, "In all three animal diseases we observed a positive effect in that the animals were significantly protected against infection".

The team also used probiotics to control disease in animals that were already infected. The results of these tests proved that administering these safe bacteria to an infected

animal was as effective as the best available antibiotic therapies in eliminating the infectious agent and resolving the symptoms.

In each instance the protection was linked to a particular bacterial species, and the mechanism of action varied from direct antagonism (where the probiotic directly kills the pathogenic bacteria) to effects mediated by the host immune system. For example *Lactobacillus salivarius* UCC118 protected mice against listeriosis (a disease which can affect pregnant women) by producing an antimicrobial peptide that eliminates *Listeria monocytogenes* in the gut of the animal. In another mechanism, *Lactococcus lactis* could be used to treat mastitis by eliciting an immune response that overwhelmed the infectious bacterium.

Dr Hill added, "It is likely that using probiotics rather than antibiotics will appeal to at-risk individuals since they are safe, non-invasive, do not create resistant bacteria and can even be administered in the form of tasty foods or beverages".

"We have shown that we can protect and even treat animals against pathogenic bacteria by introducing harmless bacteria at the site of the infection," said Dr Hill. "In order to use similar strategies in preventing or treating human disease we must understand the molecular basis of their efficacy. This understanding will provide the basis for intelligent screening and selection of the most appropriate protective bacterial cultures to go forward into human trials".

Public release date: 1-Apr-2009

Omega-3 kills cancer cells

Docosahexanoic acid (DHA), an omega-3 fatty acid found in fish oils, has been shown to reduce the size of tumours and enhance the positive effects of the chemotherapy drug cisplatin, while limiting its harmful side effects. The rat experiments, described in BioMed Central's open access journal Cell Division, provide some support for the plethora of health benefits often ascribed to omega-3 acids.

Professor A. M. El-Mowafy led a team of researchers from Mansoura University, Egypt, who studied DHA's effects on solid tumours growing in mice, as well as investigating how this fatty acid interacts with cisplatin, a chemotherapy drug that is known to cause kidney damage. El-Mowafy said, "DHA elicited prominent chemopreventive effects on its own, and appreciably augmented those of cisplatin as well. Furthermore, this study is the first to reveal that DHA can obliterate lethal cisplatin-induced nephrotoxicity and renal tissue injury."

DHA is an omega-3 fatty acid that is commonly found in cold-water fish oil, and some vegetable oils. It is a major component of brain gray matter and of the retina in most

mammalian species and is considered essential for normal neurological and cellular developments. According to the authors, "While DHA has been tentatively linked with protection against cardiovascular, neurological and neoplastic diseases, there exists a paucity of research information, in particular regarding its interactions with existing chemotherapy drugs". **The researchers found that, at the molecular level, DHA acts by reducing leukocytosis (white blood cell accumulation), systemic inflammation, and oxidative stress – all processes that have been linked with tumour growth.**

El-Mowafy and his colleagues have called for greater deployment of omega-3 in the fight against cancer. They write, "Our results suggest a new, fruitful drug regimen in the management of solid tumors based on combining cisplatin, and possibly other chemotherapeutics, with DHA".

Public release date: 1-Apr-2009

Source of major health benefits in olive oil revealed

Scientists have pinned down the constituent of olive oil that gives greatest protection from heart attack and stroke. In a study of the major antioxidants in olive oil, Portuguese researchers showed that one, DHPEA-EDA, protects red blood cells from damage more than any other part of olive oil.

"These findings provide the scientific basis for the clear health benefits that have been seen in people who have olive oil in their diet," says lead researcher Fatima Paiva-Martins, who works at the University of Porto.

Heart disease is caused partly by reactive oxygen, including free radicals, acting on LDL or "bad" cholesterol and resulting in hardening of the arteries. Red blood cells are particularly susceptible to oxidative damage because they are the body's oxygen carriers.

In the study, published in *Molecular Nutrition & Food Research*, Paiva-Martins and colleagues compared the effects of four related polyphenolic compounds on red blood cells subjected to oxidative stress by a known free radical generating chemical.

DHPEA-EDA was the most effective and protected red blood cells even at low concentrations. The researchers say the study provides the first evidence that this compound is the major source of the health benefit associated with virgin olive oils, which contain increased levels of DHPEA-EDA compared to other oils. In virgin olive oils, DHPEA-EDA may make up as much as half the total antioxidant component of the oil.

Paiva-Martins says the findings could lead to the production of "functional" olive oils specifically designed to reduce the risk of heart disease. "Now we have identified the importance of these compounds, producers can start to care more about the polyphenolic

composition of their oils," she says

Public release date: 1-Apr-2009

Einstein scientists propose new theory of autism

Symptoms of the disorder may be reversible: Fever may hold clues

April 1, 2009 — (BRONX, NY) — Scientists at Albert Einstein College of Medicine of Yeshiva University have proposed a sweeping new theory of autism that suggests that the brains of people with autism are structurally normal but dysregulated, meaning symptoms of the disorder might be reversible.

The central tenet of the theory, published in the March issue of *Brain Research Reviews*, is that autism is a developmental disorder caused by impaired regulation of the locus coeruleus, a bundle of neurons in the brain stem that processes sensory signals from all areas of the body.

The new theory stems from decades of anecdotal observations that some autistic children seem to improve when they have a fever, only to regress when the fever ebbs. A 2007 study in the journal *Pediatrics* took a more rigorous look at fever and autism, observing autistic children during and after fever episodes and comparing their behavior with autistic children who didn't have fevers. This study documented that autistic children experience behavior changes during fever.

"On a positive note, we are talking about a brain region that is not irrevocably altered. It gives us hope that, with novel therapies, we will eventually be able to help people with autism," says theory co-author Mark F. Mehler, M.D., chairman of neurology and director of the Institute for Brain Disorders and Neural Regeneration at Einstein.

Autism is a complex developmental disability that affects a person's ability to communicate and interact with others. It usually appears during the first three years of life. Autism is called a "spectrum disorder" since it affects individuals differently and to varying degrees. It is estimated that one in every 150 American children has some degree of autism.

Einstein researchers contend that scientific evidence directly points to the locus coeruleus–noradrenergic (LC-NA) system as being involved in autism. "The LC-NA system is the only brain system involved both in producing fever and controlling behavior," says co-author Dominick P. Purpura, M.D., dean emeritus and distinguished professor of neuroscience at Einstein.

The locus coeruleus has widespread connections to brain regions that process sensory information. It secretes most of the brain's noradrenaline, a neurotransmitter that plays a key role in arousal mechanisms, such as the "fight or flight" response. It is also involved

in a variety of complex behaviors, such as attentional focusing (the ability to concentrate attention on environmental cues relevant to the task in hand, or to switch attention from one task to another). Poor attentional focusing is a defining characteristic of autism.

"What is unique about the locus coeruleus is that it activates almost all higher-order brain centers that are involved in complex cognitive tasks," says Dr. Mehler.

Drs. Purpura and Mehler hypothesize that in autism, the LC-NA system is dysregulated by the interplay of environment, genetic, and epigenetic factors (chemical substances both within as well as outside the genome that regulate the expression of genes). They believe that stress plays a central role in dysregulation of the LC-NA system, especially in the latter stages of prenatal development when the fetal brain is particularly vulnerable.

As evidence, the researchers point to a 2008 study, published in the *Journal of Autism and Developmental Disorders*, that found a higher incidence of autism among children whose mothers had been exposed to hurricanes and tropical storms during pregnancy. Maternal exposure to severe storms at mid-gestation resulted in the highest prevalence of autism.

Drs. Purpura and Mehler believe that, in autistic children, fever stimulates the LC-NA system, temporarily restoring its normal regulatory function. "This could not happen if autism was caused by a lesion or some structural abnormality of the brain," says Dr. Purpura.

"This gives us hope that we will eventually be able to do something for people with autism," he adds.

The researchers do not advocate fever therapy (fever induced by artificial means), which would be an overly broad, and perhaps even dangerous, remedy. Instead, they say, the future of autism treatment probably lies in drugs that selectively target certain types of noradrenergic brain receptors or, more likely, in epigenetic therapies targeting genes of the LC-NA system.

"If the locus coeruleus is impaired in autism, it is probably because tens or hundreds, maybe even thousands, of genes are dysregulated in subtle and complex ways," says Dr. Mehler. "The only way you can reverse this process is with epigenetic therapies, which, we are beginning to learn, have the ability to coordinate very large integrated gene networks."

"The message here is one of hope but also one of caution," Dr. Mehler adds. "You can't take a complex neuropsychiatric disease that has escaped our understanding for 50 years and in one fell swoop have a therapy that is going to reverse it — that's folly. On the other hand, we now have clues to the neurobiology, the genetics, and the epigenetics of autism. To move forward, we need to invest more money in basic science to look at the genome and the epigenome in a more focused way."

Public release date: 6-Apr-2009

Broccoli sprouts may prevent stomach cancer by defeating *Helicobacter pylori*

PHILADELPHIA – Three-day-old broccoli sprouts, a widely available human food, suppressed *Helicobacter pylori* (*H. pylori*) infections, according to a report in *Cancer Prevention Research*, a journal of the American Association for Cancer Research. *H. pylori* infections are one of the most common bacterial infections worldwide and are a major cause of stomach cancer.

The cancer protective effects of sulforaphane, a phytochemical from broccoli, have been known for almost two decades, but this is the first study to show an effect of broccoli in humans on the bacterial infection that leads to stomach cancer. In this study, researchers enrolled 48 *Helicobacter*-infected Japanese men and women and randomly assigned them to **eat 70 grams of fresh broccoli sprouts daily for eight weeks** or an equivalent amount of alfalfa sprouts.

"Broccoli has recently entered the public awareness as a preventive dietary agent. This study supports the emerging evidence that broccoli sprouts may be able to prevent cancer in humans, not just in lab animals," said Jed Fahey, Sc.D., a faculty research associate in the Department of Pharmacology at Johns Hopkins School of Medicine.

Researchers assessed the severity of *H. pylori* infection at enrollment, and again at four and eight weeks using standard breath, serum and stool tests. **H. pylori levels were significantly lower at eight weeks on all three measures among those patients who had eaten broccoli sprouts**, while they remained the same for patients who had eaten alfalfa sprouts.

A reduction in *H. pylori* is expected to lead to a reduction in stomach cancer due to their well-established cause-and-effect link. Stomach cancer has a grim prognosis and is the second most common and the second deadliest cancer worldwide.

Public release date: 6-Apr-2009

Biology of flushing could renew niacin as cholesterol drug

DURHAM, N.C. – **Deft molecular detective work at Duke University Medical Center suggests that scientists may soon be able to resurrect niacin as one of the best and cheapest ways to manage cholesterol.**

Niacin, also known as nicotinic acid or vitamin B3, has long been regarded as one of the most effective weapons in managing cholesterol. It can lower levels of triglycerides, fatty acids and to a lesser extent, the "bad" kind of cholesterol (LDL)

while at the same time powerfully increasing the "good" kind (HDL). But there's a catch – a big one. Patients don't like to take niacin because in most of them, it causes embarrassing, uncontrollable intense flushing, a rush of blood to the face and other skin surfaces accompanied by a prickling sensation.

Now, however, scientists have identified the discrete molecular pathways that are triggered when niacin enters the body, and they say that knowledge may lead to a revival of niacin-based treatments as therapies of choice. Their discovery appears online in the *Journal of Clinical Investigation* and is scheduled to appear in the journal's May 1 issue.

"This opens up whole new realms for drug discovery," says Robert Walters, M.D., a dermatologist at Duke and the lead author of the study. "Not only could it lead to new niacin-based therapies for cholesterol that patients could actually stick with, but it could also mean new treatments for flushing that comes with some types of allergic reactions, hives and other disorders."

The discovery builds upon a growing body of knowledge at Duke about G protein coupled receptors, molecules that dot cell surfaces throughout the body and manage its response to drugs, hormones, pain, growth factors and many other incoming chemical signals. Robert Lefkowitz, M.D., a Howard Hughes Medical Institute investigator at Duke and the senior author of the study, was the first to identify these receptors and some of the roles they play in health and well-being.

Working together, Lefkowitz and Walters conducted various laboratory and animal experiments to track exactly what happens when niacin enters the body. Earlier, others had found that it first activates a specific G protein coupled receptor known as GP109A. This receptor, in turn, alerts other sets of proteins, including G proteins and a group referred to as beta-arrestins. One particular protein in that group, beta-arrestin1, was found to trigger the chemical reaction that led to flushing.

"Niacin stimulates production of a vasodilator that dramatically increases blood flow to the face, causing the flush and the hot, prickly sensation – and beta-arrestin1 is the culprit that enables that to happen," says Walters. "Interestingly, however, beta-arrestin1 plays no role whatsoever in niacin's ability to lower cholesterol and fatty acids. The G proteins do that."

The finding reinforces some of Lefkowitz's recent research that demonstrated that beta-arrestins, which often work in tandem with G proteins, can sometimes work independently of them, initiating their own signals.

Lefkowitz says the discovery opens the door to the possibility of developing a "biased ligand," a drug that would trigger GP109A, but not the beta-arrestins. "That might give us a way to keep all the lipid-modifying benefits of niacin, but isolate its downside," he said.

That might not be as simple as it sounds, however. Other studies suggest that enhancing niacin's ability to boost HDL may be more complex than what appears at, well, first

blush.

"GPR109A receptors are most often found in fat, the spleen, adrenal glands and lungs – they are absent from the liver and intestines, where most HDL is made and metabolized, so there may well be other mechanisms of action for the beneficial effects of niacin in addition to those performed by GPR109A," says Lefkowitz.

Lefkowitz is a scientific founder of Trevena, a company that is developing G protein coupled receptor-targeted drugs.

Public release date: 7-Apr-2009

Oral contraceptives associated with increased risk of lupus

Study found use of oral contraceptives was associated with an increased risk of SLE, particularly among women who had recently started taking them

The ratio of women to men with the autoimmune disease systemic lupus erythematosus (SLE) is nine to one and the incidence increases after puberty. Hormones secreted by the body are therefore believed to play an important role in the origins of the disease. A new large, population-based observational study found that the use of oral contraceptives was associated with an increased risk of SLE, particularly among women who had recently started taking them. The study was published in the April issue of *Arthritis Care & Research* (<http://www3.interscience.wiley.com/journal/77005015/home>).

Led by Dr. Samy Suissa of the Centre for Clinical Epidemiology at Jewish General Hospital of McGill University in Montreal, researchers obtained data on more than 1.7 million women ages 18-45 from the U.K. General Practice Research Database, which contains more than 6 million people. The women all had prescriptions for combined oral contraceptives (COCs) containing estrogen and progestogen. During an average of eight years of follow-up, 786 women had a first-time diagnosis of SLE. Each case was matched with up to 10 controls among women without SLE at the time of the case's diagnosis.

The results showed that the use of COCs was associated with a significant increased risk of newly diagnosed SLE. This was mostly limited to the first three months of use with first- and second-generation contraceptives containing higher doses of estrogen, suggesting "an acute effect in susceptible women and possibly a dose-response effect of estrogen on SLE onset," according to the authors. They note that estrogen can directly modulate the immune response, which could complete the action of some sex-linked genes and contribute to the genetic predisposition of the disease, and it has also been shown to have an effect on the breakdown of immune tolerance seen in SLE.

Previous studies on the risk of SLE following use of oral contraceptives have had conflicting results, but the results of the current study are consistent and complement those of the NIH-sponsored Nurses' Health Study. **"Our findings that longer-term use of contraceptives is associated with an increased risk of incident SLE (albeit of lower magnitude) and that current use of contraceptives with higher doses of ethinyl estradiol is associated with an increased risk of incident SLE, suggest a possible dose-response effect of estrogen on SLE onset, which** could be an alternative or additional mechanism to favor occurrence of the disease," the authors state. They note that the absence of significant increased risk in third-generation contraceptives may be related to the lower doses of estrogen compared to earlier generations.

Public release date: 8-Apr-2009

Soybean component reduces menopause effects

Soy aglycons of isoflavone (SAI), a group of soybean constituent chemicals, have been shown to promote health in a rat model of the menopause. The research, described in BioMed Central's open access journal Nutrition & Metabolism, shows how dietary supplementation with SAI lowers cholesterol, increases the anti-oxidative properties of the liver and prevents degeneration of the vaginal lining.

Robin Chiou led a team of researchers from National Chiayi University, Taiwan, who studied the effects of the dietary supplement on a group of female rats that had undergone ovary removal. He said, "These ovariectomized animals are a good model for study of the menopause as the loss of oestrogen from the ovaries mimics the natural reduction in oestrogen seen in menopausal women. SAI itself has weak oestrogenic properties and we've shown here that menopause-related syndromes can be prevented or improved by dietary supplementation with the compounds it contains".

In comparison to control animals, the authors found that the ovariectomized rats fed a diet enriched with SAI showed increased liver antioxidative activities and improved lipid profiles. Levels of harmful LDL cholesterol were reduced, while beneficial HDL cholesterol was increased. According to Chiou, "It is generally agreed that the higher HDL and the lower LDL concentrations are of benefit in chemoprevention of cardiovascular diseases. Our findings support the indication that soybean consumption may prevent coronary heart disease".

The authors hope that dietary soy supplementation may provide an alternative to hormone replacement therapy (HRT), which has been linked to the development of uterus and breast cancers.

Public Release: 8-Apr-2009

Vitamin D Deficiency Related to Increased Inflammation in Healthy Women, MU Study Finds

COLUMBIA, Mo. - According to a recent study in the Archives of Internal Medicine, 75 percent of Americans do not get enough Vitamin D. Researchers have found that the deficiency may negatively impact immune function and cardiovascular health and increase cancer risk. Now, a University of Missouri nutritional sciences researcher has found that vitamin D deficiency is associated with inflammation, a negative response of the immune system, in healthy women.

Increased concentrations of serum TNF- α , an inflammatory marker, were found in women who had insufficient vitamin D levels. This study is the first to find an inverse relationship between vitamin D levels and concentrations of TNF- α in a healthy, non-diseased population. This may explain the vitamin's role in the prevention and treatment of inflammatory diseases, including heart disease, multiple sclerosis and rheumatoid arthritis.

"The findings reveal that low vitamin D levels negatively impact inflammation and immune response, even in healthy women," said Catherine Peterson, assistant professor in the MU College of Human Environmental Sciences. "Increased inflammation normally is found in people with obesity or chronic diseases; a small decrease in vitamin D levels may aggravate symptoms in people who are sick."

The results support the need to re-examine the biological basis for determining the dietary reference intake (DRI) of vitamin D, Peterson said. The Institute of Medicine's DRI for vitamin D is 200 IU for people age 50 and younger and 400 IU for people 50 to 70 years old. The guidelines, created in 1997, are being revised to reflect new research, and Peterson is confident the DRI will be increased.

"Adequate vitamin D levels identified in this study are consistent with recent research that suggests the DRI should be increased," Peterson said. "To improve vitamin D status and achieve its related health benefits, most people should get at least 1000 IU of vitamin D per day. Sunlight is a readily-available, free source of vitamin D. Exposing 25 percent of the skin's surface area to 10 minutes of sunlight three days per week will maintain adequate levels in the majority of people; however, people with darkly-pigmented skin need more. Only a few foods contain vitamin D naturally, such as fatty fish; other sources are dietary supplements and vitamin-D-fortified foods, including milk and orange juice."

In future studies, Peterson will determine the effectiveness of Vitamin D in reducing disease symptoms and reducing blood glucose levels in diabetics. The study, "Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH) D concentrations in healthy women," was published in the July, 2008 issue of the Journal of Inflammation.

Public release date: 8-Apr-2009

Parkinson's disease medication triggers destructive behaviors

Mayo Clinic study identifies at-risk patients

ROCHESTER, Minn. -- A new study conducted at Mayo Clinic reports that one in six patients receiving therapeutic doses of certain drugs for Parkinson's disease develops new-onset, potentially destructive behaviors, notably compulsive gambling or hypersexuality.

VIDEO ALERT: Additional audio and video resources including excerpts from an interview with Dr. J. Michael Bostwick describing the research, are available on the Mayo Clinic News Blog.

The study extends findings from two Mayo case series published in 2005 that reported a connection between dopamine agonist medications and compulsive gambling or hypersexuality.

Dopamine agonists are a class of drugs that include pramipexole and ropinirole. They are commonly used to treat Parkinson's disease, but low doses also are used for restless legs syndrome. They uniquely stimulate brain limbic circuits, which are thought to be fundamental substrates for emotional, reward and hedonistic behaviors.

"The 2005 case series alerted us that something bad was happening to some unfortunate people. This study was done to assess the likelihood that this effect would happen to the average Parkinson's patient treated with these agents," says J. Michael Bostwick, M.D., Mayo Clinic psychiatrist who spearheaded the new study. It is published in the April issue of Mayo Clinic Proceedings.

The researchers analyzed the medical records of patients with Parkinson's disease residing in counties surrounding Rochester, Minn., who received their primary neurological care at Mayo Clinic in Rochester between 2004 and 2006. This group included 267 patients. Of those, 66 were taking dopamine agonists for their Parkinson's disease. Of those 66, 38 were taking the drugs in therapeutic doses (doses expected to be at least minimally beneficial).

The findings were definitive. Seven patients experiencing new-onset compulsive gambling or hypersexuality were taking dopamine agonists in therapeutic doses. None of the other Parkinson's disease patients developed compulsive gambling habits or hypersexuality, including the 28 patients on subtherapeutic dopamine agonist doses or the other 201 patients not taking dopamine agonists. None of the 178 patients treated only with the standard drug for Parkinson's disease, carbidopa/levodopa, developed these behaviors.

"It is crucial for clinicians prescribing dopamine agonists to apprise patients as well as their spouses or partners about this potential side effect. The onset can be insidious and overlooked until life-altering problems develop," says J. Eric Ahlskog, M.D., Ph.D., Mayo Clinic neurologist who co-authored and treated many of the patients in the 2005 study. "It also is worth noting that the affected patients were all taking therapeutic doses. Very low doses, such as those used to treat restless legs syndrome, carry much less risk."

"For some patients, a reduction in the dose of the dopamine agonist may prove to be sufficient treatment," says Dr. Ahlskog, "although total elimination of the offending drug is often necessary."

Public release date: 13-Apr-2009

Aspirin and similar drugs may be associated with brain microbleeds in older adults

Individuals who take aspirin or other medications that prevent blood clotting by inhibiting the accumulation of platelets appear more likely to have tiny, asymptomatic areas of bleeding in the brain, according to a report posted online today that will appear in the June print issue of Archives of Neurology, one of the JAMA/Archives journals.

Cerebral microbleeds—small deposits of the iron-storing protein hemosiderin in the brain—may be a sign of cerebral small-vessel disease, according to background information in the article. This condition, common among older adults, occurs when the walls of blood vessels in the brain become weakened. When microbleeds occur in certain brain areas, they may indicate a type of small vessel disease known as cerebral amyloid angiopathy, in which the accumulation of amyloid (a protein often related to Alzheimer's disease) causes degeneration of smooth muscle cells and increases the susceptibility of blood vessels to ruptures and hemorrhages.

Meike W. Vernooij, M.D., and colleagues at Erasmus MC University Medical Center, Rotterdam, the Netherlands, investigated the relationship between cerebral microbleeds and the use of anti-clotting medications in 1,062 individuals without dementia involved in the Rotterdam Scan Study. Participants (average age 69.6) underwent magnetic resonance imaging examinations in 2005 and 2006. Pharmacy records were used to assess whether any of the individuals took anti-clotting drugs. These included aspirin and carbasalate calcium—called platelet aggregation inhibitors because they prevent the accumulation of platelets that form blood clots.

In the years before MRI, 363 (34.2 percent) of the participants had used any anti-clotting drugs, including 245 (23.1 percent) who took platelet aggregation inhibitors (67 taking aspirin and 141 taking carbasalate calcium). **Compared with patients who did not use anti-clotting drugs, those who took aspirin or carbasalate calcium were more likely to have cerebral microbleeds visible on MRI.**

This association was particularly strong among individuals taking these drugs at higher doses, typically used to treat or prevent heart disease. Microbleeds in the frontal lobe were more common among aspirin users than carbasalate calcium users. There was no association between other types of anti-clotting drugs and cerebral microbleeds.

"There is currently major interest in bleeding risks with the use of antithrombotic or thrombolytic treatment in persons who have microbleeds that are apparent on MRI because this may affect treatment in patients with cardiovascular or cerebrovascular disease," the authors write. "The cross-sectional design of our analyses prohibited an investigation of whether persons with cerebral microbleeds are at increased risk for symptomatic hemorrhage [excessive bleeding] when using platelet aggregation inhibitors."

The beneficial effects of anti-clotting drugs for individuals at risk for heart attack and stroke typically outweigh any risks of bleeding, they note. "Nevertheless, it may be that in selected persons (e.g., those with signs of cerebral amyloid angiopathy), this risk-benefit ratio may differ for certain drugs (e.g., aspirin), thus influencing treatment decision," they conclude.

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The new 'epigenetics:' Poor nutrition in the womb causes permanent genetic changes in the offspring

New research study in the FASEB Journal explains how poor maternal nutrition passes health risk across generations

The new science of epigenetics explains how genes can be modified by the environment, and a prime result of epigenetic inquiry has just been published online in The FASEB Journal (<http://www.fasebj.org>): You are what your mother did not eat during pregnancy. In the research report, scientists from the University of Utah show that rat fetuses receiving poor nutrition in the womb become genetically primed to be born into an environment lacking proper nutrition. As a result of this genetic adaptation, the rats were likely to grow to smaller sizes than their normal counterparts. At the same time, they were also at higher risk for a host of health problems throughout their lives, such as diabetes, growth retardation, cardiovascular disease, obesity, and neurodevelopmental delays, among others. Although the study involved rats, the genes and cellular mechanisms involved are the same as those in humans.

"Our study emphasizes that maternal–fetal health influences multiple healthcare issues across generations," said Robert Lane, professor of pediatric neonatology at the University of Utah, and one of the senior researchers involved in the study. "To reduce adult diseases such as diabetes, obesity, and cardiovascular disease, we need to understand how the maternal–fetal environment influences the health of offspring."

The scientists made this discovery through experiments involving two groups of rats. The

first group was normal. The second group had the delivery of nutrients from their mothers' placentas restricted in a way that is equivalent to preeclampsia. The rats were examined right after birth and again at 21 days (21 days is essentially a preadolescent rat) to measure the amount of a protein, called IGF-1, that promotes normal development and growth in rats and humans. They found that the lack of nutrients caused the gene responsible for IGF-1 to significantly reduce the amount of IGF-1 produced in the body before and after birth.

"The new 'epigenetics' has taught us how nature is changed by nurture," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. "The jury's in and, yes, expectant moms really are eating for two. This study shows not only that we need to address problems such as preeclampsia during pregnancy, but also that prenatal care is far more important than anyone could have imagined a decade ago."

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Low glycemic breakfast may increase benefits of working out

The benefits of physical activity and a balanced diet are well documented and form the basis of many public health recommendations. This is because each of these factors can independently influence risks for many chronic diseases such as obesity, type 2 diabetes, and some forms of cancer. Some research also suggests that exercise and diet interact to influence health. For instance, exercising after short-term fasting (such as before breakfast) may increase the amount of fat burned. Similarly, consumption of a meal eliciting a low blood glucose response prior to exercise may also boost the use of body fat (instead of glucose). However, most of these studies have used either trained athletes or recreational exercisers, and none has looked at effects of the type of pre-exercise meal on metabolism during and after exercise. To better understand the effects of pre-exercise meal composition on fat metabolism in more typical (sedentary) individuals, a group of researchers headed by Dr. Emma Stevenson at the University of Nottingham conducted a controlled human intervention trial. The results of their study are published in the May 2009 issue of The Journal of Nutrition.

As expected, blood glucose concentrations were higher after the HGI than the LGI meals and had returned to baseline levels by the time exercise was commenced, after which they were not influenced by breakfast type. Plasma free fatty acids (FFA; a marker for adipose oxidation) fell after consumption of both HGI and LGI breakfasts, but began to rise at ~2 h post-breakfast in the LGI (but not HGI) treatment. Exercise caused a rapid increase in FFA in both groups, but this was higher in the LGI trial compared to the HGI trial ($P < 0.001$). Circulating concentrations of FFA were not different between treatments following lunch. Overall, fat oxidation was higher in the LGI treatment than in the HGI treatment ($P < 0.05$) during the post-breakfast and exercise periods. Following lunch, fullness scores were higher in the LGI trial than in the HGI trial ($P < 0.05$). The authors concluded that consuming a LGI breakfast increases fat oxidation during subsequent exercise and improved satiety during recovery in sedentary females. As such, individuals trying to shed fat may consider choosing LGI foods eaten prior to when they exercise.

**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.**