## GUMC study may help explain 'awakenings' that occur with popular sleep-aid Ambien

Washington, DC -- Some people who take the fast-acting sleep-aid zolpidem (Ambien) have been observed walking, eating, talking on the phone and even driving while not fully awake. Many often don't remember doing any of these activities the next morning. Similarly, this drug has been shown to awaken the minimally conscious into a conscious state. A new study by Georgetown University Medical Center (GUMC) researchers may help explain why these "awakenings" occur.

The study, published online in the Proceedings of the National Academy of Sciences Monday, suggests that while some powerful brain circuits are shut down with zolpidem, the powerful sedative activates other circuits when deprived of activity.

"Brain cells or neurons are highly reactive to incoming activity throughout life," explains Molly M. Huntsman, an assistant professor in the department of pharmacology at Georgetown University Medical Center and corresponding author for the study. "When brain activity is silenced, many neurons automatically react to this change. We see this in our study which suggests that inhibitory neurons responsible for stopping neural activity are themselves shut down by zolpidem. The excitatory neurons, responsible for transmitting activity, are then allowed to re-awaken and become active again, without monitoring because the inhibitory neurons are 'asleep'."

Rodents are especially dependent upon their whiskers to explore their environment; for the study, researchers trimmed the whiskers of mice (while under anesthesia). They then studied the region of the brain responsive to whisker movements to examine activity-dependent brain circuits. After removing the whiskers and depriving neural activity, the inhibitory neurons that normally don't respond to sedation by zolpidem underwent a change, becoming more sensitive. The researchers posited that these neurons are shut down and, in turn, not able to monitor other brain circuits.

"This was really unexpected. It appears the receptors on some inhibitory neurons were changed and were able to be inhibited by zolpidem, preventing them from performing their normal functions. We merely wanted to use zolpidem as a tool to examine which type of functional inhibitory receptor is expressed in certain neurons. Yet it turns out that sensory deprivation in the form of whisker trimming is enough to alter the receptor composition expressed in these cells." Huntsman says.

Researchers say that while the study suggests that zolpidem shuts down active neural pathways and perhaps then triggers others, the activation of this trigger is unknown.

"Nevertheless, the paradoxical activation of brain circuits by a powerful sedative definitely needs more attention in additional studies both human and in animal models," Huntsman concludes.

*Other authors of the paper include Peijun Li of GUMC and Uwe Rudolph of McLean Hospital, a Harvard Medical School affiliate. The authors report no related financial interests.*

*This work was funded by a grant from the National Institutes of Health.*

## Magic ingredient in breast milk protects babies' intestines

Scientists at Queen Mary, University of London have discovered that an ingredient in human breast milk protects and repairs the delicate intestines of newborn babies. The ingredient called pancreatic secretory trypsin inhibitor, or PSTI, is found at its highest levels in colostrum - the milk produced in the first few days after birth.

The lining of a newborn's gut is particularly vulnerable to damage as it has never been exposed to food or drink. The new study* highlights the importance of breastfeeding in the first few days after the birth.

The researchers found small amounts of PSTI in all the samples of breast milk they tested but it was seven times more concentrated in colostrum samples. The ingredient was not found in formula milk.

The researchers examined the effects of PSTI on human intestinal cells in the lab. When they inflicted damage to the cells they found that PSTI stimulated the cells to move across the damaged area forming a natural protective 'plaster'. They also found that PSTI could prevent further damage by stopping the cells of the intestine from self-destructing. Additional research suggests that PSTI could reduce damage by 75 per cent.

PSTI is a molecule which is normally found in the pancreas where it protects the organ from being damaged by the digestive enzymes it produces. Research suggests that it plays a similar protective role in the gut.

The team at Queen Mary have also found that PSTI is produced in the breast but until now they did not know exactly why.

Professor Ray Playford of Barts and the London School of Medicine and Dentistry, part of Queen Mary, University of London led the study. He said: "We know that breast milk is made up of a host of different ingredients and we also know that there are a number of health benefits for babies who are breast-fed.

"This study is important because it shows that a component of breast milk protects and repairs the babies delicate intestines in readiness for the onslaught of all the food and drink that are to come.

"It reinforces the benefits of breast feeding, especially in the first few days after birth."

***Note to editors*** **Pancreatic secretory trypsin inhibitor is a major motogenic and protective factor in human breast milk, Marchbank et al, Am J Physiol Gastrointest Liver Physiol 296: G697-G703, 2009*

## Ovarian transplantation: First baby is born after a new technique

Amsterdam, The Netherlands: A new technique for transplanting the ovaries of women who have lost their fertility as a result of cancer treatment was outlined to the 25th annual conference of the European Society of Human Reproduction and Embryology today (Monday 29 June). Dr. Pascal Piver, manager of the IVF Centre at Limoges University Hospital, Limoges, France, described a new, two-step method of ovarian transplant that has produced excellent results in women whose ovaries have been frozen because of cancer treatment. He said that his team's technique worked to restore ovarian function quickly and already one patient from his clinic had had a baby and another had become pregnant.

"On June 22, a baby girl was born to a mother who had been menopausal for two years as a result of treatment for sickle cell anaemia. After transplanting her own ovarian tissue she started ovulating in four months and became pregnant naturally six months after transplantation. Both mother and baby are doing well", he said.

Dr. Piver and colleagues set out to tackle one of the biggest problems of ovarian transplantation: the low response to stimulation caused by insufficient vascularisation of the transplanted tissue.

"In order for a woman to become pregnant, the ovaries need to be responsive to the action of hormones that cause them to release eggs each month," he explained. "If the blood supply to the ovaries is insufficient, this will not happen, even though the transplant may look as though it has been successful."

To overcome this problem they carried out a two-stage procedure, first grafting small pieces of the frozen ovarian tissue in the ovarian and peritoneal areas three days before the real transplant. The first graft encourages the growth of blood vessels and paves the way for the ovary to become fully functioning in a shorter time scale than would be possible if all the tissue were to be transplanted at the same time.

The researchers have so far utilised this technique with two patients who had been treated for cancer and had their ovaries frozen. In addition to the first patient, treated for sickle cell anaemia, the second patient had been treated for periarteritis nodosa, an inflammation of medium-sized arteries, which become swollen and damaged from attack by rogue immune cells.

"She suffered menopause for eight and a half years before transplantation," said Dr. Piver. "But after transplanting half of the frozen ovary, she recovered spontaneous ovulation in four months. Her right fallopian tube had been destroyed by the ovarian retrieval, and the function of the ovary and hence the chances of pregnancy are limited in time. Hence we decided to collect the highest number of eggs we could, and carry out an IVF procedure on this patient.

"Six months after the operation, we transferred two blastocysts. A total of 22 oocytes were retrieved and produced 16 embryos, which in turn produced seven blastocysts. Unfortunately the first time round this patient developed an ectopic pregnancy, but she is now pregnant again."

The technique was developed by Dr. Piver and his team, he told the conference. "This is the first time that a pregnancy has been obtained after a ten year gap between ovarian cryopreservation and grafting. We believe that it represents a considerable advance on the methods of ovarian transplantation used until now, not least because we are able to obtain large numbers of oocytes. We hope that it will enable more young patients who have been cured of cancer to regain their reproductive health and become pregnant with their own children," he said.

## 4 out of 106 heart replacement valves from pig hearts failed

Pig heart valves used to replace defective aortic valves in human patients failed much earlier and more often than expected, says a report from cardiac surgeons at Washington University School of Medicine in St. Louis. This is the first report to demonstrate this potential problem, the researchers say.

Between 2001 and 2005, four out of 106 patients with the pig valves implanted in the aortic position developed severe impairment after less than four years, and the patients required surgery to replace the valves. The findings are published in the June issue of the Journal of Thoracic and Cardiovascular Surgery.

Lead author Jennifer S. Lawton, M.D., a Washington University cardiothoracic surgeon at Barnes-Jewish Hospital, notes that the valves are expected to last 10 to 15 years in patients over 70. All four patients who needed a "redo" operation were over 70.

"We noticed an increased incidence of this complication," says Lawton, associate professor of surgery. "We were very concerned, and we believe it is important for others to know about it. A four percent failure rate may not sound like a lot, but we would not expect that many of the valves to fail in such a short period of time."

In the four patients affected, the pig valves failed after 3, 14, 19 and 44 months. Each patient underwent a second operation to replace the defective valve with a valve made from cow heart tissue. No patient died as a direct consequence of the pig heart valve impairment.

The pig heart valves that failed early were Medtronic Mosaic porcine valves produced by Medtronic Inc. The company indicated that the four valves that failed were not from the same production lot, the researchers report.

Pathologists at the University and at the valve manufacturer examined the failed pig heart valves. The valves' leaflets had thickened and stiffened making them much less mobile than normal, which would interfere with blood leaving the heart through the aorta. The leaflets were covered with numerous bumps, but the exact nature of these tissue growths couldn't be determined. No specific cause for the valve failure was identified. The cause of early valve failure, whether it is related to patient factors or valve factors, remains unclear, the researchers say.

Estimates are that one in eight people age 75 or older in the United States have at least moderate heart valve disease, and more than 100,000 heart valve procedures are performed each year. These include procedures to either repair defective heart valves or replace them with mechanical valves or with tissue replacement valves - usually pig heart valves or valves formed from the pericardial sac of cow hearts. In general, mechanical valves tend to last longer than tissue valves, but patients who receive them have an increased risk of blood clots and must take anticoagulants.

"After valve replacement surgery, patients typically get an echocardiogram to check valve structure at three, six and twelve months and then yearly after that," Lawton says. "If symptoms such as shortness of breath, chest pain or lightheadedness occur, more frequent exams may be conducted. If patients have had a pig valve implanted, I would tell them that most likely they will be fine, but if they have symptoms they need to see their cardiologist and get an echocardiogram."

Lawton first realized there might be a problem when one of her patients developed symptoms of valve impairment and needed a new valve after about a year. That prompted her to examine the records to see if other such cases had occurred.

Cardiovascular surgeons prefer not to operate again on these patients soon after their first replacement surgery because redo operations are more difficult. Patients also often have atrial fibrillation, a history of coronary artery disease and are elderly.

"At Barnes-Jewish Hospital and Washington University, we are no longer implanting this valve, and we are waiting for further data about it," Lawton says. "We have alternatives available for our patients."

*Lawton JS, Moazami N, Pasque MK, Moon MR, Damiano RJ. Early stenosis of Medtronic Mosaic porcine valves in the aortic position. Journal of Thoracic and Cardiovascular Surgery. 2009 Jun;137(6):1556-7.*

*This study received no external funding. Ralph J. Damiano Jr. is a consultant for Medtronic Inc.*

## Physios recommend a healthy dose of gaming

* 30 June 2009 **by Jim Giles**

BOB ROHRMAN has never had much time for computer games. He was given a console a year ago, but stopped using it after a few weeks. It's not surprising: Rohrman is 67 and suffers from tremors caused by Parkinson's disease. "The only thing I knew how to play was solitaire," he says.

But in January, Rohrman got gaming again, thanks to Ben Herz, an occupational therapist at the Medical College of Georgia in Augusta. Herz had the retired truck driver play sports games on the Nintendo Wii, a console controlled by a hand-held wand that detects movement and gestures. In tennis games, for example, players swing this "Wiimote" as they would a racket. That meant Rohrman was getting a regular workout.

After playing 3 hours a week for about a month, he claimed he was a changed man. "I can move better, walk better, coordinate better," he said.

The benefits of exercise are well known, but active console games have several advantages over traditional workouts. Video games are designed to be engaging but not too challenging - players should spend most of their time in the sweet spot between too easy and too hard. And unlike jogging or swing-ball, video games can be played in the living room, where bulging waistlines and appalling skill levels can be kept safely from public view.

Now physical therapists are starting to think that devices like the Wii, which are relatively cheap and come with addictive games, can help patients fight disease and speed rehabilitation. There have not been any large-scale trials of the consoles, but several published case studies suggest that the technology has big therapeutic potential. "It's transforming the kind of interactions patients can have with a computer," says Bob Hone, a software engineer who has developed Wii applications to help people with Parkinson's.

Herz has begun to assemble the data that could prove the idea. In a study of about 20 subjects, he has showed that playing bowling, tennis and baseball games improved the performance of people with Parkinson's on a range of physical tests, such as the ability to stand up and walk a short distance. The participants also got a boost to their mental health: about three-quarters showed at least a 10 per cent improvement on a standard assessment for depression.

This effect may be due to changes in levels of the brain chemical dopamine. Parkinson's disease is caused by a lack of the chemical, and both exercise and computer games have been shown to increase levels. "My hope is that this will slow the progression of the disease," says Herz, who presented his results at the Games for Health conference in Boston this month.

Other researchers are modifying games in a bid to expand the range of patients who can be helped. Jacob Vogelstein at Johns Hopkins University in Baltimore, Maryland, and Jonathan Kuniholm of Duke University in Durham, North Carolina, are developing a new kind of prosthetic limb. Many hand amputees retain muscle function in their forearms, and Vogelstein's prosthetics can be controlled by the electrical signals generated by these muscles. But these artificial limbs are not due for completion until 2010, so he needed a way of keeping his patients' muscles from atrophying in the meantime.

The solution: a hacked controller from Guitar Hero, a game that challenges players to tap out a melody using five buttons on the neck of a mock guitar. Vogelstein modified the device so that it could be driven by signals picked up by electrodes placed on the arms of amputees instead. The same signals will be used to control the prosthetic limb. Guitar Hero is more compelling than any "gimmicky rehab game", says Vogelstein, and amputees quickly learn how to use the modified controller.

Promising case studies abound, but the field is still short on hard evidence. Herz, Hone and Vogelstein are all planning large-scale clinical trials, but no game has undergone rigorous testing yet. As a result, almost nothing is known about how long patients should play for, or which types of game bring the most benefit.

Boredom with the games may also be an issue. In 2005, Brock Dubbels at the University of Minnesota in Minneapolis started studying the potential fitness benefits of Dance Dance Revolution, a game in which players copy on-screen dance moves on a touch-sensitive mat. He could not get enough children to play regularly enough to produce meaningful results.

These questions will be addressed in upcoming clinical trials, but Rohrman is not waiting on the results. His Wii console is no longer mothballed: "When I saw what it could do for me, I thought I should stick with it."

**Whole-body gaming**

The gaming industry sat up this month as Microsoft unveiled Project Natal - a device that turns a player's body into a game controller. Two cameras monitor the player and map their movements onto an on-screen avatar. In a demonstration at the E3 gaming conference, held in Los Angeles, a player kicked and batted virtual balls as they bounced towards her virtual self.

It is not just the gaming community that is hanging on the release date for this new device. Software engineer Bob Hone of Red Hill Studios in Larkspur, California, says that Project Natal could be used to help Parkinson's patients with their balance. He imagines a game in which players assume different poses and receive real-time feedback from the console as they close in on their target position.

And there is certainly more to come. The video games market is intensely competitive and Microsoft's announcement is in part a response to Nintendo's successful "Wiimote" controller. If Project Natal is a hit, Nintendo and Sony will aim to make even more sophisticated controllers. Since console makers sell new controllers relatively cheaply, they are always within reach of physical therapists and their patients. So every new launch brings with it a potential therapeutic benefit. "We're just at the beginning," says Hone.

## Researchers Find a Way to Reduce Patient Radiation Dose During Pulmonary CT Angiography

While screening for possible pulmonary emboli using pulmonary CT angiography, a new study shows that radiologists can effectively lower the patient radiation dose by approximately 44% and improve vascular enhancement without deterioration of image quality, according to a study performed at Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

A total of 400 patients believed to have a pulmonary embolism were evaluated using pulmonary CT angiography. Two hundred patients were evaluated using the standard peak kilovoltage setting of 130 or 120 kVp and the other 200 patients were evaluated using a low peak kilovoltage setting of 110 or 100 kVp. "Results showed that lowering the peak kilovoltage setting by 20-kVp lead to superior vascular enhancement without deterioration of image quality - allowing us to effectively reduce the patient radiation dose," said Shin Matsuoka, MD, lead author of the study.

"CT has become an essential tool for the diagnosis of pulmonary embolism. However because of the high percentage of negative results, radiation exposure has become an important issue. Our study shows that lowering the kilovoltage setting may be an effective method of lowering the radiation dose for most patients," he said. Lowering the kilovoltage setting is something that could be easily incorporated into daily clinical practice because there is no additional equipment needed and there are no extra costs," said Dr. Matsuoka.

*This study appears in the June issue of the American Journal of Roentgenology. For a copy of the full study, please contact Heather Curry via email at hcurry@arrs.org.*

**Really?**

## The Claim: Drinking Tea Can Lower Your Levels of Iron

**By ANAHAD O'CONNOR**

**Leif Parsons**

**THE FACTS** With its bounty of antioxidants and relatively moderate levels of caffeine, tea is one of the healthiest beverages around. But drinking tea is said to block the body's absorption of dietary iron, potentially causing a deficiency.

Studies have shown that there is some truth to the idea. Compounds in tea called tannins can act as chelators, binding to minerals and inhibiting the body's ability to absorb them. Although that can reduce a person's levels of iron, studies have also found that it is unlikely to have much of an impact.

In one study, scientists examined the effect by having people eat a typical meal - a hamburger, string beans and mashed potatoes - and then measuring their iron levels after the meal was combined with various drinks. When the subjects ate the meal with tea, there was a 62 percent reduction in iron absorption. Drinking coffee resulted in a 35 percent reduction. Orange juice increased iron absorption by about 85 percent.

But there was a twist. Coffee and tea affected only the levels of non-heme iron, the kind found in grains and vegetables. Heme iron, found in meat, fish and poultry, was unaffected.

Because most Americans generally get more iron from their diets than needed, a daily cup or two of coffee or tea is unlikely to lead to low levels of iron.

**THE BOTTOM LINE** Compounds in coffee and tea can affect iron absorption.

**Personal Health**

## The Damage of Reflux (Bile, Not Acid)

**By JANE E. BRODY**

In describing an instance of intense anger, you might say, as a figure of speech, that bile rose in your throat. But for some people bile does indeed rise, perhaps not as far as the throat but far enough to cause digestive distress and serious damage to the lining of the stomach and esophagus.

The symptoms are similar to heartburn, and many sufferers are told they have gastroesophageal reflux disease, known as acid reflux. Yet treatment with popular remedies for acid reflux, like the acid-suppressing proton-pump inhibitors Prilosec, Prevacid and Nexium, fails to work or gives only partial relief.

That's because acid reflux is, at most, only part of the problem. The main culprit is bile reflux, a back-up of digestive fluid that is supposed to remain in the small intestine, where it aids the digestion of fats.

Bile is not acid. It's an alkaline fluid consisting of bile salts, bile pigments, cholesterol and lecithin. It is produced by the liver, stored in the gallbladder and released intermittently into the duodenum, the upper part of the small intestine, when needed to digest fat. (Bile continues to be produced as a digestive aid even after the gallbladder is removed.)

Misdiagnosis of bile reflux and failure to control it can result in serious, sometimes life-threatening problems - stomach ulcers that bleed and Barrett's esophagus, a possible precursor to esophageal cancer. Yet misdiagnosis is common, and even when the condition is properly identified, doctors are often fatalistic about its management.

**'Shadow Land'**

Raymond Kozma of Staten Island said his wife, Lynne, 52, developed bile reflux after surgery to remove her gallbladder and had been "in constant daily pain" for the last two years.

"We have had doctors say everything from 'There's no such thing as bile reflux' to 'There's bile reflux but we can't do anything about it' to 'You just have to learn to live with the pain,' " Mr. Kozma wrote in an e-mail message. He urged me to write about the condition, saying that "thousands of suffering people live in a 'shadow land' because of the denial and disinterest of the medical profession" in bile reflux.

Although the condition is certainly not unknown, there is a relative lack of information on it in major medical journals read by nonspecialists. Mr. Kozma said his wife had now developed Barrett's esophagus and, instead of being offered treatment, was told to return in three years to have another endoscopic look at her damaged esophagus. "What are we supposed to do? Wait and see if this develops into cancer?"

No one with bile reflux needs to just wait for worse to come, although the remedies are not as simple and well known as they are for acid reflux. The condition usually can be managed with medications, but severe cases may require surgery.

**Symptoms and Causes**

Both acid reflux and bile reflux may afflict the same person, which can make diagnosis a challenge. But the stomach inflammation that results from bile reflux often causes a burning or gnawing pain in the upper abdomen that is not felt with acid reflux, according to experts at the Mayo Clinic. Other symptoms of bile reflux may include frequent heartburn (the main symptom of acid reflux), nausea, vomiting bile, sometimes a cough or hoarseness and unintended weight loss.

A brief anatomy lesson makes the problem easier to understand. The main organs of the digestive tract are separated by valvelike tissues that, when functioning properly, allow food and digestive fluids to pass in only one direction: down. Thus, as food and liquids pass through the digestive process, they normally travel from the mouth to the throat, then down the esophagus into the stomach, and finally into the small intestine. The opening between the esophagus and stomach, a muscular ring called the lower esophageal sphincter, is meant to keep stomach acid from backing up. When it malfunctions, acid reflux - chronic heartburn - is the usual result.

Likewise, the pyloric valve, the muscular ring between the stomach and small intestine, is supposed to open just enough to permit a fraction of an ounce of liquefied food to pass into the small intestine, but not enough to allow bile to back up into the stomach. When this valve fails to close properly, refluxed bile can cause gastritis, an irritation and inflammation of the stomach lining. Untreated, that can result in a bleeding ulcer or even stomach cancer.

If the esophageal sphincter malfunctions at the same time, or there is a build-up of pressure in the stomach, bile and acid can reach the lower portion of the esophagus, inflaming the delicate lining of this organ. If the problem persists, it can cause scarring that narrows the esophagus, which may result in choking, or the cellular abnormality called Barrett's esophagus, which can become precancerous and eventually develop into cancer that is nearly always fatal.

Gastroenterologists have recently demonstrated that Barrett's esophagus can often be effectively treated with radiofrequency therapy, which might help patients like Mrs. Kozma.

Bile reflux can occur as a complication of certain surgeries, like the gallbladder surgery Mrs. Kozma underwent. More often, though, damage to the pyloric valve results from gastric surgery - total removal of the stomach or the gastric bypass operation used to treat morbid obesity.

Occasionally, the pyloric valve is obstructed by a peptic ulcer, for example, or scar tissue, which prevents the valve from opening enough to permit quick transport of stomach contents into the intestine. That causes pressure to build up in the stomach, pushing both acid and bile into the esophagus.

**Diagnosis and Treatment**

The main diagnostic tests include an endoscopic examination of the esophagus and stomach to check for inflammation or ulceration; a test to check for acid in the esophagus (this would be negative if bile reflux is the only problem), and a test to determine if gas or liquids reflux into the esophagus.

A medication called ursodeoxycholic acid can be prescribed to promote the flow of bile and reduce the symptoms and pain of bile reflux. Other drugs might be used to speed the rate at which food leaves the stomach.

Surgery is a treatment of last resort, used if nothing else reduces severe symptoms of bile reflux or when the esophagus develops precancerous changes. The most common operation, called Roux-en-Y surgery, involves creation of a new connection to the small intestine to keep bile away from the stomach.

If acid reflux is also a problem, treatment with a proton-pump inhibitor should help, as should nonmedical remedies including weight loss; limiting high-fat foods and alcohol; avoiding carbonated and acidic beverages, spicy foods, onions, vinegar, chocolate and mint; eating small meals; practicing stress-reducing techniques like meditation or exercise; not eating within two to three hours of bedtime; and sleeping with the upper body and head elevated.

**Global Update**

## Drug-Resistant Flu Strain Turns Up in Denmark but Doesn't Last Long

**By DONALD G. McNEIL Jr.**

The first case of swine flu resistant to the antiviral drug Tamiflu has been found in Denmark, according to Danish health officials. The patient appears to have recovered without infecting anyone else, and experts said the recent history of Tamiflu resistance made it unlikely that the short-lived Danish strain would have been good at spreading to others.

An executive of Roche, the Swiss maker of Tamiflu, held a telephone news conference to describe the progress of the Danish patient, who apparently developed the resistant strain while being protectively treated with a low Tamiflu dose because a close contact had the swine flu. Doctors switched treatment to a different but related drug, Relenza, and the patient recovered.

In the past, Tamiflu-resistant strains of the seasonal flu have been found in Japan, which has used more than half the world's supply of the drug each year. But those strains were weak and did not spread. A Tamiflu-resistant strain of the H5N1 bird flu was also isolated from a Vietnamese patient being treated with low-dose Tamiflu in 2005, but it also died out.

Tamiflu resistance that did spread in seasonal flu emerged last year from a spontaneous mutation known as H274Y on the N gene. The mutant strain dominated the seasonal H1N1 flu during the past flu season in the United States, before swine flu was discovered in Mexico.

Virologists fear swine flu will soon pick up resistance by merging with seasonal H1N1 flu, perhaps in the Southern Hemisphere, where the flu season is just beginning.

## Risk of tuberculosis from arthritis medication examined

***Research news from Arthritis & Rheumatism***

Treatment with anti-tumor necrosis factor (TNF) agents is recognized as a risk factor for tuberculosis (TB) in patients with immune-mediated inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, psoriatic arthritis and psoriasis. Most TB cases develop as a result of reactivation of a latent TB infection, and health authorities worldwide recommend screening for latent TB and treating patients before initiating anti-TNF treatment. A new study examined cases of TB associated with anti-TNF therapy and found that the risk of TB is higher for patients receiving anti-TNF monoclonal antibody therapy (infliximab or adalimumab) than for those receiving soluble TNF receptor therapy (etanercept). The study is published in the July issue of Arthritis & Rheumatism (http://www3.interscience.wiley.com/journal/76509746/home).

Led by Xavier Mariette of the Université Paris-Sud, researchers set up a national registry in France to collect all cases of TB occurring during a three-year period in patients receiving anti-TNF therapy for any reason. Researchers collected data on 69 cases of TB, assessing risk factors for TB before anti-TNF therapy began and anti-TNF treatment history.

The results showed that the risk of TB for patients receiving anti-TNF therapy compared with the French population differed depending on the anti-TNF agent used; those receiving monoclonal anti-TNF therapy had a higher risk than those receiving sTNFR therapy. The risk of TB was higher during the first year of anti-TNF treatment, which favored the reactivation of latent TB. None of the patients who received correct prophylactic treatment for TB which is in France in most of the cases the association of INH and rifampicione for 3 months. Two thirds of TB cases occurred in patients with negative skin tests.

The authors note that other countries have set up registries to investigate the safety of anti-TNF agents, but TB rates were so low that it was difficult to discern a difference in risk between the different types of anti-TNF agents; the current study, however, clearly demonstrates this difference. This study examined TB cases in the entire French population and researchers were therefore able to collect many more cases. In addition, it is the only registry to collect safety data for patients receiving anti-TNF therapy for any indication.

The mechanism by which TNF antagonists reactivate latent TB is not fully understood, but the authors suggest that differences in the action of the two types of anti-TNF agents in specific T helper cells (which play an important role in maximizing the capabilities of the immune system) and T regulatory cells (which suppress activation of the immune system) may help explain the differences in the risk of TB that were observed. The authors conclude that the differences seen with the two types of anti-TNF treatment may also explain the better efficacy of monoclonal antibody therapy in certain diseases, such as Crohn's disease, sarcoidosis and uveitis.

*Article: "Risk of Tuberculosis Higher with Monoclonal Antibody Therapy Than with Anti-Soluble Tumor Necrosis Factor Receptor Therapy," F. Tubach, D. Salmon, P. Ravaud, Y. Allanore, P. Goupille, M. Bréban, B. Pallot-Prades, S. Pouplin, A. Sacchi, R.M. Chichemanian, S. Bretagne, D. Emilie, M. Lemann, O. Lorthololary, X. Mariette, Arthritis & Rheumatism, July 2009.*

**Observatory**

## When a Hybrid Takes Hold, the Outcome Can Be Bad

**By HENRY FOUNTAIN**

The ecological effects of invasive species are often well known, particularly their impact on native plants or animals. But the invaders sometimes make love as well as war: they mate with related local species, producing hybrids. And the effects of such hybridization have not been the subject of much study.

Now, research involving invasive and native salamanders in the Salinas Valley of California shows how devastating this can be: the hybrids have voracious appetites and can practically wipe out other species.

Maureen E. Ryan and Jarrett R. Johnson of the University of California, Davis, and Benjamin M. Fitzpatrick of the University of Tennessee studied hybrids

between native California tiger salamanders and barred tiger salamanders, brought in huge numbers from Texas beginning 60 years ago by California bait dealers. Tiger salamander larvae are high on a pond's food chain, gulping down larvae of other species with their big mouths.

The researchers built artificial ponds, stocked them with salamanders and other species, notably the California newt and the Pacific chorus frog (both of which are found in the Salinas Valley) and monitored what happened. Their findings appear in The Proceedings of the National Academy of Sciences.

Hybrid larvae had a greater effect on the newts and frogs than native salamander larvae did, nearly wiping them out. Hybrids even affected the survival of native salamanders in the ponds. "The implication is they're ecologically quite different than the native species," Ms. Ryan said. That could spell trouble for other "third-party" species in the valley, like the California red-legged frog and the Santa Cruz long-toed salamander.

**Observatory**

## Like Bats, Shrews Let Echoes Be Their Guide

**By HENRY FOUNTAIN**

Shrews are noisy little mammals, and among their vocalizations are faint high-pitched twittering sounds. Some research has suggested that shrews might use these sounds for echolocation - like bats, only simpler.

***Using vocalizations to find the way: a shrew operates in the moss.*** **iStockphoto**

Studying common and greater white-toothed shrews, Bjorn M. Siemers of the Max Planck Institute for Ornithology in Germany and colleagues reasoned that if the twittering was useful for echolocation, then it should vary based on the habitat. If the sounds were used only for communication, then the calls should vary based on whether other shrews were around.

Simulating the presence of other shrews, the researchers found no variation in the calls. But by altering the habitat - putting down increasingly thick layers of straw - they found that the calls increased. In field experiments, they played shrewlike sounds in shrew habitats like meadows and forest floors and found that they produced distinct echoes. The study appears in Biology Letters.

The findings suggest that the shrews may indeed use these calls for echolocation - sonically examining their surroundings and analyzing the reverberations to determine the nature of a particular location and how best to travel through it.

## Study Provides Greater Understanding of Lyme Disease-Causing Bacteria

Lyme disease in the U.S. is caused by the tick-borne bacteria Borrelia burgdorferi and usually begins with a skin lesion, after which the bacteria spread throughout the body to the nervous system, heart or joints. About 60 percent of untreated individuals develop arthritis, which affects the knees in particular. Lyme disease usually responds well to antibiotic therapy, but in rare cases arthritis can persist for months or years after treatment, a rare condition known as antibiotic-refractory Lyme arthritis. Joint fluid usually tests negative for B burgdorferi after treatment, indicating that joint inflammation may persist even after the bacteria has been eradicated.

Two genetic marker systems are used to correlate the variation of this bacterial strain with clinical outcomes: OspC typing divides B burgdorferi strains into 21 types, while the ribosomal RNA intergenic spacer type (RST) system divides them into just three groups, with certain RST groups corresponding uniquely to specific OspC types.

A new study led by Allen Steere of Massachusetts General Hospital and Harvard Medical School analyzed joint fluid samples from 124 patients with Lyme arthritis who were seen over a 30-year period. It identified B. burgdorferi strains in the joints of patients with Lyme arthritis and found that the genotype frequencies in joints reflected those in skin lesions. However, RST1 strains were the most frequent in patients with antibiotic-refractory arthritis. The study was published in the July issue of Arthritis & Rheumatism (http://www3.interscience.wiley.com/journal/76509746/home).

The researchers were able to identify 10 of the 16 B burgdorferi OspC types found in the northeastern U.S. and all three RST types in the joint fluid of patients with Lyme arthritis. Although it was only possible to determine B burgdorferi phenotypes in 40 percent of the samples, the researchers feel confident that the distribution reflects what has been observed in the skin because they were able to identify numerous OspC and RST types, and the distribution was similar to what has been reported in previous studies of skin lesions.

One might presume that the association of RST1 strains with antibiotic-refractory arthritis may reflect a greater ability of these strains to survive in the joint despite antibiotic therapy. However, this seems not to be

the case. Rather, RST1 strains seem to induce a more marked immune response, which may set the stage for joint inflammation that persists after antibiotic therapy in genetically susceptible individuals.

"We hypothesize that RST1 strains are more virulent, leading to larger numbers of organisms in blood, and more inflammation in joints," the authors state. They conclude that the results of this study "add to the emerging literature concerning the differential pathogenicity of strains of B burgdorferi."

***Article**: "Analysis of Borrelia burgdorferi Genotypes in Patients with Lyme Arthritis," Kathryn L. Jones, Gail A. McHugh, Lisa J. Glickstein, Allen C. Steere, Arthritis & Rheumatism, July 2009.*

## The genetic secrets of younger-looking skin

* 30 June 2009 **by Linda Geddes**

GENETIC analyses of human skin are revealing more about what makes us look old. As well as throwing up ways to smooth away wrinkles, the studies may provide a quantifiable way to test claims made for skin products.

In the past, cosmetics companies relied on subjective assessments of skin appearance, and changes in its thickness, colour and protein composition, to evaluate the effectiveness of their products and work out the quantities of ingredients needed to get the best results. "It was totally hit and miss," says Rosemary Osborne of Procter and Gamble in Cincinnati, Ohio.

Now skin researchers, including those at P&G, are starting to use DNA microarrays, common in the drugs industry, to measure the expression of thousands of genes in skin of different ages. "It's a way of finding mechanisms that were not known before," says Fernand Labrie, who studies skin genomics at Laval University in Quebec City, Canada.

P&G recently compared gene expression in skin samples from the buttocks and forearms of 10 young and 10 older women. In older skin, they found a decrease in the expression of genes involved in cholesterol and fatty acid synthesis. More surprisingly, the opposite was true for genes associated with inflammation and other components of the immune system, suggesting that the immune system may play a role in ageing.

In older skin there was an increase in the expression of genes associated with inflammation

Treating the older skin with niacinamide, which helps skin retain moisture, damped down expression of genes related to inflammation. "We believe that improving the barrier results in a 'resignalling' of key molecular components of the skin," says Jay Tiesman of P&G. Targeting this inflammation might one day help to keep wrinkles at bay. The findings will appear in the Journal of Drugs in Dermatology in July.

Identifying a "genetic signature" of younger skin should also provide a benchmark for testing existing skin products. For example, P&G is measuring the effects on gene expression of a skin cream ingredient called pal-KT. Previous approaches suggested it increased production of structural skin proteins like collagen and laminin. Gene analysis indicates it also affects the expression of genes involved in wound healing.

P&G isn't alone, cosmetics firm L'Oréal claims to have identified differences in the way genes in old and young skin respond to physical damage: changes in gene expression began just 6 hours after damage in young skin but took around 30 hours to kick in with older skin. What's more, around 25 genes differ in their response to skin damage in young and old skin, says L'Oréal.

Rigorous studies in people are needed to confirm that changing gene expression in older skin to match younger skin improves skin quality. "You could find that a molecule is up or down-regulated, but whether that relates to a consumer noticing a difference is a big jump," says Diona Damian at the University of Sydney, Australia.

If new tools become available for assessing skin products, this could force cosmetics companies to back up claims about their products with hard evidence.

"If you really want to bring cosmetics into the field of rigorous scientific evidence, genomics may be the best and most quantitative way of doing it," says Labrie.

## Chimpanzees learn from video demo

**By Victoria Gill** Science reporter, BBC News

Copycat chimps build their own tools after watching video demonstrations.

During a study, the animals were shown footage of a trained chimp combining two components to construct a tool that enabled it to reach a food reward. When given the same two components, the chimps made their own tools and used them to drag over a tasty treat. Reporting in the Royal Society journal Proceedings B, scientists say this demonstrates what a "potent effect" social learning has in the primates.

Elizabeth Price, from the University of St Andrews in Scotland, led the research. "With video, we can control exactly how much information the animals see, so we can understand exactly how much information they need to work out how to do the task," she explained.

Dr Price and her colleagues put the chimps into five groups during the test.

One of the groups was shown the whole demonstration - where a chimp was handed a rod and a tube that it slotted together. The demonstrator then used this longer composite tool to retrieve a grape from a platform outside its cage. The other groups were shown progressively less information - with one group just shown the chimp eating its grape.

The researchers then recreated the set-up for the subjects. They placed a grape on a platform against the outside of each chimp's cage, and handed the animals a rod and a plastic tube.

"Those chimps that saw the full demonstration learned better how to construct the necessary tool (to reach the food)," Dr Price told BBC News. "The fact that they can learn how to build a better tool for a particular task is very exciting. This type of behaviour is very rare in the wild, and it's an essential part of human tool use."

**Watch and learn**

"A handful of the chimps that weren't shown the full demonstration learned how to make the tool on their own," said Dr Price. "What was interesting about this group was that, when we presented them with the grape at different distances from the cage, they made the appropriate tool to reach it."

Rather than faithfully copy the demonstration, these animals switched between using the unmodified tube or rod, and using the combined tool, depending on how far away the grape was.

"Those that had been shown the full demonstration, and had socially learned to make the longer tool, continued to make it even when the grape was so close that it was more awkward to use," said Dr Price.

"It could be that social learning is such a strong force for the chimps that they apply a blanket rule of 'go with what you've seen' (rather than work out what's most appropriate for the task)."

The team is now planning to carry out the same test in young children to find out how much they rely on social learning.

What the team still do not know why this type of tool-building is not seen more commonly in the wild.

"We've shown that they're clever enough, so there must be something else at play," said Dr Price.

"It may be that when chimpanzees reach an age at which they are... capable of performing these higher level techniques, they may be too old to have access to sufficiently tolerant demonstrators."

## Plants save the earth from an icy doom

New Haven, Conn. - Fifty million years ago, the North and South Poles were ice-free and crocodiles roamed the Arctic. Since then, a long-term decrease in the amount of $CO_2$ in the atmosphere has cooled the Earth. Researchers at Yale University, the Carnegie Institution of Washington and the University of Sheffield now show that land plants saved the Earth from a deep frozen fate by buffering the removal of atmospheric $CO_2$ over the past 24 million years.

While the upper limit for atmospheric $CO_2$ levels has been a focus for discussions of global warming and the quality of life on Earth, this study points to the dynamics that maintain the lower sustainable limits of atmospheric $CO_2$.

Volcanic gases naturally add $CO_2$ to the atmosphere, and over millions of years $CO_2$ is removed by the weathering of silica-based rocks like granite and then locked up in carbonates on the floor of the world's oceans. The more these rocks are weathered, the more $CO_2$ is removed from the atmosphere.

"Mountain building in places like Tibet and South America during the past 25 million years created conditions that should have sucked nearly all the $CO_2$ out of the atmosphere, throwing the Earth into a deep freeze," said senior author Mark Pagani, associate professor of geology and geophysics and a member of the Yale Climate and Energy Institute's executive committee. "But as the $CO_2$ concentration of Earth's atmosphere decreased to about 200 to 250 parts per million, $CO_2$levels stabilized."

The study, published in the XX issue of Nature, looked for a possible explanation They used simulations of the global carbon cycle and observations from plant growth experiments to show that as atmospheric $CO_2$ concentrations began to drop towards near-starvation levels for land plants, the capacity of plants and vegetation to weather silicate rocks greatly diminished, slowing the draw-down of atmospheric $CO_2$.

"When $CO_2$ levels become suffocatingly low, plant growth is compromised and the health of forest ecosystems suffer," said Pagani. "When this happens, plants can no longer help remove $CO_2$ from the atmosphere faster than volcanoes and other sources can supply it."

"Ultimately, we owe another large debt to plants" said co-author Ken Caldeira from the Carnegie Institution of Washington at Stanford University. "Aside from providing zesty dishes like eggplant parmesan, plants have also stabilized Earth's climate by inhibiting critically low levels of $CO_2$ that would have thrown Earth spinning into space like a frozen ice ball."

Co-author David Beerling from Sheffield University adds, "Our research supports the emerging view that plants should be recognized as a geologic force of nature, with important consequences for all life on Earth"

*Robert Berner, professor emeritus of geology and geophysics at Yale, is also an author on the study. The Yale Climate and Energy Institute; the National Science Foundation; the Department of Energy; the Leverhulme Trust and a Royal Society-Wolfson Research Merit Award supported the research.*
*An interview with Mark Pagani is available at http://tinyurl.com/yale-pagani-052909*
*Citation: Nature, (doi:10.1038/nature08133)*

## Study strongly supports many genetic contributions to schizophrenia, bipolar disorder

### *Study helps explain diseases' complex genetic makeup*

An international research consortium has discovered that many common genetic variants contribute to a person's risk of schizophrenia and explain at least a third of the risk of inheriting the disease, providing the first molecular evidence that this form of genetic variation is involved in schizophrenia. The researchers also found that many of these DNA variations also are involved in bipolar disorder but not in several non-psychiatric diseases. The findings, reported by the International Schizophrenia Consortium and published online in the journal Nature, represent a new way of thinking about the genetics of psychiatric diseases, which seem to involve not only rare variants but also a significant number of common ones as well.

"While our study finds a surprising number of genetic effects, we fully expect that future work will assemble them into meaningful pathways that will teach us about the biology of schizophrenia and bipolar disorder," says Pamela Sklar, MD, PhD, of the Massachusetts General Hospital (MGH) Department of Psychiatry and Center for Human Genetic Research (CHGR), a senior associate member of the Broad Institute of MIT and Harvard and corresponding author of the Nature paper.

Co-corresponding author Shaun Purcell, PhD – also of MGH Psychiatry and the CHGR, and an associate member of the Broad Institute – emphasizes that "how these genetic variants translate into schizophrenia or bipolar disorder for a given patient is not yet known." Sklar and Purcell stress that, although these results are remarkably robust and give insight into the underlying genetics of these diseases, they cannot currently be used as a diagnostic test or to predict an individual's personal risk.

Schizophrenia is a common and often devastating brain disorder characterized by persistent delusions and hallucinations. It affects about 1 percent of the world's population and usually strikes in late adolescence or early adulthood. Despite the availability of treatments, the course of the illness is usually chronic, and response to treatments is often incomplete, leading to prolonged disability and personal suffering. Family history, which reflects genetic inheritance, is a strong risk factor for both schizophrenia and bipolar disorder, and it has generally been assumed that dozens of genes, along with environmental factors, contribute to disease risk.

Formed in 2006, the International Schizophrenia Consortium is led by senior researchers from 11 institutes in Europe and the USA. Major funding and resources for the current work were provided by the Broad Institute's Stanley Center for Psychiatric Research. Equally crucial to the success of the project was the willingness of consortium groups to share thousands of patient DNA samples collected over many years.

In the current study, the researchers tested hundreds of thousands of genetic variants (single nucleotide polymorphisms) in more than 3,300 individuals with schizophrenia and 3,600 individuals without the disorder. The work used novel analytical techniques based on theoretical models developed by consortium members Naomi Wray, PhD, and Peter Visscher, PhD, of the Queensland Institute of Medical Research, Brisbane, Australia.

The most critical – and surprising – finding was that the same large group of genetic variants was more common in all groups of schizophrenia patients, even though the DNA samples were collected by different investigators and tested in different laboratories. The additional discovery that these schizophrenia-related variants were also common in people with bipolar disorder was particularly striking, since the two disorders are considered to be distinct, although related, conditions.

"The consortium has taken important steps towards unearthing the complex genomic architecture of schizophrenia and other psychotic disorders, and this paper is another example of that critical work," said Edward Scolnick, MD, director of the Stanley Center for Psychiatric Research at the Broad Institute. "To fulfill the promise of these early studies, we as a community will need to continue to fully define the genetic basis of these disorders and ensure that our insights help improve the diagnostic and therapeutic options for patients and their families."

Thomas Insel, MD, director of the National Institute for Mental Health, which partially funded the study, adds, "These new results recommend a fresh look at our diagnostic categories. If some of the same genetic risks underlie schizophrenia and bipolar disorder, perhaps these disorders originate from some common vulnerability in brain development."

Professor Ian Hickie – executive director of consortium member the Brain and Mind Research Institute, University of Sydney, Australia – says, "This is a key study from both a conceptual and a practical perspective.

It provides striking evidence for the common genetic risk factors for the major psychiatric disorders. The race will now focus on identification of the key neurodevelopmental genes that underpin these disabling conditions."

*The study was supported by grants from the Stanley Medical Research Foundation through the Stanley Center for Psychiatric Research, and the Sylvan Herman Foundation. Other major funding bodies include the U.K. Medical Research Council, Wellcome Trust, and the Science Foundation Ireland.*

**About Massachusetts General Hospital**

Massachusetts General Hospital, established in 1811, is the original and largest teaching hospital of Harvard Medical School. The MGH conducts the largest hospital-based research program in the United States, with an annual research budget of more than $500 million and major research centers in AIDS, cardiovascular research, cancer, computational and integrative biology, cutaneous biology, human genetics, medical imaging, neurodegenerative disorders, regenerative medicine, systems biology, transplantation biology and photomedicine. For more information, visit www.massgeneral.org.

**About the Broad Institute of MIT and Harvard**

The Eli and Edythe L. Broad Institute of MIT and Harvard was founded in 2003 to empower this generation of creative scientists to transform medicine with new genome-based knowledge. The Broad Institute seeks to define all the molecular components of life and their connections; discover the molecular basis of major human diseases; develop effective new approaches to diagnostics and therapeutics; and disseminate discoveries, tools, methods and data openly to the entire scientific community.

Founded by MIT, Harvard and its affiliated hospitals, and the visionary Los Angeles philanthropists Eli and Edythe L. Broad, the Broad Institute includes faculty, professional staff and students from throughout the MIT and Harvard biomedical research communities and beyond, with collaborations spanning over a hundred private and public institutions in more than 40 countries worldwide. For further information about the Broad Institute, go to www.broad.mit.edu.

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## Acid-reducing medicines may lead to dependency

### *Data suggests proton pump inhibitors can induce acid-related symptoms in healthy adults*

Bethesda, MD (July 1, 2009) – Treatment with proton pump inhibitors (PPIs) for eight weeks induces acid-related symptoms like heartburn, acid regurgitation and dyspepsia once treatment is withdrawn in healthy individuals, according to a new study in Gastroenterology, the official journal of the American Gastroenterological Association (AGA) Institute.

"The observation that more than 40 percent of healthy volunteers, who have never been bothered by heartburn, acid regurgitation or dyspepsia, develop such symptoms in the weeks after cessation of PPIs is remarkable and has potentially important clinical and economic implications," said Christina Reimer, MD, of Copenhagen University and lead author of the study. "This study indicates unrecognized aspects of PPI withdrawal and is a very strong indication of a clinically significant acid rebound phenomenon that needs to be investigated in proper patient populations."

The use of PPIs for acid-related symptoms and disorders is extensive and rapidly escalating. While the incidence of new patients being treated with PPIs remains stable, the prevalence of long-term treatment is rising, the reasons for which are not fully known. Studies have shown that up to 33 percent of patients who initiate PPI

treatment continue to refill their prescriptions without an obvious indication for maintenance therapy. Rebound acid hypersecretion, defined as an increase in gastric acid secretion above pre-treatment levels following antisecretory therapy, is observed within two weeks after withdrawal of treatment and could theoretically lead to acid-related symptoms such as heartburn, acid regurgitation or dyspepsia that might result in resumption of therapy.

In a randomized double-blind placebo-controlled trial, researchers aimed to determine the clinical relevance of rebound acid hypersecretion in order to establish if long-term treatment with a PPI creates a need for continuous treatment. A total of 120 healthy participants were randomized to 12 weeks of placebo or eight weeks of esomeprazole (40 mg per day) followed by four weeks with placebo. The Gastrointestinal Symptom Rating Scale (GSRS) was filled out weekly.

The symptoms observed in this trial caused mild to moderate discomfort and appeared for the majority of subjects in the first two weeks after withdrawal of therapy. While there were no significant differences between the groups in GSRS scores at baseline, GSRS scores for acid-related symptoms were significantly higher in the PPI group in weeks 10, 11 and 12. Of those randomized to PPIs, 44 percent reported at least one relevant acid-related symptom in weeks nine through 12 compared to 15 percent in the placebo group. The proportion reporting dyspepsia, heartburn or acid regurgitation in the PPI group was 22 percent in week 10, 22 percent in week 11 and 21 percent in week 12. Corresponding figures in the placebo group were 7 percent, 5 percent and 2 percent.

"We find it highly likely that the symptoms observed in this trial are caused by rebound acid hypersecretion and that this phenomenon is equally relevant in patients treated long term with PPIs. If rebound acid hypersecretion induces acid-related symptoms, this might lead to PPI dependency. Our results justify the speculation that PPI dependency could be one of the explanations for the rapidly and continuously increasing use of PPIs," Dr. Reimer added.

## Chromosomal problems affect nearly all human embryos

### *Discovery may explain low fertility rates in humans*

Amsterdam, The Netherlands: For the first time, scientists have shown that chromosomal abnormalities are present in more than 90% of IVF embryos, even those produced by young, fertile couples. Ms Evelyne Vanneste, a PhD student in the Centre for Human Genetics and the University Fertility Center, Leuven University, Belgium, told the 25th annual conference of the European Society of Human Reproduction and Embryology today (Wednesday July 1), that the surprising finding meant that current techniques used in preimplantation genetic screening (PGS), where embryos are screened genetically in order to select the best embryo for transfer, do nothing to improve pregnancy and live birth rates. Indeed, it can lead to potentially viable embryos being discarded, she said.

Ms Vanneste and her team studied each cell from 23 three or four day-old IVF embryos from young (less than 35 years old), fertile couples who had asked for preimplantation genetic diagnosis (PGD). PGD is carried out where one or both parents have a known genetic abnormality, in this case an X-linked disorder or the microdeletions (loss of a tiny piece of a chromosome) that can cause such disorders as the cancer predisposition syndrome neurofibromatosis type 1. The embryos are screened to avoid the implantation of one carrying that abnormality. Such embryos are the most representative of normal human embryogenesis, the process that begins once an egg has been fertilised.

Using new technologies that can detect chromosomal aberrations in the whole genome (all human chromosomes) of a single cell, the team was able to screen embryonic cells at a much higher resolution than previously, and hence identify more chromosomal abnormalities than has been possible using the current technique, fluorescent in situ hybridisation (FISH), which can only analyse ten of the approximately 32,000 genetic regions at the same time.

"Until now, the majority of studies analysing the genetic composition of human embryos used low resolution techniques on embryos derived from couples with fertility problems who are at risk for embryonic aneuploidy, an aberrant number of chromosomes, such as three copies of chromosome 21 that results in Down's syndrome. Therefore, little was known about the frequency and type of chromosomal imbalances in embryos from normal, fertile women," said Ms Vanneste. "Our new technique has enabled us to show that chromosomal abnormalities are far more common and complex than previously anticipated, even in embryos from young, normal fertile couples. This leads us to believe that such abnormalities must be present in all human IVF-ICSI embryos.

"Although in vitro culture conditions are known to have a limited influence on the rate of chromosomal imbalances in IVF/ICSI embryos, it is probable that the chromosome instability observed in vitro also occurs in spontaneous pregnancies since, at most, 30% of human conceptions result in a live birth and more than 50% of

spontaneous abortions carry chromosomal aberrations. The high rate of chromosomal abnormalities is almost certainly responsible for the low fecundity of humans compared with other mammals," she added.

The scientists say that their work has important implications for preimplantation genetic screening (PGS) in fertility treatment. PGS is routinely used in many fertility centres for couples who encounter problems with conception, particularly for advanced maternal age, repeated failure of implantation, repeated miscarriages, or severe male fertility problems. In PGS, a single cell is removed from the early embryo for genetic testing, since it is hypothesised that the selection of chromosomally normal embryos for uterine transfer would increase the live birth rate and decrease the spontaneous abortion rate per embryo transferred.

"Although PGS is promoted as a way of increasing the chances of a successful pregnancy," said Ms Vanneste, "there has never been any significant evidence that it does, in fact, increase live birth rates after IVF. Our findings have shown that almost every cell of a human embryo carries a different genetic composition; consequently, the one cell that is analysed genetically is not representative of the rest of the embryo. If the tested cell is genetically abnormal, the embryo will not be transferred. But the rest of the embryo might be normal and develop into a healthy person. Therefore, the use of PGS means that potentially viable embryos will be discarded. The prevalent chromosomal instability in all early human IVF embryos explains the failure of PGS to improve the live birth rate per embryo transferred.

"I think that we have made a crucial breakthrough that will change the way we do preimplantation genetic diagnosis and PGS and help to advance our ability to improve human fertility," said Ms Vanneste.

## Brain's response muted when we see other races in pain

** 14:20 01 July 2009* ***by Ewen Callaway***

The brain is not an equal opportunities organ, it seems. An imaging study of Chinese and Caucasian people has found that their brains respond less strongly to the pain of strangers whose ethnicity is different when compared with strangers of their own race.

"It's one of a string of papers that have come out in the cognitive neuroscience literature that helps us to understand some of the unfortunate ways in which racial group identity can influence our reactions to other people," says Martha Farah, a cognitive neuroscientist at the University of Pennsylvania in Philadelphia, who was not involved in the new study.

Previous research has shown that the amygdala, a brain area implicated in fear, responds more strongly to pictures of people whose ethnicity is different from the viewer's. But these responses aren't uniform; other research has shown that activity in other brain areas can dampen the amygdala.

To determine how ethnicity also sways the brain's sense of empathy, Shihui Han and colleagues at Peking University in Beijing showed 17 Chinese and 16 Caucasians volunteers videos of a person being poked in the cheek with a Q-tip cotton bud or a hypodermic syringe, while the volunteers had their brains scanned on a functional MRI machine.

**In pain**

The films sparked activity in a region called the anterior cingulate cortex (ACC), which also lights up when people are in pain themselves.

However, for Chinese volunteers the sight of another Chinese person in pain prompted more of an increase in ACC activity than the pain of a Caucasian person. Caucasian volunteers, from the US, Europe and Israel, also reacted more strongly to sight of another white person in pain.

Such automatic neural responses don't necessarily translate into behaviour, cautions Farah. "Just because there is this difference in ACC response it doesn't mean that we are inevitably going to behave less empathically toward the other group."

Indeed, when Han's team asked volunteers "how painful do you think the model feels?" or "how unpleasant do you feel when observing the video clip?" Chinese and Caucasians volunteers reported that they felt each other's pain about equally. *Journal reference: Journal of Neuroscience, DOI: 10.1523/jneurosci.2418-08.2009 (in press)*

## Scientists: Salamanders, regenerative wonders, heal like mammals, people

GAINESVILLE, Fla. - The salamander is a superhero of regeneration, able to replace lost limbs, damaged lungs, sliced spinal cord -- even bits of lopped-off brain. But it turns out that remarkable ability isn't so mysterious after all -- suggesting that researchers could learn how to replicate it in people.

Scientists had long credited the diminutive amphibious creature's outsized capabilities to "pluripotent" cells that, like human embryonic stem cells, have the uncanny ability to morph into whatever appendage, organ or tissue happens to be needed or due for a replacement. But in a paper set to appear Thursday in the journal Nature, a team of seven researchers, including a University of Florida zoologist, debunks that notion. Based on experiments on genetically modified axolotl salamanders, the researchers show that cells from the salamander's

different tissues retain the "memory" of those tissues when they regenerate, contributing with few exceptions only to the same type of tissue from whence they came.

Standard mammal stem cells operate the same way, albeit with far less dramatic results -- they can heal wounds or knit bone together, but not regenerate a limb or rebuild a spinal cord. What's exciting about the new findings is they suggest that harnessing the salamander's regenerative wonders is at least within the realm of possibility for human medical science.

"I think it's more mammal-like than was ever expected," said Malcolm Maden, a professor of biology, member of the UF Genetics Institute, and author of the paper. "It gives you more hope for being able to someday regenerate individual tissues in people." Also, the salamanders heal perfectly, without any scars whatsoever, another ability people would like to learn how to mimic, Maden said.

Axolotl salamanders, originally native to only one lake in central Mexico, are evolutionary oddities that become sexually reproducing adults while still in their larval stage. They are useful scientific models for studying regeneration because, unlike other salamanders, they can be bred in captivity and have large embryos that are easy to work on.

When an axolotl loses, for example, a leg, a small bump forms over the injury called a blastema. It takes only about three weeks for this blastema to transform into a new, fully functioning replacement leg -- not long considering the animals can live 12 or more years. The cells within the blastema appear embryonic-like and originate from all tissues around the injury, including the cartilage, skin and muscle. As a result, scientists had long believed these cells were pluripotential -- meaning they came from a variety of sites and could make a variety of things once functioning in their regenerative mode.

Maden and his colleagues at two German institutions tested that assumption using a tool from the transgenic kit: the GFP protein. When produced by genetically modified cells, GFP proteins have the useful quality of glowing livid green under ultraviolet light. This allows researchers to follow the origin, movement and destination of the genetically modified cells.

The researchers experimented on both adult and embryonic salamanders. With the embryos, the scientists grafted transgenic tissue onto sites already known to develop into certain body parts, then observed how and where the cells organized themselves as the embryo developed. This approach allowed them to see, literally, what tissues the transgenic tissue made.

In perhaps the most vivid result, the researchers grafted GFP-modified nerve cells onto the part of the embryo known to develop into the nervous system. Once the creatures developed, ultraviolet light exams of the adults revealed the GFP cells stretched only along nerve pathways -- like glowing green strings throughout the body

With the adults, they took tissue from specific parts or organs from transgenic GFP-producing axolotls, grafted it onto normal axolotls, then cut away a chunk of the grafted tissue to allow regeneration. They could then determine the fate of the grafted green cells in the emerging blastema and replacement tissue.

The researchers' main conclusion: Only 'old' muscle cells make 'new' muscle cells, only old skin cells make new skin cells, only old nerve cells make new nerve cells, and so on. The only hint that the axolotl cells could revamp their function came with skin and cartilage cells, which in some circumstances seemed to swap roles, Maden said.

Maden said the findings will help researchers zero in on why salamander cells are capable of such remarkable regeneration. "If you can understand how they regenerate, then you ought to be able to understand why mammals don't regenerate," he said.

Maden said UF researchers will soon begin raising and experimenting on transgenic axolotls at UF as part of The Regeneration Project, an effort to treat human brain and other diseases by examining regeneration in salamanders, newts, starfish and flatworms.

## Emerging techniques put a new twist on ankle repair

### *Using cells grown in a lab, new treatments eliminate risks of traditional procedures*

Rosemont, Ill. — People with ankle injuries who do not respond successfully to initial treatment may have a second chance at recovery, thanks to two new procedures developed to restore the injured area, according to a study published in the July 2009 issue of the Journal of the American Academy of Orthopaedic Surgeons (JAAOS).

The study reviews emerging techniques that have proven successful in treating injuries to the talus, the small bone, which is located between the heel bone and the lower bones of the leg. The talus helps form the ankle joint.

Although most injuries to the talus can be successfully treated using traditional "first-line" therapies involving removal of dead tissue (called "debridement") and drilling, about one-fifth to one-quarter of people with ankle injuries need additional "second-line" restorative treatment to heal successfully, said lead author Matthew Mitchell, MD, an orthopaedic surgeon in private practice in Casper, Wyoming.

The two new techniques rely on cells grown in a lab, and eliminate the need for ostetomy (cutting the bone of the tibia) in some cases, he said.

* Autologous chondrocyte implantation, or ACI, involves removing cartilage cells from the knee or the ankle and growing them in a lab. Once grown, the cartilage is transplanted to the talus. ACI usually involves an ostetomy in order to implant the cells.

* In matrix-induced autologous chondrocyte implantation, or MACI, cells are grown on a special backing material, or "matrix," and then transplanted to the talus. In the authors' experience, an ostetomy is not necessary to implant the cells.

Of these two techniques, the newer MACI technique may offer the most benefits to the patient, according to Dr. Mitchell.

"Both ACI and MACI show a lot of promise, but I think the advantage of MACI is that an ostetomy is not necessary in order to successfully implant the matrix," he said. "You only need to make an incision to place the graft, which decreases the morbidity of the procedure quite a bit. In my experience so far with this emerging technique in Australia, the results have been as good as, or better than, other restorative techniques," he added. MACI is currently considered investigational by the FDA in the United States.

Traditional restorative techniques involve removing a cartilage donor plug from the knee and implanting it over the ankle injury, or "lesion." This requires an operation on the knee and cutting the bone (ostetomy) of the tibia to accommodate the graft.

As a result, these traditional techniques involve potential problems, including:

* pain in the donor knee
* tissue damage in the donor knee
* tissue damage in the ankle as a result of ostetomy

"In most individuals, results are favorable with reparative techniques, such as debridement and drilling," said Dr. Mitchell. "The lesions that are problematic and which don't respond well to reparative treatments are lesions that are larger, and those which are fairly deep, as well as lesions which have a cyst-like structure. Whether or not an ankle "lesion" requires additional treatment after an initial reparative procedure often depends upon several factors, including: size, depth and structure of the legion.

"Once you've performed a reparative technique and the patient still doesn't heal properly, then we would move on to a second-line restorative treatment," he said

## Researchers find clear difference in quality, type of lung cancer info available in US and Japan

Aurora, COLO. -- A study published in the July 2009 issue of the Journal of Thoracic Oncology revealed that internet-based lung cancer information was of a higher quality in the United States (US) than in Japan. Dr. Yasushi Goto of the National Cancer Center Hospital in Tokyo and his team of researchers from both the US and Japan evaluated 150 Web sites and determined noticeable differences in the quality and type of information on lung cancer available over the internet in the two countries.

Dr. Goto and his team conducted the online review by searching the term "lung cancer" on Google United States, Google Japan and Yahoo! Japan. The first 50 Web sites returned by each search engine were analyzed for validity, ethical perspective and the reliability of the site's administrator. Most remarkably, the team found distinct differences in the validity of the information on treatment methods and options for lung cancer. Eighty percent of US-Google sites discussed the most common treatment methods and standard treatment protocol, compared to only 50% of the sites from the Japanese Google and Yahoo! search engines. Additionally, more than 10% of the Japanese sites advertised alternative therapies.

Other differences between the two countries include the visibility of ethical policies, which were more noticeable in the US, and the affiliation of site administrators. Nonprofit organizations and public institutions were frequently the primary administrators in the United States, whereas commercial or personal Web sites were more common in Japan.

"The internet can be a valuable source of health information, but with the expanding global online community it has become a challenge to discern the quality of the information available," says Dr. Goto. "By stressing the importance of performing critical Web searches, we provide users with one of many skills to effectively evaluate sites for themselves."

Despite the several cultural differences between the United States and Japan, lung cancer is the leading cause of cancer-related deaths in both countries.

## Dinosaur mummy gives up organic material

* 01 July 2009 **by Jeff Hecht**

A MUMMIFIED dinosaur unearthed in North Dakota may contain traces of 66-million-year old organic material, which could provide vital information about its evolution.

The well-preserved fossil of a plant-eating hadrosaur, complete with skin and tendons, was discovered in 1999. Named "Dakota", it was a rare find as bacteria in the soil usually break down soft tissue quickly. However, the rapid burial of Dakota in a waterlogged, low-oxygen environment allowed fossilisation to outpace the normal processes of microbial decay, preserving areas of soft tissue.

Phil Manning and Roy Wogelius at the University of Manchester, UK, used electron microscopy and X-ray imaging to study Dakota's fossilised skin, as well as a claw and a tendon. They found cell-like structures comparable to those of living vertebrates.

Further analysis of the skin and claw revealed the presence of amino acids - the building blocks of proteins - suggesting that the cell-like structures were indeed cells and that organic material may have been preserved (Proceedings of the Royal Society B, DOI: 10.1098/rspb.2009.0812).

Previous studies claim to have found whole proteins inside fossilised bones. Yet researchers often argue that such proteins may originate not from the dinosaur, but from soil bacteria, handling of fossils, and the preparation of samples.

Manning says the presence of amino acids, rather than whole proteins, is a good sign. After 66 million years, proteins in soft tissue should have broken down into amino acids, so finding large proteins would likely be a sign of contamination. The high concentrations of amino acids in the fossil, compared with only traces found in the surrounding sediment, support the idea that they came from the fossil.

The authors hope that further analysis will confirm the presence of organic material and provide fundamental information about the evolution of this species and its descendants.

## New Treatment for Receding Gums: No Pain, Lots of Gain

### *Tufts Dental Researchers Show Tissue Regeneration Application*

BOSTON (July 1, 2009, 7 a.m. ET) — Tufts dental researchers conducted a three-year follow-up study that examined the stability of a treatment option for receding gums and found that complete root coverage - the goal of the surgery - had been maintained. This specific tissue regeneration application, developed at Tufts, reduces the considerable pain and recovery time of gum grafting surgery. The case study of six patients is published in the July 2009 issue of the Journal of Periodontology.

“Patients have a less invasive treatment option for receding gums and we now have evidence to support the stability of this relatively painless procedure. Instead of leaving the dental office with stitches in the roof of their mouth, a patient leaves with a small bandage on the arm that can be removed in an hour,” said Terrence Griffin, DMD, associate professor, chair of the department of periodontology, and director of postdoctoral periodontology at Tufts University School of Dental Medicine in Boston.

“One of our previous research studies showed that all of the post-operative bleeding and most of the post-operative pain were related to the gum tissue removed from the roof of the mouth for use as a graft,” he continued.

Traditional gum grafting surgery requires surgically excising tissue from the roof of the mouth (the palate) to replace the gum tissue lost around the teeth. Unfortunately, removing tissue from the roof of the mouth extends recovery time and is a major source of patients’ discomfort or pain. According to the American Academy of Periodontology, periodontal disease is the primary cause of tooth loss in adults aged 35 and older. Periodontal disease includes gum recession, also called gingival recession, which can result in tooth root decay and tooth loss.

The new tissue regeneration application from Tufts uses platelet concentrate gel applied to a collagen membrane as the graft instead of using tissue from the roof of the mouth. The graft is soaked in the patient’s platelets, using blood drawn in the same visit. Placed over the receding tooth root, the graft is then surgically secured.

In order to examine three-year efficacy of the treatment, measurements were taken from six patients in the gum recession area at baseline, 6, and 36 months after surgery. At six months, 24 out of 37 teeth from the six patients had complete root coverage (65 percent). At 36 months, 21 out of 37 teeth from the six patients had complete root coverage (57 percent). The authors said that the recession over three years was minimal and that the results are comparable to traditional gum grafting surgery.

“Our previous research determined that pain and discomfort were barriers to receiving traditional gum grafting surgery.* We have also shown previously that this treatment for gum recession results in proper coverage of the tooth root, better esthetics than those found with traditional gum grafting surgery, and enhanced

patient satisfaction with the results,"** said co-author Wai Cheung, DMD, MS, assistant professor in the department of periodontology at Tufts University School of Dental Medicine.

Over the last decade, Griffin and his colleagues, including Cheung, have studied alternatives to traditional gum grafting surgery and have more than 20 publications on the topic.

"Gum disease affects most American adults and research is linking periodontal disease to other health problems, including heart disease. Encouraging patients to undergo surgery to fix receding gums can be difficult because the mere thought of this dental surgery is often associated with considerable pain. This treatment, while only marginally more expensive for the patient, is more time-consuming and technically more difficult for us but the end result - improved esthetics, reduced pain, and, most importantly, improved oral health for the patient - make it a valuable and important alternative," said Griffin.

*Griffin TJ, Cheung WS. Journal of Periodontology. 2009. (July); 80 (7): 1192-1199. "Guided tissue regeneration-based root coverage with a platelet concentrate graft: A 3-year follow-up case series." Published online July 1, 2009, doi: 10.1902/jop.2009.080609*

## UCLA collaboration identifies immune system link to schizophrenia

### *Disruptions also found in cellular pathways involved in memory and cognition*

Schizophrenia is a devastating mental disease, thought to be caused by the interaction of both genetic and environmental factors. Because there is no biochemical test that can identify the disorder, physicians rely upon the recognition of its symptoms - which can include auditory hallucinations and paranoia - in order to make their diagnosis.

Now following on their earlier work that identified three gene locations that may be implicated in schizophrenia, researchers at UCLA and colleagues from around the world have, for the first time, identified additional genes that confirm what scientists have long suspected - that the immune system may play a role in the development of the disorder. Further, they have also identified genetic anomalies that disrupt the cellular pathways involved in brain development, memory and cognition, all markers of schizophrenia.

Roel Ophoff, the co-lead author and an assistant professor at the Center for Neurobehavioral Genetics at the UCLA Semel Institute for Neuroscience and Human Behavior, and his collaborators from nearly 50 institutions worldwide, performed a genome-wide scan of 2,663 people diagnosed with schizophrenia and 13,498 controls from eight European locations. They were looking for single nucleotide polymorphisms (SNP), genetic variations that are commonly present in the general population but more often present in those suffering from the disorder. In total, nearly 314,000 SNPs were included in their analysis.

They found significant associations with genetic markers on the Major Histocompatibility Complex (MHC), a group of genes that controls several aspects of the immune response. Further, they discovered additional variations in two other genes, called NRGN and TCF4, which points to perturbation of pathways involved in brain development, memory and cognition.

"This is another step forward in understanding the biological basis of this disorder, one that robs people of their lives," said Ophoff, who holds a joint appointment at the University of Utrecht, The Netherlands. "It also shows the importance of worldwide collaborations for the study of schizophrenia genetics, because it allows us to do very large numbers of scans."

The findings are significant yet not without challenge, said Ophoff, since the study aimed at the "common variants" in the human genome. "In other words," he said, "these are not rare mutations present in only a few individuals, but these genetic variants are abundantly present in the population. Anybody could carry this variant, but that doesn't mean they will necessarily develop the disease. Yet, when you look at the population at large, these variants are more often present in patients than in healthy control subjects."

And that's important, he noted, in developing new techniques to thwart the disease. "Knowing these specific genes are involved in the pathway leading to schizophrenia provides unique clues as to which molecular mechanisms are involved," he said.

While the association between schizophrenia and the immune system has long been suspected, the evidence for it has, until now, been mostly circumstantial. And impaired cognitive and memory functions are increasingly being recognized as core features of schizophrenia, which are poorly addressed by current medications.

"The three common genetic variants we describe, then, which we feel predisposes certain individuals to schizophrenia, have the potential to be translated into targets for the development of new and novel medications," Ophoff said. The research appears in the July 1 online edition of the journal Nature.

*Some 40 other authors and institutions contributed to the paper, and there were multiple funding sources; for UCLA, funding was provided by the National Institute of Mental Health. Other UCLA authors included Dr. Nelson Freimer, director of the Center for Neurobehavioral Genetics and professor of psychiatry, and Rita Cantor, professor of human genetics, both members of the David Geffen School of Medicine. The UCLA authors report no conflicts of interest.*

## Blood stem cell growth factor reverses memory decline in mice

### *The new study shows GCSF impacts both bone marrow and brain to improve cognition*

Tampa, FL (July 1, 2009) -- A human growth factor that stimulates blood stem cells to proliferate in the bone marrow reverses memory impairment in mice genetically altered to develop Alzheimer's disease, researchers at the University of South Florida and James A. Haley Hospital found. The granulocyte-colony stimulating factor (GCSF) significantly reduced levels of the brain-clogging protein beta amyloid deposited in excess in the brains of the Alzheimer's mice, increased the production of new neurons and promoted nerve cell connections.

The findings are reported online in Neuroscience and are scheduled to appear in the journal's print edition in August.

GCSF is a blood stem cell growth factor or hormone routinely administered to cancer patients whose blood stem cells and white blood cells have been depleted following chemotherapy or radiation. GCSF stimulates the bone marrow to produce more white blood cells needed to fight infection. It is also used to boost the numbers of stem cells circulating in the blood of donors before the cells are harvested for bone marrow transplants. Advanced clinical trials are now investigating the effectiveness of GCSF to treat stroke, and the compound was safe and well tolerated in early clinical studies of ischemic stroke patients.

"GCSF has been used and studied clinically for a long time, but we're the first group to apply it to Alzheimer's disease," said USF neuroscientist Juan Sanchez-Ramos, MD, PhD, the study's lead author. "This growth factor could potentially provide a powerful new therapy for Alzheimer's disease – one that may actually reverse disease, not just alleviate symptoms like currently available drugs."

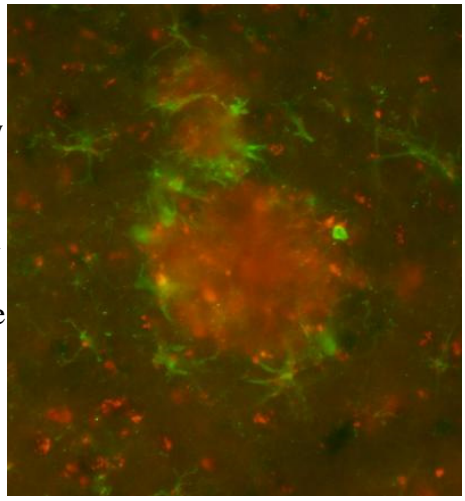
The researchers showed that injections under the skin of filgrastim (Neupogen®) -- one of three commercially available GCSF compounds -- mobilized blood stem cells in the bone marrow and neural stem cells within the brain and both of these actions led to improved memory and learning behavior in the Alzheimer's mice. "The beauty in this less invasive approach is that it obviates the need for neurosurgery to transplant stem cells into the brain," Dr. Sanchez-Ramos said.

Based on the promising findings in mice, the Alzheimer's Drug Discovery Foundation is funding a pilot clinical trial at USF's Byrd Alzheimer's Center. The randomized, controlled trial, led by Dr. Sanchez-Ramos and Dr. Ashok Raj, will test the safety and effectiveness of filgrastim in 12 patients with mild to moderate Alzheimer's disease

The researchers worked with 52 elderly mice, equivalent to the human ages of 60 to 80 years. About half (24) were mice genetically altered to develop symptoms mimicking Alzheimer's disease by the time they reach 5-months old. The others (28 normal, or non-Alzheimer's, mice) were not. The researchers confirmed through a series of tests that the Alzheimer's mice were memory impaired before beginning the experiments.

Some mice were treated for three weeks with injections of the GCSF compound filgrastim. At the end of study, the Alzheimer's mice treated with GCSF demonstrated clearly improved memory, performing as well on behavioral tests as their non-Alzheimer's counterparts. The Alzheimer's mice administered saline injections instead of GCSF continued to perform poorly. GCSF treatment did not boost the already excellent memory performance demonstrated by the non-Alzheimer's mice tested before the study began.

Further experiments showed that the size and extent of beta amyloid deposited in the brains of the Alzheimer's mice was significantly less in those treated with GCSF. Depending on their ages, mice treated with GCSF had a 36 to 42-percent reduction in beta amyloid, the protein considered a major culprit in the development of Alzheimer's disease.



GCSF reduced the burden of beta amyloid deposited in the brains of the Alzheimer's mice by several means, the researchers found. One was by recruiting reinforcements to clear beta amyloid accumulating abnormally in the brain. The growth factor prodded bone-marrow derived microglia outside the brain to join forces with the brain's already-activated microglia in eliminating the Alzheimer's protein from the brain. Microglia are brain cells that act as the central nervous system's main form of immune defense Like molecular "Pac-men," they rush to the defense of damaged or inflamed areas to gobble up toxic substances.

The growth factor also appeared to increase the production of new neurons in the area of the brain (hippocampus) associated with memory decline in Alzheimer's disease and to form new neural connections.

***Microglia (in green) attack the beta amyloid (red) deposited in the brain of a GCSF-treated Alzheimer's mouse.*** **Photo courtesy of University of South Florida**

"The concept of using GCSF to harness bone marrow-derived cells for Alzheimer's therapy is exciting and the findings in mice are promising, but we still need to prove that this works in humans," said Dr. Raj, a physician researcher at the Byrd Alzheimer's Center at USF Health.

*In addition to Dr. Sanchez-Ramos, other authors of the Neuroscience paper were Shijie Song, PhD; Vasyl Sava, PhD; Briony Catlow, PhD; Xiaoyang Lin; Takashi Mori, PhD; Chuanhai Cao, PhD; and Gary Arendash, PhD.*

## New targeted therapy finds and eliminates deadly leukemia stem cells

New research describes a molecular tool that shows great promise as a therapeutic for human acute myeloid leukemia (AML), a notoriously treatment-resistant blood cancer. The study, published by Cell Press in the July 2nd issue of the journal Cell Stem Cell, describes exciting preclinical studies in which a new therapeutic approach selectively attacks human cancer cells grown in the lab and in animal models of leukemia.

AML is a cancer of the white blood cells that has an extremely poor prognosis and does not respond well to conventional chemotherapy. "The cellular and molecular basis for this dismal picture is unclear," offers senior study author Associate Professor Richard Lock from the Children's Cancer Institute Australia and the University of New South Wales. "However, previous research has suggested that leukemia stem cells (LSCs) may lie at the heart of post-treatment relapse and chemoresistance." LSCs are cells that can initiate AML and are critical for its long-term growth.

Associate Professor Lock and colleagues exploited the fact that the molecule CD123 is expressed at very high levels on LSCs but not on normal blood cells. CD123 is part of the interleukin-3 receptor, a protein that interacts with a growth factor (called a cytokine) that influences cell survival and proliferation. The researchers created a therapeutic antibody that recognized and bound to CD123 with the hope that this antibody would selectively interfere with AML-LSC survival.

When AML-LSCs from human patients were transplanted into mice treated with the antibody, called 7G3, cytokine signaling in the tumor cells was blocked. Further, 7G3 impaired migration of the AML-LSCs to bone marrow and activated the innate immune system of the host mouse to destroy the AML-LSCs. Overall, treatment with 7G3 substantially improved mouse survival when compared with control groups. The researchers go on to report that a CD123-targeting antibody is currently being used in phase 1 clinical trials of advanced AML and that there are no signs of treatment-related toxicity.

These results hold substantial promise for future cancer therapeutics. "The recent characterization of defined populations of cancer stem cells in a range of human malignancies, as well as their relative resistance to conventional chemotherapy and radiotherapy, supports the broad applicability of our approach and provides rationale for the progression of AML-LSC-targeted therapeutics from preclinical evaluation to clinical trials," concludes Associate Professor Lock.

*The researchers include Liqing Jin, University Health Network, Toronto, Canada; Erwin M. Lee, University of New South Wales, Sydney, Australia; Hayley S. Ramshaw, Centre for Cancer Biology, Adelaide, Australia; Samantha J. Busfield, CSL Limited, Melbourne, Australia; Armando G. Peoppl, University Health Network, Toronto, Canada; Lucy Wilkinson, Queensland Institute of Medical Research, Brisbane, Australia; Mark A. Guthridge, Centre for Cancer Biology, Adelaide, Australia; Daniel Thomas, Centre for Cancer Biology, Adelaide, Australia; Emma F. Barry, Centre for Cancer Biology, Adelaide, Australia; Andrew Boyd, Queensland Institute of Medical Research, Brisbane, Australia; David P. Gearing, CSL Limited, Melbourne, Australia; Gino Vairo, CSL Limited, Melbourne, Australia; Angel F. Lopez, Centre for Cancer Biology, Adelaide, Australia; John E. Dick, University Health Network, Toronto, Canada; and Richard B. Lock, University of New South Wales, Sydney, Australia.*

## Doubts cast on credibility of some published clinical trials

Randomised Controlled Trials (RCTs) are considered the 'gold standard' research method for assessing new medical treatments. But research published in BioMed Central's open access journal Trials shows that the design of a remarkable 93 percent of 2235 so-called RCTs published in some Chinese medical journals during 1994 to 2005 was flawed, casting doubt on the reliability of research that is likely to influence medical decision-makers.

Researchers led by Taixiang Wu of the Chinese Cochrane Centre at Sichuan University, China and Ottawa Hospital Research Institute investigated clinical trials published in China between 1994 and 2005, searching the China National Knowledge Infrastructure (CNKI) electronic database for RCTs on 20 common diseases. To determine how many of these met recognised standards for randomly allocating participants to treatment groups, trained investigators interviewed the first or co-authors of 2235 trial reports by phone.

Less than seven percent of self-described RCTs published in some Chinese medical journals meet criteria for authentic randomisation. The researchers looked at both conventional and traditional Chinese medicine trials, but there was no difference between these in terms of study authenticity rates. However, all RCTs of pre-market drug clinical trial were authentic, and RCTs conducted at hospitals affiliated with medical universities were more likely to be authentic than trials conducted at lower tier level three and level two hospitals. More than half

of the trials at university-affiliated hospitals met RCT criteria, which means lower-tier hospital research is the least rigorous in design terms.

"The fact that so many non-RCTs were published as RCTs reflected that peer-review needs to be improved and a Good Practice of Peer Review, including how to identify the authenticity of the study, urgently needs to be developed," says Wu.

Misleading reporting of medical research is not unique to China. Studies labelled as RCTs are more likely to influence health policy-makers meaning falsely reported RCTs have the potential to mislead health care providers, consumers and policy-makers. The results of this study suggest authors of systematic reviews - articles that combine the results of multiple RCTs - need to be aware that RCTs in some Chinese journals may not be RCTs at all.

The approximately 1100 medical journals now active in China are rapidly increasing their output of research reports, including many identified by their authors as RCTs. But these trials present mostly positive results (they favour the treatment being investigated), which can be influenced by inadequate randomisation of patients when designing the study.

***Notes to Editors***

*1. Randomized trials published in some Chinese journals: How many are randomized?*
*Taixiang Wu, Youping Li, Zhaoxiang Bian, Guanjian Liu and David Moher*
*Trials (in press)*
*During embargo, article available here: http://www.trialsjournal.com/imedia/1756122426222937_article.pdf?random=263457*
*After the embargo, article available at the journal website: http://www.trialsjournal.com/*

## Computer reveals stone tablet 'handwriting' in a flash

* 18:00 02 July 2009 **by Ewen Callaway**

***See a gallery of images showing the tablet-reading process***

You might call it "CSI Ancient Greece". A computer technique can tell the difference between ancient inscriptions created by different artisans, a feat that ordinarily consumes years of human scholarship.

"This is the first time anything like this had been done on a computer," says Stephen Tracy, a Greek scholar and epigrapher at the Institute for Advanced Study in Princeton, New Jersey, who challenged a team of computer scientists to attribute 24 ancient Greek inscriptions to their rightful maker. "They knew nothing about inscriptions," he says.

Tracy has spent his career making such attributions, which help scholars attach firmer dates to the tens of thousands of ancient Athenian and Attican stone inscriptions that have been found.

***Archaeologists have discovered more than 50,000 stone inscriptions from ancient Athens and Attica so far. However, attributing the pieces to particular cutters so they can be dated has proven tricky*** **Image:Michail Panagopolous, et al.**

"Most inscriptions we find are very fragmentary," Tracy says. "They are very difficult to date and, as is true of all archaeological artefacts, the better the date you can give to an artefact, the more it can tell you."

Just as English handwriting morphed from ornate script filled with curvy flourishes to the utilitarian penmanship practiced today, Greek marble inscriptions evolved over the course of the civilisation.

"Lettering of the fifth century BC and lettering of the first century BC don't look very much alike, and even a novice can tell them apart," Tracy says.

**Eye for detail**

But narrowing inscriptions to a window smaller than 100 years requires a better trained eye, not to mention far more time and effort; Tracy spent 15 years on his first book.

"One iota [a letter of the Greek alphabet] is pretty much like another, but I know one inscriber who makes an iota with a small little stroke at the top of the letter. I don't know another cutter who does. That becomes, for him, like a signature," says Tracy, who relies principally on the shape of individual letters to attribute authorship.

However, these signatures aren't always apparent even after painstaking analysis, and attributions can vary among scholars, says Michail Panagopoulos, a computer scientist at the National Technical University of Athens, who led the project along with colleague Constantin Papaodysseus.

"I could show you two 'A's that look exactly the same, and I can tell you they are form different writers," Panagopoulos says.

**Average letter**

Panagopoulos' team determined what different cutters meant each letter to look like by overlaying digital scans of the same letter in each individual inscription. They call this average a letter's "platonic realisation".

After performing this calculation for six Greek letters selected for their distinctness – A, P, M, N, O and Σ – across all 24 inscriptions, Panagopoulos' team compared all the scripts that Tracy provided.

The researchers correctly attributed the inscriptions to six different cutters, who worked between 334 BC and 134 BC – a 100-per-cent success rate. "I was both surprised and encouraged," Tracy says of their success.

"This is a very difficult problem," agrees Lambert Schomaker, a researcher at University of Groningen, Netherlands, who has developed computational methods to identify the handwriting of mediaeval monks, which is much easier to link to a writer compared with chisel marks on stone.

**Database plan**

Although Panagopoulos' team correctly attributed all the inscriptions to their rightful chiseller, Schomaker worries that shadows could distort the digital photographs used in the analysis. Three-dimensional lasers scans of the inscriptions may offer more precision, he says.

Panagopoulos says his team is looking to use 3D images in the future.

The Greek computer scientists would also like to build a comprehensive database of digital inscriptions and attributions, so any newly discovered or analysed inscription could be quickly attributed and dated.

***See also: Decoding antiquity: Eight scripts that still can't be read***

*Journal references: Panagopoulos' study – IEEE Transactions on Pattern Analysis and Machine Intelligence (DOI: 10.1109/TPAMI.2008.201); Tracy's report – American Journal of Archaeology (Vol 113 (2009), No 1, p 99-102)*

## Scientists 'rebuild' giant moa using ancient DNA

***The paper published in the Proceedings of the Royal Society of London Series B. [PDF] (2.35M)***

Scientists have performed the first DNA-based reconstruction of the giant extinct moa bird, using prehistoric feathers recovered from caves and rock shelters in New Zealand.

Researchers from the University of Adelaide and Landcare Research in New Zealand have identified four different moa species after retrieving ancient DNA from moa feathers believed to be at least 2500 years old.

The giant birds - measuring up to 2.5 metres and weighing 250 kilograms - were the dominant animals in New Zealand's pre-human environment but were quickly exterminated after the arrival of the Maori around 1280AD.

PhD student Nicolas Rawlence from the University's Australian Centre for Ancient DNA says until now, the scientific community has not known what the 10 different species of moa looked like. "By using ancient DNA we have been able to connect feathers to four different moa species," he says.

The researchers compared the feathers to others found in the sediments from red-crowned parakeets that are still living today, determining they had not faded or changed in colour. They then reconstructed the appearance of the stout-legged moa, heavy-footed moa, upland moa and the South Island giant moa.

Their findings were published today in the Proceedings of the Royal Society of London Series B.

"The surprising thing is that while many of the species had a similar, relatively plain brown plumage for camouflage, some had white-tipped feathers to create a speckled appearance," Mr Rawlence says.

A co-author of the study, Dr Jamie Wood from Landcare Research, says it is likely that the drab colouring was driven by selection to avoid predation by the extinct Haast's eagle, the largest and most powerful eagle in the world.

The research team also demonstrated that it is possible to retrieve DNA from all parts of the ancient feathers, not just the tip of the quill, as previously thought.

"This important finding opens the way to study DNA from museum bird skins while causing almost no damage to these valuable specimens, just by clipping a small part of a single feather," says Dr Kyle Armstrong from the Australian Centre for Ancient DNA (ACAD).

ACAD Director Professor Alan Cooper says this finding suggests it may be possible to reconstruct the appearance of other extinct birds using feathers from fossil deposits.

"There are so many enigmatic extinct species that it would be great to see `clothed'," Professor Cooper says.

## Incredible shrinking sheep blamed on climate change

* 19:00 02 July 2009 **by Michael Marshall**

Sheep living on a remote island off the coast of Scotland have been shrinking for 20 years. Now it seems shorter winters caused by climate change are responsible.

Soay sheep are a primitive breed of domestic sheep, which live on the island of Hirta, in the St Kilda archipelago, without human interference. From 1955 onwards, the population has been closely studied.

Over the last 20 years, the average size of the sheep has been getting smaller, but it has been unclear why – particularly as natural selection would tend to drive the development of bigger bodies.

**Sheep stats**

To explore the effects of environmental change and natural selection, Timothy Coulson of Imperial College London and colleagues modified the Price equation, which is used to describe how natural selection changes a population from one generation to the next.

Coulson's team extended the equation so that it could reproduce the effects of a variable environment: how weather and seasons have changed from one year to the next, for example. They also modified it so that they could split the population up into different age groups, and describe changes in them separately.

*Shrinking will just make this Soay lamb cuter* **Image: Gross L/Public Library of Science**

This modification allowed them to pin down the factors that have affected the size of the sheep.

Natural selection pushes the sheep to get bigger, as the smallest individuals tend not to survive through hard winters to reproduce, they found.

However, this size increase is largely offset by the so-called "young mum effect" – the tendency for female sheep in their first breeding seasons to have offspring that are smaller than they themselves were at birth. The study is the first to take this effect into account.

**Dearth of deaths**

Over and above these factors, the modelling revealed that one of the most powerful influences on size was the gradual warming of the climate, driven by changes to the North Atlantic Oscillation ocean current, which has led to shorter winters on the island. As a consequence, the vulnerable smaller sheep were more likely to survive the winter, pushing average size down over successive generations.

"Because fewer sheep are dying, I think that means the environment is getting better for them," says Coulson. "The winters are less harsh than they used to be."

Kaustuv Roy, an evolutionary biologist at the University of California San Diego, who was not involved in the study, is impressed. "Their results are really useful, because they tease apart the different processes. It's a really nice study," he says. Roy adds the team's modification of the Price equation could be used widely. "They've come up with a new approach, which people will definitely apply to other systems," he says.

*Journal reference: Science, DOI: 10.1126/science.1173668 (in press)*

## Research output in developing countries reveals 194 percent increase in five years

### *Research4Life demonstrates profound impact on scholarly landscape*

London, 2 July 2009 – The partners of Research4Life announced today at the World Conference of Science Journalists 2009 that a new research impact analysis has demonstrated a dramatic rise in research output by scientists in the developing world since 2002. By comparing absolute growth in published research before (1996 – 2002) and after (2002 - 2008) the advent of the Research4Life programmes, the analysis has revealed a 194% or 6.4-fold increase in articles published in peer reviewed journals.

Research4Life is the collective name given to HINARI, AGORA and OARE, the three public-private partnerships that offer health, agriculture and environmental research for free or at very low cost to developing countries. Key partners include WHO,FAO,UNEP, Cornell and Yale Universities, the International Association of Scientific, Technical and Medical Publishers and Microsoft as the technology partner. Over 150 publishers, among them Elsevier, Springer, Wiley-Blackwell and Oxford University Press provide the journal content.

The analysis, conducted by Elsevier's Associate Director of Scientometrics & Market Analysis, Dr Andrew Plume, showed that absolute growth in research between 1996 - 2002 was 25% in non Research4Life countries (countries not eligible due to their GNI per capita), 22% in Band 1 countries (eligible countries with less than $1250 annual per capita income or GNI) and 30% in Band 2 countries (eligible countries with $1251 to $3500 GNI). Five years on, between 2002 - 2008, the same figures are dramatically higher at 67%, 145% and 194% respectively indicating 2.6-, 6.5- and 6.4-fold increases over the 1996-2002 growth. Dr Plume used a database sourced from Thomson Reuters to count the appearance of each country in the author affiliations of indexed journal articles, and then grouped these countries by their Research4Life eligibility.

In addition, an in-depth look at three selected Band 1 countries, (Nigeria, Kenya, and Tanzania) and one Band 2 country (Bulgaria) reveals a remarkable progression of article output from 1996 – 2008. By contrast, the

non Research4Life country Japan (for example) showed steady and continuous growth over this period without a sharp change in output over the period analysed.

"The opportunities to conduct original scholarly research without access to the world's published literature are limited. Discoveries build on generations of research done previously," remarked Kimberly Parker, HINARI Program Manager at the WHO. "Research4Life has extended the reach of that scholarly heritage into the developing world, increasing researchers' opportunities to participate in the global research community by conducting groundbreaking research, collaborating with global colleagues, and in time contributing to evidence-based scientific policy in their own countries. We are very excited to see the growing output coming from the developing world."

Dr Andrew Plume noted, "The massive and sustained growth in scholarly output from the Research4Life countries, over and above the growth for the rest of the world, is probably the result of many related factors such as scientific policy, government and private research funding, and other global developments. However, such a dramatic increase in research output also reflects a clear correlation with the launch of the Research4Life programmes. These statistics point to Research4Life's profound impact on institutions and individual researchers' ability to publish."

"Since we have had access to Research4Life, the researchers, and especially the clinicians at the College of Medicine, University of Port Harcourt, have been able to engage more with the global science community," stated Henrietta Otokunefor, Automation Librarian at the University of Port Harcourt Library in Nigeria. "The library computers and those at the ICTC for faculty are often occupied and I've seen a growth in published research from our students as well. It is great to see that Nigeria has made progress in this area as increased scientific developments can lead to improved health and economics, and in the end, a better quality of life."

The results of the impact analysis are further illustrated by Research4Life's recent institutional growth findings announced in May 2009. OARE, the Online Access to Research in the Environment program has registered 1500 institutions since its launch in 2006, an increase of nearly 700 percent. The Health Access to Research programme: HINARI has grown by 61% since 2006 so that researchers at 3,866 not-for-profit institutions in 108 countries now have access to over 6,300 medical and health journals. AGORA or Access to Global Online Research in Agriculture has increased registrants by 77% since 2006, providing researchers at 1,760 developing world institutions with access to 1,276 food, agriculture, and related social sciences journals.

## Prostate cancer patients disease free after 5 years likely to be disease free after 10 years

Prostate cancer patients who receive brachytherapy and remain free of disease for five years or greater are unlikely to have a recurrence at 10 years, according to a study in the July 1 issue of the International Journal of Radiation Oncology*Biology*Physics, the official journal of the American Society for Radiation Oncology (ASTRO). Brachytherapy is the placement of radioactive sources in or just next to a tumor either permanently or temporarily, depending upon the cancer.

In the study, researchers at The Mount Sinai Medical Center Departments of Radiation Oncology and Urology in New York followed 742 prostate cancer patients who were treated with brachytherapy alone, brachytherapy and hormonal therapy, or combined brachytherapy and external beam radiotherapy (EBRT) between 1991 and 2002. None of these patients had recurred during their first five years post-treatment. They found that the PSA level taken at five years was an indicator of how well a patient would do in the future and the overall chance of being cancer free at 10 years was 97 percent.

Also, none of the study participants developed metastatic disease or died from prostate cancer.

"Our data have indicated that improvements in treatment are continuing and that these will continue to have an effect on prostate brachytherapy data for years to come," Richard Stock, M.D., lead author of the study and chairman of radiation oncology at The Mount Sinai Medical Center, said. "Late failure rates will continue to decrease, making prostate brachytherapy alone and combined with hormonal therapy and/or EBRT an increasingly attractive treatment option."

## New dinosaurs found in Australia

Australian palaeontologists say they have discovered three new dinosaur species after examining fossils dug up in Queensland. Writing in the journal PLoS One, they describe one of the creatures as a fearsome predator with three large slashing claws on each hand.

The other two were herbivores: one a tall giraffe-like creature, the other of stocky build like a hippopotamus.

The fossils date back nearly 100 million years. They were found in rocks known as the Winton Formation.

The dinosaurs have been named after characters in Australia's famous song Waltzing Matilda.

The carnivore, which has the scientific classification Australovenator wintonensis, has therefore been dubbed "Banjo" after Banjo Patterson, who composed the song in Winton in 1885.

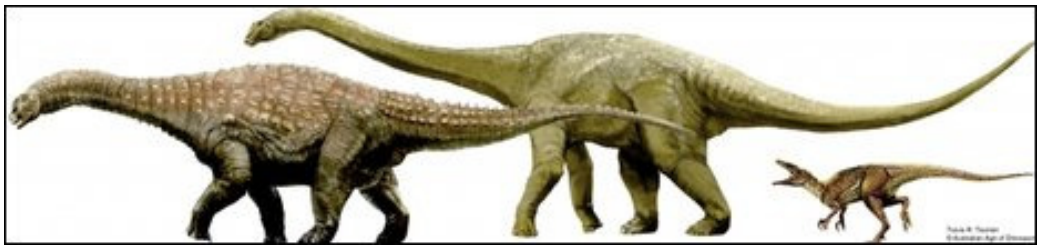
Queensland Museum palaeontologist Scott Hucknell said the creature would have been a terrifying prospect.

"The cheetah of his time, Banjo was light and agile. He could run down most prey with ease over open ground," he told reporters.

The two plant-eating, four-legged sauropod species are new types of titanosaurs - the largest animals ever to walk the Earth.

"Clancy" (scientific name: Witonotitan wattsi ) was a tall slender animal, while Matilda ( Diamantinasaurus matildae ) was more stocky and hippo-like.

Banjo and Matilda - possibly predator and his prey - were found buried together in a 98-million-year-old billabong, or stagnant pond.



*A comparison of all three: "Matilda" (L), "Clancy" (C) and "Banjo" (R)*

The findings have been published in the public access journal Public Library of Science One (PLoS One), and were announced by Queensland Premier Anna Bligh at the Australian Age of Dinosaurs Museum of Natural History in Winton. She said the discoveries were a major breakthrough in the scientific understanding of prehistoric life in Australia. Museum Victoria palaeontologist John Long described the fossils as "amazing".

The Sydney Morning Herald newspaper quoted him as saying that the creatures put Australia back on the international map of big dinosaur discoveries for the first time since 1981, when the unearthing of Muttaburrasaurus , a large four-legged herbivore that could rear up on two legs, was announced.

The new species will be part of the Australian Age of Dinosaurs Museum of Natural History under construction in Winton. It should be completed in 2015.

## Fellow students smell your exam fear

STUDENTS facing exams this month, take heart: your companions can smell your fear, and they empathise.

That's the implication of a study by Bettina Pause at the University of Dusseldorf, Germany, and colleagues. They put absorbent pads under the armpits of 49 university students an hour before they took their final oral exam and again as the same students exercised. Another set of students then sniffed the sweat samples while having their brains scanned.

None perceived a difference between the two types of sweat, but the pre-exam sweat had a different effect on brain activity, lighting up areas that process social and emotional signals, as well as several areas thought to be involved in empathy (PLoS One, DOI: 10.1371/journal.pone.0005987).

The researchers conclude that anxiety prompts the release of a chemical that bypasses conscious experience, automatically triggering similar feelings in anyone who sniffs it. This may allow fear to spread quickly and speed our ability to flee danger. A previous experiment found that sweat from skydivers activated anxiety circuits in sniffers' brains.

**Global Update**

## Tuberculosis: TB Vaccine Too Dangerous for Babies With AIDS Virus, Study Says

**By DONALD G. McNEIL Jr.**

The vaccine against tuberculosis that is routinely given to 75 percent of the world's infants is too risky to give to those born infected with the AIDS virus, says a new study published by the World Health Organization. It recommended that vaccination be delayed until babies can be tested.

The Bacille Calmette-Guérin vaccine, known as BCG, protects children well against deadly tuberculous meningitis, though it does less well against the lung form. It has been in use since 1921, and children in many countries — though not the United States, which never adopted it - bear its characteristic round scar.

But because it is a live vaccine, a weakened strain of bovine tuberculosis, it can cause its own problem - "disseminated BCG disease," a type of bacterial infection that can rage through the body. It is fatal in more than 70 percent of cases.

In countries like South Africa, where both tuberculosis and mother-to-child transmission of the AIDS virus is common, the vaccine gives infected children almost no protection against tuberculosis and instead may kill them with BCG disease, the authors found. The study, done in three South African pediatric hospitals, was complex because BCG disease and tuberculosis can look identical, so each infection had to be cultured.

Although they recommend delaying vaccination, the authors acknowledge that will not be easy. In poor countries, babies are often not brought back at 6 weeks for a test and 10 weeks for a shot. So the dangerous practice of vaccinating every baby may continue, because it protects the uninfected ones.