## Most H1N1 patients with respiratory failure treated with oxygenating system survive illness

Despite the severity of disease and the intensity of treatment, most patients in Australia and New Zealand who experienced respiratory failure as a result of 2009 influenza A(H1N1) and were treated with a system that adds oxygen to the patient's blood survived the disease, according to a study to appear in the November 4 issue of JAMA. This study is being published early online because of its public health importance.

The influenza A(H1N1) pandemic affected Australia and New Zealand during the 2009 southern hemisphere winter, causing an epidemic of critical illness. Some patients developed severe acute respiratory distress syndrome (ARDS) and were treated with extracorporeal membrane oxygenation (ECMO), according to background information in the article.

ARDS is a lung condition that leads to respiratory failure due to the rapid accumulation of fluid in the lungs. ECMO is a type of life support that circulates blood through a system that adds oxygen. ECMO was used for the patients in this study because they developed very low blood oxygen levels that developed rapidly despite standard ventilator (or respirator) settings. ECMO is generally used for a limited time because of the risks of bleeding, clotting, infection, and organ failure.

The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators in collaboration with the Australian and New Zealand Intensive Care Research Centre at Monash University in Melbourne, conducted an observational study of patients with 2009 influenza A(H1N1)-associated ARDS treated with ECMO in 15 intensive care units (ICUs) in Australia and New Zealand between June 1 and August 31, 2009. The researchers looked at incidence, clinical features, the degree of lung dysfunction, technical characteristics, the duration of ECMO, complications, and survival.

The study found that 68 patients with severe influenza-associated ARDS were treated with ECMO, including 53 with confirmed 2009 influenza A(H1N1). An additional 133 patients with influenza A received mechanical ventilation, but not ECMO, in the same ICUs. The 68 patients who received ECMO had a median (midpoint) age of 34.4 years and half were men.

"Affected patients were often young adults, pregnant or postpartum, obese, had severe respiratory failure before ECMO, and received prolonged mechanical ventilation and ECMO support," the authors write.

The median duration of ECMO support was ten days. At the time of reporting, 54 of the 68 patients had survived and 14 (21 percent) had died. Six patients remained in ICU, including two who were still receiving ECMO. Sixteen patients were still hospitalized, but out of ICU, and 32 had been discharged from the hospital.

"Despite their illness severity and the prolonged use of life support, most of these patients survived," the authors conclude. "This information should facilitate health care planning and clinical management for these complex patients during the ongoing pandemic."

*(JAMA. 2009;302(17):doi:10.1001/JAMA.2009.1535. Available pre-embargo to the media at www.jamamedia.org)*

## Investment in Parkinson's disease data bank yields potential therapy

Individuals with Parkinson's disease who have higher levels of a metabolite called urate in their blood and in cerebrospinal fluid (CSF) have a slower rate of disease progression, according to a study funded by the National Institutes of Health. A clinical trial is under way to examine the safety and potential benefits of supplemental urate elevation for recently diagnosed Parkinson's patients who have low urate levels.

Investigators demonstrated the link with urate by mining a repository of clinical data and tissue samples collected from Parkinson's patients more than 20 years ago as part of a pioneering study called DATATOP, funded by NIH's National Institute of Neurological Disorders and Stroke (NINDS). The new study appears in Archives of Neurology. It was funded primarily by NINDS, with additional support from the Department of Defense and private organizations.

"This study speaks to the value of saving data and biospecimens from large clinical studies, and making them available to the research community to pursue new, unanticipated ideas," said Michael Schwarzschild, M.D., Ph.D., an associate professor of neurology at Massachusetts General Hospital in Boston, who lead the study together with Alberto Ascherio, M.D., Dr.PH, a professor of epidemiology and nutrition at the Harvard School of Public Health.

Experts emphasize there is no proof that elevating urate levels will help against Parkinson's disease, and that it should not be attempted outside of a clinical trial, where physicians can closely monitor possible benefits and risks, such as gout and heart disease.

Parkinson's disease attacks cells in the brain that regulate movement by releasing a chemical called dopamine. The loss of those cells leads to progressively disabling symptoms, including involuntary shaking, slow movement, stiffened muscle tone, and impaired balance. Levodopa, a precursor of dopamine, provides some relief from those symptoms but does not alter the disease course.

"Effective treatments for Parkinson's disease have been elusive. By taking a fresh look at the repository of clinical data and stored samples from the two-decade old DATATOP trial, this study has identified urate as a biomarker for the progression of the disease and suggests a potential new pathway for targeted therapy development," said Margaret Sutherland, Ph.D., a program director at NINDS.

Urate (or uric acid) is a product of the body's metabolism. Diets high in liver, seafood, and dried beans and peas tend to cause higher levels of urate in the blood, and are also associated with gout – a painful buildup of urate crystals in the joints. Urate is a natural antioxidant, and many studies have found that antioxidants slow the course of Parkinson's disease in animal models. Also, prior research from Dr. Ascherio's epidemiology group has shown that people who have gout or who consume foods associated with high urate have a lower incidence of Parkinson's disease.

Drs. Ascherio and Schwarzschild and their collaborators in the Parkinson Study Group are the first to examine whether urate levels are related to the course of Parkinson's disease. Last year, after mining data from another large clinical trial, they reported that high levels of urate in blood were associated with a slower disease course. The new study is an expansion of that work and the first time that investigators have looked for a connection between the course of Parkinson's and levels of urate in CSF, the fluid that fills spaces in the brain and spinal cord.

The DATATOP trial began in the late 1980s, and was designed to test whether vitamin E, the drug deprenyl (selegiline), or a combination of both could slow the course of early-stage Parkinson's disease. The trial enrolled 800 patients and followed them for two years. Deprenyl, which inhibits the breakdown of dopamine, was found to provide short-term relief from symptoms. Vitamin E showed no significant benefit.

As part of the DATATOP trial, samples of blood and CSF were acquired from more than 90 percent of the participants at enrollment. In the new study, the researchers analyzed whether blood and CSF urate levels were related to the course of Parkinson's by relying on blood measurements done at the time of the DATATOP trial and by taking new measurements from the 20-year-old, frozen samples of CSF.

Looking across all of the treatment groups in the study, the researchers found that patients with the highest urate levels in their blood and CSF had a slower functional decline as measured by their need for levodopa treatment. The results suggest that urate elevation might slow the course of Parkinson's in patients with early-stage disease and low urate levels.

*The Safety of URate Elevation in Parkinson Disease (SURE-PD) study, led by Dr. Schwarzschild, is a placebo-controlled trial designed to test that hypothesis. Patients in the treatment arm of the trial will take daily, oral doses of a urate precursor called inosine for up to two years. The trial is funded by the Michael J. Fox Foundation, and is recruiting recently diagnosed patients who do not yet require Parkinson's medication at 11 sites across the United States. For more information, visit www.clinicaltrials.gov and search by the identifier NCT00833690.*

*Reference: Ascherio A et al. "Urate as a Predictor of the Rate of Clinical Decline in Parkinson Disease." Archives of Neurology, published online October 12, 2009.*

## Sick American dogs get first shot at cancer drugs

* 01:00 13 October 2009 **by Andy Coghlan**

Dogs with cancer in the US are now entitled to receive experimental drugs – before the drugs are available for humans. Twelve trials are under way on groups of 15 to 60 dogs, and in several of them cancers have disappeared.

"We've had dramatic remissions in dogs with really aggressive cancers," says Chand Khanna, head of the Comparative Oncology Trials Consortium newly formed in Bethesda, Maryland, by the US National Cancer Institute. "We've also had responses allowing dogs to have their original cancers surgically removed," he says.

**Forget mice and rats**

The rationale is that unlike mice and rats, which are kept in a highly regimented experimental setting, pet dogs experience cancer in a similar way to humans. As in people, cancers in dogs spread to form secondaries and can become resistant to drugs, and the animals can have relapses.

Not only that, but dogs suffer from cancers as variable as those affecting humans, so treating them gives us a much better idea of what would happen in a cross-section of humans than we could gain from lab studies of mice.

The consortium consists of 19 veterinary schools, and there are plans to extend it to Europe. Owners can opt for conventional drugs or experimental ones, including some that are untested in humans and others that are already undergoing trials, but that need additional animal data – for example on dosing – before they can proceed to the next stage.

As well as looking after their sick dog, owners can help gather data for the researchers. "They're given notebooks so that they can complete assessments of quality of life, appetite, demeanour and perhaps even collect some specimens," says Khanna.

**Sensitive area**

Because owners carry on caring for the dogs, and because the hope is that pet dogs will get better as a result of the treatment, the approach also challenges claims by antivivisectionists that all experimentation on animals is wrong. "I understand their sensitivities, and we've had informed discussions with individuals, and some do see the value of helping dogs with cancer in this way," says Khanna.

But some antivivisectionists think the trials will provide an excuse to try out risky procedures and drugs seen as unacceptably dangerous in people. "This raises serious concerns with respect to what the dogs may have to endure," says Nedim Buyukmihci, a vet consultant to the British Union for the Abolition of Vivisection. Instead, he favours giving untested drugs directly to people.

**Every dog matters**

Khanna says, however, that the top priority for every dog is their well-being. "It's important that the trials are designed with the care of the animals as priority, and also that there's an informed consent process each time," he says.

Cancer researchers in Europe are watching closely to see whether to join the consortium. "Studying dogs, with their owners' consent and following ethical guidelines, after they have naturally developed cancer, is an interesting approach to learning more about the disease," says Joanna Owens, communications manager at the Cancer Research UK charity in London. "We look forward to following the progress of this initiative and the findings that come out of their research."

*Journal reference: PLoS Medicine, DOI: 10.1371/journal.pmed.1000162 (in press)*

## Remote controlled bugs buzz off

**By Patrick Jackson** BBC News


***Three varieties of beetles have been used in the project***

A Pentagon-sponsored project to control flying insects remotely has sent ripples of excitement across the scientific pond. Part insect, part machine, the "cyborg beetle" has been tested successfully by its developers at the University of California, Berkeley.

Video footage shows a beetle being "flown" around a room by a man using a laptop. At one point it is tethered to a transparent plastic plate, and its tiny limbs can be seen twitching in response to the operator's joy stick.

The developers, Michel Maharbiz and Hirotaka Sato, "demonstrated the remote control of insects in free flight via an implantable radio-equipped miniature neural stimulating system", they told the current edition of Frontiers in Neuroscience magazine.

Noel Sharkey, professor of robotics and artificial intelligence at the UK's Sheffield University, says that while attempts to control insects such as cockroaches are not new, this is the first time man has managed to remotely control a flying insect. What intrigues him is the Berkeley project's ultimate military application.

**Pupal stage**

At Berkeley, electrodes are implanted when the beetle is in the pupal stage of its growth.

"It's because we have got much better at nanotechnology and making small probes that we are able to do this," Professor Sharkey told the BBC's World Today programme.

"You are plugging electrical devices into its nervous system and then triggering its muscles so that when it is flying, if you put a little bit more zorch into the muscle on the left-hand side, that will flap a bit harder and that will control the direction it is going in."

The team at Berkeley have been using beetles from Cameroon as large as the palm of a human hand, which leaves Professor Sharkey slightly puzzled. “The electronics is simply too heavy for a smaller beetle to carry," he says. "They can remotely control its muscles but it can't actually take off and I'm not sure really what they're playing at here.

"You talk about the payload of a flying object such as a plane or model aeroplane, the payload being the amount it can carry while staying in the air.

"Now with these big beetles, they can get the electronics aboard but nothing else. For instance, for this to be useful at all for the military, it would have to have a GPS receiver/transmitter so they could tell what position it was in."

Nor, the professor suggests, would the beetle be much good for surveillance without a camera equipped with a decent-sized lens.

**CYBORG BEETLES**


***Fitted with three electrodes, a microbattery and a microcontroller***

***Three beetles used: cotinis texana (2cm long, 0.3g payload), mecynorhina torquata (7cm, 1.8g) and megasoma elephas (20cm, 4.0g)***

***Project funded by the US Defense Advanced Research Projects Agency***

"Other purposes you could use it for - but which would be totally illegal under the current laws of war - would be carrying any kind of chemical or biological weapons, so you could do personal assassinations," he adds.

**'Insect couriers'**

Cyborg beetles may serve as useful models for "micro air vehicles", the Berkeley team say in their findings.

The US Defense Advanced Research Projects Agency (Darpa), which funds their research, has been pursuing a Nano Air Vehicle (NAV).

Set to be extremely small (less than 7.5cm) and ultra-light (less than 10g), this would "provide the warfighter with unprecedented capability for urban mission operations", Darpa says on its website.

The Berkeley scientists suggest that the beetles themselves could serve "as couriers to locations not easily accessible to humans or terrestrial robots".

As well as beetles, they are investigating flies, moths and dragonflies because of their "as-yet unmatched flight capabilities and increasingly well understood muscular and nervous systems".

Professor Sharkey concedes that ten or twenty years from now, such ideas might work.

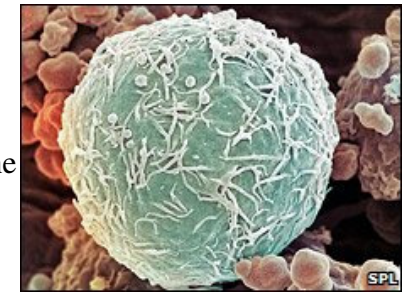
"It's pretty creepy really," he says, chuckling. "I'm laughing now but this really has sinister underpinnings. You remember the Wright Brothers, you see all those comedy films where they are trying to fly a plane and everyone is laughing at them - it's at that sort of stage."

Whether or not the US military eventually adds some kind of insect launch or surveillance vehicle to its growing fleet of unmanned aircraft, the Californian project is increasing our knowledge of flight.

"It's actually quite useful to find out about the dynamics of flight and the biomechanics of the insect," says Professor Starkey. "It's telling the scientists more than it is the military."

## Mother can pass on cancer in womb

***Scientists have proved that it is possible for a mother's cancer cells to be passed to her unborn child.***




*Leukaemia cells crossed across the placenta*

There are very rare cases where a mother and child appear to share the same cancer, but in theory the child's immune system should block the cancer.
However, an analysis by a British-led team of one such case shows the cells which caused leukaemia in the child could only have come from the mother. The study appears in Proceedings of the National Academy of Sciences.
Whether it is possible for a mother to "infect" her unborn child with cancer has puzzled scientists for 100 years.

In theory any cancer cells that manage to cross the placenta into the baby's bloodstream should be targeted for destruction by the child's immune system. But there are records of 17 cases of a mother and baby appearing to share the same cancer - usually leukaemia or melanoma.

The latest study focused on a Japanese woman and her baby, who both developed leukaemia. The researchers used an advanced genetic fingerprinting technique to prove that the leukaemia cells found in the baby had originated from the mother. They showed that both patients' leukaemic cells carried an identical mutated cancer gene.

However, they also showed that the child had not inherited this gene from its mother - meaning it could not have developed this type of leukaemia in isolation.

**No signature**

Next, the researchers examined how the cancer cells could have neutralised the baby's immune system.

They found that the cancer cells lacked some DNA which played a crucial role in giving them their own specific molecular identity. Without this telltale molecular sign, the child's immune system was unable to recognise the cells as foreign, and thus was not mobilised to attack them.

Lead researcher Professor Mel Greaves, of the Institute of Cancer Research, said: "It appears that in this and, we presume, other cases of mother-to-offspring cancer, the maternal cancer cells did cross the placenta into the developing foetus and succeeded in implanting because they were invisible to the immune system.

"We are pleased to have resolved this longstanding puzzle. But we stress that such mother-to-offspring transfer of cancer is exceedingly rare and the chances of any pregnant woman with cancer passing it on to her child are remote."

Professor Peter Johnson, chief clinician at the charity Cancer Research UK, stressed that it was extremely unusual for cancer to pass from a mother to her baby. He said: "This is really important research as it adds to the evidence that cancers need to evade the immune system before they can grow, giving hope that by alerting a patient's immune system to a cancer we can develop new types of treatment.

"Women needing cancer treatment around the time of having a baby who are worried about this research should speak to the specialists looking after them for advice."

Dr David Grant, scientific director at Leukaemia Research, which part-funded the study, said it should help work to harness the power of the immune system to first cure and then protect patients from leukaemia.

**Really?**

## The Claim: Always Wash Your Hands With Hot Water, Not Cold.

**By ANAHAD O'CONNOR**

**THE FACTS** With swine flu sweeping across the country, health officials are reminding Americans to wash their hands often to reduce the spread of the disease.

Soap and warm water have long been said to prevent the spread of infections, but is warm or hot water really more effective than cold?

In its medical literature, the Food and Drug Administration states that hot water comfortable enough for washing hands is not hot enough to kill bacteria, but is more effective than cold water because it removes oils from the hand that can harbor bacteria.

But in a 2005 report in the Journal of Occupational and Environmental Medicine, scientists with the Joint Bank Group/Fund Health Services Department pointed out that in studies in which subjects had their hands contaminated, and then were instructed to wash and rinse with soap for 25 seconds using water with temperatures ranging from 40 degrees Fahrenheit to 120 degrees, the various temperatures had "no effect on transient or resident bacterial reduction."

They found no evidence that hot water had any benefit, and noted that it might increase the "irritant capacity" of some soaps, causing contact dermatitis. "Temperature of water used for hand washing should not be guided by antibacterial effects but comfort," they wrote, "which is in the tepid to warm temperature range. The usage of tepid water instead of hot water also has economic benefits."

**THE BOTTOM LINE** Hot water for hand washing has not been proved to remove germs better than cold water.

## Is a Virus the Cause of Fatigue Syndrome?

**By DENISE GRADY**

Could a virus be the cause of chronic fatigue syndrome?

A study published last week in the journal Science suggested that might be the case, reporting that many patients who had the syndrome were infected with a recently discovered virus.

Chronic fatigue syndrome has long been a medical mystery and the subject of debate, sometimes bitter, among doctors, researchers and patients. It affects at least one million Americans, causing extreme fatigue, muscle and joint pain, sleep problems, difficulty concentrating and other symptoms. Its cause is unknown, symptoms can last for years and there is no effective treatment. Researchers disagree about whether it is one disease or a collection of symptoms that may have different causes in different patients. It has sometimes been stigmatized as more mental than physical, with patients labeled neurotic, depressed or hypochondriacal. Many patients find even the name of the disorder offensive, a not-so-subtle hint that it is not a real disease.

The new report has intrigued scientists, been seen as vindication by some patients and inspired hope for a treatment. "I just feel like the whole future has changed for us," said Anne Ursu, 36, a writer living in Cleveland who has had the syndrome in the past.

But the new study is not conclusive, and a great deal of work remains to be done to find out whether the new virus really does play a role. Just detecting it in patients does not prove it is what made them sick; people with the syndrome may have some other underlying problem that makes them susceptible to the virus, which could be just a passenger in their cells.

Even so, thousands of patients have already contacted scientists, asking to be tested, said Dr. Judy Mikovits, the first author of the study and the research director at the Whittemore Peterson Institute in Reno, a research center created by the parents of a woman who has the syndrome. Dr. Mikovits said she expected a test to become available "within weeks."

The new suspect is a xenotropic murine leukemia virus-related virus, or XMRV, which probably descended from a group of viruses that cause cancer in mice. How or when XMRV found its way into humans is unknown. But it has also been linked to cancer in people: it was first identified three years ago, in prostate cancer, and later detected in about one-quarter of biopsies from men with that disease (and in only 6 percent of benign biopsies). It is a retrovirus, from the same notorious family that causes AIDS and leukemia in people.

Dr. Mikovits and researchers from the National Cancer Institute and the Cleveland Clinic reported in Science that 68 of 101 patients with chronic fatigue syndrome, or 67 percent, were infected with XMRV,

compared with only 3.7 percent of 218 healthy control subjects. Further testing after the paper was written found the virus in nearly 98 percent of about 300 patients with the syndrome, Dr. Mikovits said.

She said she believed that the virus would eventually be found in every patient with chronic fatigue syndrome. XMRV affects the immune system, can probably cause a variety of illnesses and may join forces with other viruses to bring on the syndrome, she said.

The study received a mixed review from Dr. William C. Reeves, who directs public health research on the syndrome at the Centers for Disease Control and Prevention. He called the research exciting but preliminary, and said he was surprised that a prestigious journal like Science had published it, because the researchers did not state the ages or sex of the patients and controls, or describe the duration of the illness or how it came on.

"If I don't know the nature of the cases and controls, I can't interpret the findings," Dr. Reeves said. "We and others are looking at our own specimens and trying to confirm it," he said, adding, "If we validate it, great. My expectation is that we will not." He noted that there had been false starts before, including a study in the 1990s linking the syndrome to another retrovirus, which could not be confirmed by later research.

Many patients and a community of doctors and researchers who specialize in the syndrome take issue with the disease centers' approach to the illness and the way it defines who is affected. They claim that the C.D.C. includes people whose problems are purely psychiatric, muddying the water and confounding efforts to find a physical cause.

Frustration with the lack of answers led Annette and Harvey Whittemore, whose 31-year-old daughter has had the syndrome for 20 years, to spend several million dollars to set up a research institute at the University of Nevada in Reno in 2004, and to hire Dr. Mikovits to direct it.

Mrs. Whittemore said she had long believed that the syndrome was an infectious disease, but that scientists had rejected the idea. She finally decided, she said, "if there was a place of our own where we could find the answers, we could do it more quickly."

Dr. William Schaffner, an infectious disease expert at Vanderbilt University, said that the notion of a lingering viral infection was plausible. He said that although some patients claiming to have the syndrome seemed more likely to have a psychological problem, others seemed to have a physical illness.

"There is a group who are young, healthy, active and engaged, and all of a sudden they are laid low by something," Dr. Schaffner said. "Everyone tells the physicians these are people who are functional and productive, and this is totally out of character. They are frustrated and often quite disheartened. You feel that medical science hasn't caught up with their illness yet."

To determine whether XMRV is to blame, more studies are needed, said Dr. John Coffin, a professor of molecular biology and microbiology at Tufts University. It would help to find an animal model, he said, and to look at stored blood samples to find out if there were people who became ill some set amount of time after contracting the virus. If antiviral drugs make patients improve, that will also help make the case against the virus, he said.

The National Cancer Institute is taking XMRV seriously, said Dr. Stuart Le Grice, head of its Center of Excellence in HIV/AIDS and Cancer Virology.

He said health officials became especially concerned last spring when several research teams looking at prostate cancer reported finding XMRV in 3 percent to 4 percent of blood samples from healthy people in control groups. That could translate into 10 million American being infected with a newly discovered, poorly understood retrovirus that has already been linked to two diseases.

"Any virus at that level is obviously cause for concern," Dr. Le Grice said, adding that it was important to find out if the virus was associated with any more diseases, and how closely.

He said that just carrying the virus did not necessarily mean a person was at high risk for disease, noting that people may harbor other viruses that will never harm them. The immune system probably keeps the viruses in check. But he asked: "If it is a problem, how well can we diagnose it and how well can we treat it?"

Even though antiretroviral drugs have already been developed to treat H.I.V. infection, he said this virus was different and might need its own line of drugs.

He said more studies were needed to find out how common the virus is and how it is being transmitted. It is not known whether people can catch the disease from mice, or can infect one another. Retroviruses are often spread by blood and bodily fluids.

"How significant a risk is this to blood banks?" Dr. Le Grice asked. "Do we need to consider large-scale screening in blood banks?" He said the institute would be working to develop reliable diagnostic tests.

Dr. Le Grice emphasized that there is no evidence that the virus is spreading through the population. "I don't want to scare anyone at the moment," he said.

## Don't block folic acid in early pregnancy

***Medications that block folic acid are associated with increased abnormalities***

Using medication that reduces or blocks the actions of folic acid during the first trimester of pregnancy (weeks 1-12), increases the risk that the growing baby will develop abnormalities. This conclusion was reached by a team of Epidemiologists, Paediatricians, Clinical Pharmacologists, Obstetricians and Gynaecologists who examined birth and abortion data collected in Israel between 1998 and 2007.

The study drew information from 84,832 babies born at Soroka Medical Center, in Beer-Sheva, Israel. It was carried out as part of the PhD dissertation of Mgr. Ilan Matok, supervised by principal investigators Dr. Amalia Levy and Prof. Rafael Gorodischer from Ben-Gurion University of the Negev in Israel, in collaboration with the Division of Clinical Pharmacology, Hospital for Sick Children in Toronto, Canada (the BeMORE collaboration).

"After studying the data we concluded that first trimester exposure to folic acid antagonists is associated with increased risk for neural tube, cardiovascular and urinary tract defects," says paediatrician and clinical pharmacologist Rafael Gorodischer.

Healthcare professionals now encourage women to take folic acid supplements or eat food fortified with folic acid if they are planning to get pregnant as well as during early pregnancy, because there is clear evidence that this reduces the risk of any resulting baby having neural tube defects and possibly other birth defects (congenital malformations).

The team considered the effects of two groups of medications on pregnancy. Each group consists of drugs that prevent folic acid working in the body. One group (dihydrofolate reductase inhibitors), prevents folate being converted into its active metabolites and includes trimethoprim, sulfasalazine and methotrexate. The other medications are known to lower serum and tissue concentrations of folate by various mechanisms, and include antiepileptics (carbamazepine, phenytoin, lamotrigine, primidone, valproic acid and phenobarbital), and cholestyramine.

"The study shows that exposure to folic acid antagonists in the first trimester of pregnancy, more than doubled the risk of congenital malformations in the fetus, and that neural tube defects, such as spina bifida and malformations of the brain, are increased by more than six fold after exposure to these antagonists," said epidemiologist Dr. Amalia Levy.

"Clinicians should try to avoid the use of these drugs whenever possible in women contemplating pregnancy," concluded Gorodischer.

## Study finds rise in rate of undesirable events at start of academic year

***Research: Rate of undesirable events at beginning of academic year: Retrospective cohort study***

The rate of undesirable events in teaching hospitals increases at the beginning of the academic year, regardless of trainees' level of clinical experience, concludes new research from Australia published on bmj.com today.

At the beginning of an academic year, teaching hospitals around the world accept an influx of new trainees and fellows, and doctors who are already in specialist training move on to the next post within their training scheme. This transition phase is often considered to be the worst time of the year to be admitted to hospital. Previous studies have been inconclusive, but most have concluded that the quality of care remains uniform throughout the academic year.

To investigate this further, an international team of researchers set out to examine whether patients having an anaesthetic procedure carried out by first to fifth year trainees at the beginning of the academic year had a higher rate of undesirable events than patients operated on later in the year. They also analysed the trend in the rate of undesirable events throughout the year.

Using administrative and patient record data from a University affiliated hospital in Melbourne, Australia, the team analysed 19,560 patients over a period of five years (1995-2000). The rate of undesirable events was higher at the beginning of the academic year compared with the rest of the year (137 v 107 events per 1000 patient hours). This excess risk was seen for all trainees regardless of their level of clinical experience, suggesting that seniority of trainees does not protect patients from undesirable events.

The effect decreased progressively after the first month, and the trend disappeared fully after the fourth month of the year, particularly for events related to technical performance and overall management of patients. The fact that more experienced trainees have as many undesirable events as new trainees suggests that lack of technical skills is not the only mechanism explaining this phenomenon, say the authors. They suggest that new trainees are unfamiliar with the working environment, supervision is insufficient, and communication suffers.

Possible strategies to minimise this include improving trainees' orientation and integration during their first weeks of employment, increasing intensity of supervision of advanced trainees, and developing early training sessions aimed at improving technical and teamwork skills, they conclude.

These findings suggest that the current clinical system cannot absorb the effects of new personnel at the beginning of a new academic year, say researchers in an accompanying editorial.

Professor Paul Barack from Utrecht Medical Center in the Netherlands and Professor Julie Johnson from the University of New South Wales in Australia believe that reducing variation in patient care at the start of the academic year requires developing resilient systems in which individuals, teams, and their organisations can adapt and compensate for the disruptions of incoming inexperienced trainees.

Trainees need practice and mentorship, with increased patient awareness, closer supervision, and graduated clinical responsibilities, they conclude.

## New type of flying reptile discovered

***Discovered by scientists at the University of Leicester and the Geological Institute, Beijing, Darwin's pterodactyl preyed on flying dinosaurs and shows how a controversial type of evolution may have powered the origin of major new groups***

An international group of researchers from the University of Leicester (UK), and the Geological Institute, Beijing (China) have identified a new type of flying reptile – providing the first clear evidence of an unusual and controversial type of evolution.

Pterosaurs, flying reptiles, also known as pterodactyls, dominated the skies in the Mesozoic Era, the age of dinosaurs, 220-65 million years ago. Scientists have long recognized two different groups of pterosaurs: primitive long-tailed forms and their descendants, advanced short-tailed pterosaurs some of which reached gigantic size These groups are separated by a large evolutionary gap, identified in Darwin's time, that looked as if it would never be filled – until now.

Details of a new pterosaur, published today in the Proceedings of the Royal Society B: Biological Sciences fits exactly in the middle of that gap. Christened Darwinopterus, meaning Darwin's wing, the name of the new pterosaur honours the 200th anniversary of Charles Darwin's birth and the 150th anniversary of the publication of On the origin of species.

***This is the fossil skeleton of Darwinopterus (skull 185 mm long).*** **Lü Junchang**

Gaps in the fossil record are common – only a tiny proportion of all the animals and plants that ever lived were fortunate enough to become fossilised, and only a tiny proportion of these have been collected so far. Consequently, our understanding, both of the history of particular groups such as pterosaurs, and of the evolutionary processes that generated those histories, is still patchy and often controversial.

More than 20 fossil skeletons of Darwinopterus, some of them complete, were found earlier this year in north-east China in rocks dated at around 160 million years old. This is close to the boundary between the Middle and Late Jurassic and at least 10 million years older than the first bird, Archaeopteryx. The long jaws, rows of sharp-pointed teeth and rather flexible neck of this crow-sized pterosaur suggest that it might have been hawk-like, catching and killing other contemporary flying creatures. These included various pterosaurs tiny gliding mammals and small, pigeon-sized, meat-eating dinosaurs that, aided by their feathered arms and legs had recently taken to the air, and would later evolve into birds.

"Darwinopterus came as quite a shock to us" explained David Unwin part of the research team and based at the University of Leicester's School of Museum Studies. "We had always expected a gap-filler with typically intermediate features such as a moderately elongate tail – neither long nor short – but the strange thing about Darwinopterus is that it has a head and neck just like that of advanced pterosaurs, while the rest of the skeleton, including a very long tail, is identical to that of primitive forms".

***This is a drawing of Darwinopterus hunting a small feathered dinosaur (Anchiornis).*** **Mark Witton, University of Portsmouth**

Dr Unwin added: "The geological age of Darwinopterus and bizarre combination of advanced and primitive features reveal a great deal about the evolution of advanced pterosaurs from their primitive ancestors. First, it was quick, with lots of big changes concentrated into a short period of time. Second, whole groups of features

(termed modules by the researchers) that form important structures such as the skull, the neck, or the tail, seem to have evolved together. But, as Darwinopterus shows, not all these modules changed at the same time. The head and neck evolved first, followed later by the body, tail, wings and legs. It seems that natural selection was acting on and changing entire modules and not, as would normally be expected, just on single features such as the shape of the snout, or the form of a tooth. This supports the controversial idea of a relatively rapid "modular" form of evolution.

The research team warns that much more work is needed to substantiate this idea of modular evolution but, if it proves to be true, then it might help explain not just how primitive pterosaurs evolved into more advanced forms, but many other cases among animals and plants where we know that rapid large scale evolution must have taken place. The extraordinary evolutionary radiation of mammals following the extinction of dinosaurs is just one of many examples.

Said Dr Unwin: "Frustratingly, these events, which are responsible for much of the variety of life that we see all around us, are only rarely recorded by fossils. Darwin was acutely aware of this, as he noted in the Origin of species, and hoped that one day fossils would help to fill these gaps. Darwinopterus is a small but important step in that direction."

## Conservation targets too small to stop extinction

Conservation biologists are setting their minimum population size targets too low to prevent extinction.

That's according to a new study by University of Adelaide and Macquarie University scientists which has shown that populations of endangered species are unlikely to persist in the face of global climate change and habitat loss unless they number around 5000 mature individuals or more.

The findings have been published online in a paper 'Pragmatic population viability targets in a rapidly changing world' in the journal Biological Conservation.

"Conservation biologists routinely underestimate or ignore the number of animals or plants required to prevent extinction," says lead author Dr Lochran Traill, from the University of Adelaide's Environment Institute.

"Often, they aim to maintain tens or hundreds of individuals, when thousands are actually needed. Our review found that populations smaller than about 5000 had unacceptably high extinction rates. This suggests that many targets for conservation recovery are simply too small to do much good in the long run."

A long-standing idea in species restoration programs is the so-called '50/500' rule. This states that at least 50 adults are required to avoid the damaging effects of inbreeding, and 500 to avoid extinctions due to the inability to evolve to cope with environmental change.

"Our research suggests that the 50/500 rule is at least an order of magnitude too small to effectively stave off extinction," says Dr Traill. "This does not necessarily imply that populations smaller than 5000 are doomed. But it does highlight the challenge that small populations face in adapting to a rapidly changing world."

Team member Professor Richard Frankham, from Macquarie University's Department of Biological Sciences, says: "Genetic diversity within populations allows them to evolve to cope with environmental change, and genetic loss equates to fragility in the face of such changes."

Conservation biologists worldwide are battling to prevent a mass extinction event in the face of a growing human population and its associated impact on the planet.

"The conservation management bar needs to be a lot higher," says Dr Traill. "However, we shouldn't necessarily give up on critically endangered species numbering a few hundred of individuals in the wild. Acceptance that more needs to be done if we are to stop 'managing for extinction' should force decision makers to be more explicit about what they are aiming for, and what they are willing to trade off, when allocating conservation funds."

*Other researchers in the study are Associate Professor Corey Bradshaw and Professor Barry Brook, both from the University of Adelaide's Environment Institute. The paper is online at http://dx.doi.org/10.1016/j.biocon.2009.09.001*

## Report Documents the Risks of Giant Invasive Snakes in the U.S.

Five giant non-native snake species would pose high risks to the health of ecosystems in the United States should they become established here, according to a U.S. Geological Survey (USGS) report released today.

The USGS report details the risks of nine non-native boa, anaconda and python species that are invasive or potentially invasive in the United States. Because all nine species share characteristics associated with greater risks, none was found to be a low ecological risk. Two of these species are documented as reproducing in the wild in South Florida, with population estimates for Burmese pythons in the tens of thousands.

Based on the biology and known natural history of the giant constrictors, individuals of some species may also pose a small risk to people, although most snakes would not be large enough to consider a person as suitable prey. Mature individuals of the largest species—Burmese, reticulated, and northern and southern African pythons—have been documented as attacking and killing people in the wild in their native range,

though such unprovoked attacks appear to be quite rare, the report authors wrote. The snake most associated with unprovoked human fatalities in the wild is the reticulated python. The situation with human risk is similar to that experienced with alligators: attacks in the wild are improbable but possible.

"This report clearly reveals that these giant snakes threaten to destabilize some of our most precious ecosystems and parks, primarily through predation on vulnerable native species," said Dr. Robert Reed, a coauthor of the report and a USGS invasive species scientist and herpetologist.

High-risk species—Burmese pythons, northern and southern African pythons, boa constrictors and yellow anacondas—put larger portions of the U.S. mainland at risk, constitute a greater ecological threat, or are more common in trade and commerce. Medium-risk species—reticulated python, Deschauensee's anaconda, green anaconda and Beni anaconda—constitute lesser threats in these areas, but still are potentially serious threats.

The USGS scientists who authored the report emphasized that native U.S. birds, mammals, and reptiles in areas of potential invasion have never had to deal with huge predatory snakes before—individuals of the largest three species reach lengths of more than 20 feet and upwards of 200 pounds. The reticulated python is the world's longest snake, and the green anaconda is the heaviest snake. Both species have been found in the wild in South Florida, although breeding populations are not yet confirmed for either.

Breeding populations have been confirmed in South Florida for Burmese pythons and the boa constrictor, and there is strong evidence that the northern African python may have a breeding population in the wild as well.

"Compounding their risk to native species and ecosystems is that these snakes mature early, produce large numbers of offspring, travel long distances, and have broad diets that allow them to eat most native birds and mammals," said Dr. Gordon Rodda, a USGS scientist at the Fort Collins Science Center and the other coauthor of the report. In addition, he said, most of these snakes can inhabit a variety of habitats and are quite tolerant of urban or suburban areas. Boa constrictors and northern African pythons, for example, already live wild in the Miami metropolitan area.

The report notes that there are no control tools yet that seem adequate for eradicating an established population of giant snakes once they have spread over a large area. Making the task of eradication more difficult is that in the wild these snakes are extremely difficult to find since their camouflaged coloration enables them to blend in well with their surroundings.

"We have a cautionary tale with the American island of Guam and the brown treesnake," said Reed. "Within 40 years of its arrival, this invasive snake has decimated the island's native wildlife - 10 of Guam's 12 native forest birds, one of its two bat species, and about half of its native lizards are gone. The python introduction to Florida is so recent that the tally of ecological damage cannot yet be made."

USGS researchers used the best available science to forecast areas of the country most at risk of invasion by these giant snakes. Based on climate alone, many of the species would be limited to the warmest areas of the United States, including parts of Florida, extreme south Texas, Hawaii, and America's tropical islands, such as Puerto Rico, Guam, and other Pacific islands. For a few species, however, larger areas of the continental United States appear to exhibit suitable climatic conditions. For example, much of the southern U.S. climatic conditions are similar to those experienced by the Burmese python in its native range. However, many factors other than climate alone can influence whether a species can establish a population in a particular location, the report notes.

The Fish and Wildlife Service and the National Park Service will use the report to assist in further development of management actions concerning the snakes when and where these species appear in the wild. In addition, the risk assessment will provide current, science-based information for management authorities to evaluate prospective regulations that might prevent further colonization of the U.S. by these snakes. The 300-page report provides a comprehensive review of the biology of these species as well as the risk assessment.

***Resources*** * *View the risk-assessment report*

## Make 'em sweat: resin keeps insect pests at bay

* 15:41 13 October 2009 **by Shanta Barley**

Sticky fly traps? So twentieth century, darling. Scientists have identified a cheap, durable and eco-friendly chemical that, when painted onto walls, baby bottles and crops, gets rid of pests by making their feet "sweat".

Insects normally have no trouble strolling up walls and across slippery surfaces. Tiny pads on their feet secrete a ketchup-like glue - part oil, part water - that holds them in place.

Now, Jan-Henning Dirks and colleagues at the Department of Zoology at the University of Cambridge say they have found a way to turn this glue into a slippery lubricant.

Dirks' team painted glass rods with a range of chemicals and compared how these affected the ability of cockroaches to climb up the rods to a piece of apple. They also measured the frictional force between the roach's feet and the surface of the rod.

**Greasy insect**

They found that roaches effortlessly shimmied up rods coated in PTFE, a non-stick coating commonly found on cooking pans. But when the rods were covered in polyimide resin, the creatures lost their grip. In fact, the resin reduced the friction between the insects' feet and the glass rods by around 60 per cent. "The cockroaches simply slid off the rod," Dirks says.


*Video: Cockroach slipping off coated glass rod*

Using interference reflection microscopy, the scientists discovered that polyimide resin sucks up the water contained in the insect's glue - leaving behind a slippery layer of oil with no adhesive properties.

"In the future, this could prove to be a powerful tool to prevent pests from scuttling around on many hard-to-reach surfaces," says Dirks. Because the water absorbed by the resin evaporates quickly, the resin never needs to be replaced. "As a result, it's far cheaper and more eco-friendly than conventional pest-controlling methods."

Whether the technology will control flies, earwigs and geckoes, which use a slightly different form of "glue", remains to be seen, says Dirks. Any possible side-effects of the resin on wildlife will also need to be investigated.

## Penn archaeologist recreates ancient brews

**By Susan Snyder** Inquirer Staff Writer

Patrick McGovern had just emerged from the ancient burial chamber in one of the most extensively excavated archaeological sites in China when a local scientist presented him with what he calls "the real treasure." It was a sealed bronze drinking vessel that resembled a teapot from 1200 B.C. With liquid still inside.

"I just about dropped over - a liquid sample from 3,000 years ago," said McGovern, a researcher at the University of Pennsylvania.

He whisked a sample back to his lab in the basement of Penn's Museum of Archaeology and Anthropology. An analysis confirmed what he had suspected: a yellowish wine.

It was another eureka moment for McGovern, 64, who has spent the last two decades traversing the globe, from ancient capitals to remote villages, in a quest to uncover the secrets of ancient wine- and beer-making.

He has become internationally recognized as an authority on ancient potables. When he and other museum researchers were on the budget chopping block earlier this year, nearly 4,000 supporters signed a petition, among them archaeologists, curators, and government officials from countries around the world. Egypt's director of antiquities was one of them.

"You find out who your friends are," said McGovern, whose job was spared.

This month, he released a book, Uncorking the Past, which describes his research, including his collaboration with Delaware beer brewer Sam Calagione of Dogfish Head to re-create ancient beverages with recipes he found.

Last week, at an event at the University Museum, he and Calagione detailed their latest quirky foray: making an ancient Peruvian beer that required them to spend hours chewing purple corn - using their saliva as part of the fermentation process.

Two months ago, McGovern traveled to Lebanon's Bekaa Valley at the behest of a Syrian Lebanese winemaker who wants to open a wine museum there. He'll be heading back this month for further consultation.

"My husband loves what he does," McGovern's wife, Doris, said during an interview in the couple's woodsy Media home, where a wine magazine and a beer book sat atop a reading table. "It's a consuming passion."

His first experience with potables came on a student bicycle tour through the German Alps when he was 16. He drank Coca-Cola until he discovered beer was cheaper.

When he returned home to Upstate New York, he wanted more beer. So he dressed in lederhosen and a green hat, went to a bar and, pretending to be foreign, asked for a beer in German. He got it.

His first acquaintance with wine came in 1971 as he and his wife backpacked around Europe with little money. They visited towns along the Mosel River in Germany, seeking work at vineyards. The couple landed a three-week gig in Trittenheim. "That's where I really got the whole notion of vintage worked out," McGovern said. "By the end, you knew 1959 was a superb year. Sixty-nine was awful. The year we worked there - 1971 - was like the vintage of the century."

Born in Texas, McGovern - the son of an engineer and teacher - grew up in New York, earned a degree in chemistry from Cornell University, and considered becoming a neuroscientist. But his interest turned to archaeology, and in 1977, he began working at Penn, where he got his doctorate in 1980.

"I was really wondering what man's place in the universe was, how we got here," he said.

It was, at times, a hard life. On research trips, he sometimes slept in buildings with no mattresses or heat.

He hasn't seen his face in 35 years. He gave up shaving after trips to spots lacking much hot water; his bushy beard and mustache have gone from black to white.

McGovern and his wife, an academic turned bird-bander whom he met as an undergraduate at Cornell, never had children or pets; that would have hindered their extensive traveling, he explained.

Over time, McGovern became interested in ancient pottery, then discovering what was inside the pottery.

A colleague presented him with a large jar from Iran from 3500 B.C. that had a reddish deposit. She sought his analysis. The vessel contained tartaric acid, a key ingredient found in grapes from the Middle East.

"That started us off on the wine odyssey," he recalled.

In 1999, McGovern began studying residue collected from drinking and eating vessels that were excavated in 1957 from what was believed to be King Midas' tomb in the ancient Turkish city of Gordion. There, researchers had found the largest Iron Age bronze drinking set to date.

The samples, brought back to the museum by Penn researchers, sat largely untouched until another researcher told McGovern.

One was the residue of a spicy, barbecued lamb or goat stew with lentils. Another was a drink with grape wine, barley beer, and honey mead. McGovern decided to re-create the dinner that the ancients must have had, but he needed beverage help.

After a beer-tasting at the museum in 2000, he invited 15 local brewers into his lab and issued a challenge: Here's an ancient recipe. Brew it. Whoever does the best will make the drink for a forthcoming dinner.

One of the brewers was Calagione.

"I was immediately struck by his passion," Calagione said. "It wasn't just a pedantic academic suit. He, like me, is truly passionate about the history and the romance of the stories behind these beverages."

Calagione added saffron to his brew; other brewers used coriander. McGovern preferred Calagione's version.

"Midas Touch" - the first brew the pair collaborated on - was served. It was 9 percent alcohol.

Later, Calagione and McGovern re-created the dinner at the tomb site in Gordion, with locals dressed in period costumes taking part.

After McGovern made a trip to China, the pair next collaborated on Chateau Jiahu, a re-creation of the oldest confirmed alcoholic beverage in the world, dating to 7000 B.C. Named after the ancient city of Jiahu, it contained hawthorn fruit, rice, and honey. That brew won a gold medal at the Great American Beer Festival last month in Denver. Calagione invited McGovern - whom he calls "Dr. Pat" - to accompany him to the dais and accept the medal. He gave it to McGovern to keep.

Dogfish donates part of the proceeds from the re-created ancient beverages to McGovern's research, in recognition of his contribution. Most of the brews are available commercially from Dogfish.

The pair collaborated next on Theobroma, a chocolate-based ale from Central America. McGovern obtained the recipe from Honduras.

Last summer, they re-created their fourth ancient beer, the Peruvian Chicha, after McGovern made a trip to Peru earlier in the year. Colleague Clark Erickson, a Penn anthropology professor, joined McGovern and Calagione at the Rehoboth Beach, Del., brewery last summer to help chew the corn - saliva turns the corn into sugar - and make the concoction. Both Erickson and McGovern wince when thinking of the six hours spent chewing brittle corn. "The following day, your jaw is sore," McGovern said.

But it was fun telling his 150 guests at the museum event about the raw research.

"It may not sound appetizing," he told his guests, assuring them that a boiling process and alcohol killed off bacteria. "And it may add some special flavors."

With dozens of beverages at the gathering to sample, the line for Chicha was one of the longest.

McGovern, meanwhile, said he preferred the powerful flavor of Chateau Jiahu as he ruminated on the larger significance of his passion, which has crossed continents and time.

"It has contributed to how culture around the Earth has developed," he said of his research.

**Four Ancient Beers**

***Midas Touch:*** *Made with white grapes, saffron, thyme, honey, and barley from a recipe from King Midas' tomb in central Turkey. Alcohol: 9 percent.*

***Chateau Jiahu:*** *The oldest confirmed fermented beverage, from a recipe found in China, made with yeast, rice, honey, and hawthorn fruit. Alcohol: 10 %.*

***Theobroma:*** *From Central America, made with cocoa powder, honey, chiles, and annatto seeds. Alcohol: 9 %.*

***Chicha:*** *From Peru, made with organic purple corn, pepper tree seeds, and strawberries. Alcohol: 6 %.*

***SOURCE:*** *Dogfish Head and Patrick McGovern*

## Here's a Technology That Will Revolutionize Publishing

Regular readers will know that I'm not an intertubez triumphalist. But I read that the Harvard Book Store has bought itself a fancy gizmo to print any book in about four minutes:

Battered booksellers, especially independent ones, have so far withstood the punishing shock-and-awe offensive of Internet Age marauders like Amazon. Now, they have a secret weapon that they hope will continue to lure customers into their stores: would you believe it's a machine that can print up a fresh new paperback copy from a menu of 3.6 million books?

Harvard Book Store cleared out space behind its History, Politics, and Religion sections to make room for the three-foot-by-six-foot-by-four-foot robot retailer, called the Espresso Book Machine. In a public unveiling slated for September 29, the Harvard Book Store will become only the second US merchant to install such an apparatus, which prints, binds, and trims perfect-bound books -- complete with full-color covers and black-and-white guts -- in about four minutes.

"Books will be produced on a massively decentralized way," promises Dane Neller, CEO of On Demand Books, the manufacturer of the machines that will let customers select from millions of titles in less time than it takes to comb the teetering stacks of a used bookstore. "The life of the book will be infinite."

Says Harvard Book Store owner Jeffrey Mayersohn, "I had developed a notion that the ability to produce books in stores was an important part of the future of bookselling."

Despite all of the hullabaloo about Napster, I think this is a revolutionary technology. Unlike Napster, which made music publishing financially unsustainable, the Espresso Book Machine does not make the production of media 'open source'--it's too expensive. Publishing remains profitable, although less so. While anyone with an internet connection and a computer can distribute mp3's, most people can't buy the Espresso Book Machine. This means there is actually a way to make money from this because it lowers the cost of buying books. I am working under the assumption that most people who read books like books. If that changes all bets are off.

While the major publishers ultimately might get creamed (why pay $25 list, when you can buy a book for $8?), smaller publishers and authors could do very well from this. Hardcover books might become the equivalent of vinyl: a collector's item, but books will be more affordable. Book stores will be able to spend less money on stocking books, giving them a new lease on life. Something to keep an eye on.

## Information Craving

Posted on: October 13, 2009 12:43 PM, **by Jonah Lehrer**

Over at Mind Matters, Chadrick Lane reviews a fascinating experiment that revealed the rewarding properties of information, regardless of whether or not the information actually led to more rewards:

In the experimental design, monkeys were placed in front of a computer screen and were trained to perform a saccade task, in which they learned to direct their gaze at specific areas. The monkeys were first given the option of choosing between one of two colored targets. One of these targets would give the monkey advance information about its future reward. The advance information came in the form of visual cues, one representing a large reward and the other a small reward. Choosing the other initial colored target revealed cues that were randomly associated with reward size, thus possessing no informative value. After only a few days of training, the monkeys showed a clear preference for choosing the informative colored target.

The researchers then tested to see when the monkeys wanted the information. In this scenario, the monkeys were again initially presented with two colored targets. One of these targets had informative value while the other did not. The difference was that the monkeys always received informative cues just before their rewards. The choice each monkey had to make was whether to see an earlier informative cue. Despite always having a delayed informative cue, regardless of which initial target they selected, the monkeys preferred to have advance information as soon as possible. Like high-school seniors waiting on their SAT results, the monkeys wanted to know, and they wanted to know right now.

Forgive the far-fetched connection, but this experiment makes me think about health care costs. In recent years, it has become clear that an important driver of health care costs concerns unnecessary medical tests and imaging. From CT and PET scans to MRIs, Americans are given these tests at a far higher rate than citizens of other developed nations. The end result is tens of billions of dollars squandered on useless technology.

Obviously, many factors play a role in the overuse of high-tech imaging. There's the problem of defensive medicine, in which doctors prescribe tests that they don't think are relevant just to avoid a potential lawsuit. And then there's "technology creep," in which shiny new tools always seem better, even if they actually work worse. (This helps explain why spending on new health technology - from surgical robots to proton beam therapy - makes up more than 65 percent of the more than 6 percent annual increase in healthcare costs.)

But I think our need for more information, even if the information doesn't increase our understanding, also plays a role. Just look at chronic back pain, a medical conundrum that I explore in my book. When MRI was

first introduced in the late 1980s, the medical community believed that the imaging tool would transform the diagnosis of back problems. For the first time, doctors would have access to stunningly accurate images of the interior body. Since doctors could finally image the spine and surrounding soft tissue in lucid detail, they should be able to offer precise diagnoses, locating the aggravated nerves and structural problems that caused the pain in the first place. This, in turn, would lead to better medical care.

Unfortunately, MRI's haven't solved the problem of back pain. The problem is that the machine sees too much. Doctors are overwhelmed with information, and struggle to distinguish the significant from the irrelevant. Take, for example, spinal disc abnormalities. While X-rays can only reveal tumors or problems with the vertebrae, MRI's can image spinal discs - the supple buffers between the vertebrae - in meticulous detail. After the imaging machines were first introduced, the diagnosis of various disc abnormalities began to skyrocket. The MRI pictures certainly looked bleak: people with pain seemed to have seriously degenerated discs, which everyone assumed caused inflammation of the local nerves. Doctors began administering epidurals to quiet the pain, and, if the pain still persisted, would surgically remove the necessary disc tissue.

The vivid images, however, were misleading. Those disc abnormalities are seldom the cause of chronic back pain. A 1994 study published in The New England Journal of Medicine imaged the spinal regions of ninety-eight people with no back pain or any back related problems. The pictures were then sent to doctors who didn't know that the patients weren't in pain. The end result was shocking: two-thirds of normal patients exhibited "serious problems" like bulging, protruding or herniated discs. In 38 percent of these patients, the MRI revealed multiple damaged discs. Nearly 90 percent of these patients exhibited some form of "disc degeneration". These structural abnormalities are often used to justify surgery and yet nobody would advocate surgery for people without pain. The study concluded that, in most cases, "The discovery by MRI of bulges or protrusions in people with low back pain may be coincidental."

Medical experts are now encouraging doctors not to order MRIs when diagnosing back pain. A recent report in The New England Journal of Medicine concluded that MRIs should only be used to image the back under specific clinical circumstances, when doctors are examining "patients for whom there is a strong clinical suggestion of underlying infection, cancer, or persistent neurologic deficit." In the latest clinical guidelines issued by the American College of Physicians and the American Pain Society, doctors were "strongly recommended...not to obtain imaging or other diagnostic tests in patients with nonspecific low back pain." In too many cases, the expensive tests proved worse than useless. All of the extra detail just got in the way. The doctors performed better with less information.

And yet, we all understand the motivations behind such medical practices. If it's my back that's in pain, I want to know everything possible about my abnormal spinal discs - the extra information feels essential. And if I'm a doctor, I want to see what's happening on the inside. In other words, people have strong information-seeking instincts, which tend to overwhelm the statistical evidence. It doesn't matter what the NEJM says - we know what feels right.

The larger point is that it's never easy cutting health care costs. In the abstract, the waste looks easy to fix - we should dramatically reduce the number of MRIs given to patients with back pain. The data couldn't be clearer. But when you look at the problem in detail, and try to imagine the decision-making process from the perspective of the individual patient or doctor, you often find powerful instincts behind the reckless spending. These high-tech tests, after all, have given us a new source of information. And because such information is inherently rewarding - we always want to know - we prescribe the tests, even if they're not actually informative.

## A Long, Melancholy Roar

***(Being the third and final piece in a series about predators.)***

On a recent evening at twilight, I was sitting on the grass in Regent's Park — one of London's most manicured public spaces - when I heard the fierce, melancholy sound of a lion's roar.

I wasn't dreaming: it was coming from the zoo. Listening to it, I began to reflect on predators - and us. On returning home, I did some reading. I discovered that between 1990 and 2004, lions attacked 815 people in Tanzania, killing 563. Some of the victims were pulled out of bed during the night after lions forced their way inside huts. Between January 2000 and March 2004, crocodiles in Namibia attacked 35 people, killing 23. In the 34 months from January 2005 to October 2007, leopards in the Indian state of Kashmir attacked 18 people, killing 16. In the Sundarban swamps of Bangladesh, tigers killed at least 20 people last year. Dig around, and you can also find records of deaths from attacks by bears, cougars, sharks and a number of other wild beasts.

It's hard to imagine how terrifying such a death must be. To be asleep in bed and to wake to hear a rustling sound, to see an animal leaping, to feel its breath on your face - think of the sweat, the panic, the contraction of your gut, the pounding of your heart, the gasping screams.

For many of our fellow creatures, such terrors are part of daily life: other animals exist in a world of threat that humans today rarely glimpse. These days, thankfully, we are not used to being hunted. Most of us are more likely to be struck by lightning than we are to die at the paws of a bear or the teeth of a shark. And so we spend little time in that dark, primeval place of alarm, fear, adrenaline and (perhaps) gory death. For us, death usually comes in other forms.

Of our ancient enemies, microbes are now the most fearsome. Indeed, next to the figures for viruses and other infectious agents, deaths caused by predators are barely worth mentioning.

Just think: HIV/AIDS chalked up 2 million deaths across the planet in 2007 alone; tuberculosis was close behind, with more than 1,700,000. The year before, malaria escorted almost a million people to their graves. We should be far more scared of mosquitoes than we are of bears; but we're not.

Why not? It's hard to be sure, but my guess is that it has to do with the way our brains are wired up. Just as the moose fears the wolf and the chickadee the owl, we easily fear lions and bears because the connection between danger and the animal is clear and immediate. It is harder, I suspect, to evolve fear of a mosquito because the deadly fever it brings does not happen straight after the bite. Instead, there is a time delay of days, weeks or years. In fact, the connection between mosquito bites and malarial fever is so obscure that we weren't sure of it until 1897. But our forebears have been making connections between predators and death for ages.

Although predators are not an important problem for most of us today, they surely were for our ancestors. Indeed, millions of years ago, fear of predators would have been one of the forces that caused our ancestors to evolve to live in groups. The seeds of our social lives were watered with blood and nurtured by the roar of the lion and the claw of the leopard.

More recently, however, it's been the case that the mammal most likely to kill a human is: a human. Murder and war have long been more important causes of death for us than predatory wild animals.

You can see it in the landscape. In northern Romania, monasteries were fortified against marauding armies, and painted inside and out with scenes of martyrs being massacred. Further south, in Transylvania, the churches were fortified to withstand siege. In northern India, almost every town has a fort. Southern France is littered with the ruins of fortified castles and towns. In English forests, you can often find the remnants of iron-age defenses. All traces of peoples defending themselves from attack. We are our own most fearsome predator, and have been so for thousands of years.

Some other animals are also important predators of themselves. A lion has more to fear from another lion than it does from any other animal but us. Males taking over a pride routinely kill all the cubs they can find, and lions from neighboring territories sometimes kill each other. Chimpanzees kill each other at an alarming rate; and they are far more aggressive towards each other on a daily basis than we humans are.

But here's the thing. Today, in many parts of the world, the human being most likely to cause your violent death is: you.

Yes. You are the person most likely to kill yourself violently and on purpose. Suicide rates have risen dramatically over the past 50 years. Worldwide, deaths from suicide now outnumber deaths from war and homicide together: the World Health Organization estimates that each year around one million people - predominantly men - kill themselves. The true number is probably higher, because for many countries there is no data. In some countries, suicide is now among the top ten causes of death. For the young, worldwide, it's in the top five.

A huge effort has rightly been devoted to trying to understand the particular causes of suicide in different places - unemployment, drug addiction, relationship breakdown, intelligence, predisposing genes, what your mother ate while you were in the womb and so on.

But here's another way to look at it. No other animal does this. Chimpanzees don't hang themselves from trees, slit their wrists, set themselves alight, or otherwise destroy themselves. Suicide is an essentially human behavior. And it has reached unprecedented levels, especially among the young.

I'm not sure what this means. But it has made me think. We live in a way that no other animal has ever lived: our lifestyle is unprecedented in the history of the planet. Often, we like to congratulate ourselves on the cities we have built, the gadgets we can buy, the rockets we send to the moon. But perhaps we should not be so proud. Something about the way we live means that, for many of us, life comes to seem unbearable, a long, melancholy ache of despair.

## What drives our genes? Salk researchers map the first complete human epigenome

LA JOLLA, CA—Although the human genome sequence faithfully lists (almost) every single DNA base of the roughly 3 billion bases that make up a human genome, it doesn't tell biologists much about how its function is regulated. Now, researchers at the Salk Institute provide the first detailed map of the human epigenome, the layer of genetic control beyond the regulation inherent in the sequence of the genes themselves.

"In the past we've been limited to viewing small snippets of the epigenome," says senior author Joseph Ecker, Ph.D., professor and director of the Genomic Analysis Laboratory at the Salk Institute and a member of the San Diego Epigenome Center. "Being able to study the epigenome in its entirety will lead to a better understanding of how genome function is regulated in health and disease but also how gene expression is influenced by diet and the environment."

Their study, published in the Oct. 14, 2009 advance online edition of the journal Nature, compared the epigenomes of human embryonic stem cells and differentiated connective cells from the lung called fibroblasts, revealing a highly dynamic, yet tightly controlled, landscape of chemical signposts known as methyl-groups. The head-to-head comparison brought to light a novel DNA methylation pattern unique to stem cells, which may explain how stem cells establish and maintain their pluripotent state, the researchers say.

The emergence of epigenetics has already changed the way researchers think about how disease arises and how physicians treat it. Epigenetic changes play a crucial role in the development of cancer and some drugs that directly interact with the epigenome have been approved for the treatment of lymphoma and lung cancer and are now tested against a number of other cancer types. "Unless we know how these drugs affect the entire epigenome, we don't really understand their full mechanism of action," says Ecker.

Recognizing the central role of the epigenome in many areas of biology and medicine the National Institutes of Health launched a five-year Roadmap Epigenomics Program in 2008. The San Diego Epigenome Center, headed by Bing Ren, Ph.D., Professor of Cellular and Molecular Medicine at the University of California, San Diego School of Medicine and head of the Laboratory of Gene Regulation at the Ludwig Institute for Cancer Research, is an integral part of the five-year, $190 million push to accelerate research into modifications that alter genetic behavior across the human genome.

The current study, to which Ren and additional members of the Center located at the University of Wisconsin and the Morgridge Institute for Research in Madison, Wisconsin, also contributed, is not only the first complete high-resolution map of an epigenome superimposed on the human genome, but also the first study to be published as a direct result of the Roadmap Epigenomics Program.

"This paper exemplifies the goals of the NIH Roadmap for Medical Research's Epigenomics Program," said Linda Birnbaum, Ph.D., director of the National Institute of Environmental Health Sciences, one of the NIH institutes funding this program. "The science has matured to a point that we can now map the epigenome of a cell. This paper documents the first complete mapping of the methylome, a subset of the entire epigenome, of 2 types of human cells - an embryonic stem cell and a human fibroblast line. This will help us better understand how a diseased cell differs from a normal cell, which will enhance our understanding of the pathways of various diseases."

Epigenetic signals can tinker with genetic information in at least two ways: One targets histones, the "spools" around which DNA winds and which control access to DNA. The other is DNA methylation, a chemical modification of one letter, C (cytosine), of the four letters (A, G, C, and T) that comprise our DNA. In the last couple of years, Ecker's laboratory started to zoom in on genomic methylation patterns, which are essential for normal development and are associated with a number of key cellular processes, including carcinogenesis.

Perfecting the technique in Arabidopsis thaliana, a plant whose genome is 25 times smaller than the human genome, Ryan Lister, Ph.D., a postdoctoral researcher in Ecker's lab and co-first author on the current study, developed an ultra high-throughput methodology to precisely determine whether each C in the genome is methylated or not, and layer the resulting epigenomic map upon the exact genome it regulates.

He then put the brand new technology to work to map the epigenomes of differentiated fibroblast cells and human embryonic stem cells (hESCs.) "We wanted to know how the epigenome of a differentiated cell that's programmed to perform a specific job differs from the epigenome of a pluripotent stem cell, that has the potential to turn into any other cell type," Lister says.

Just as expected, in fibroblast cells the majority of Cs followed by a G carried a methyl-group, a pattern often referred to as CG-methylation. But much to the Salk researchers' surprise, in embryonic stem cells about a quarter of all methylation events occurred in a different context.

"Non-CG methylation is not completely unheard of -- people have seen it in dribs and drabs, even in stem cells. But nobody expected that it would be so extensive," says postdoctoral researcher and co-first author Mattia Pelizzola, who along with Lister undertook the extensive task of extracting and analyzing the epigenome data from these vast sequence datasets. "The whole field had been focused on CG methylation, and non-CG methylation was often considered a technical artifact."

To confirm their finding, the authors then targeted several regions in a second hESC line, as well as in fibroblast cells that had been reprogrammed into so called induced pluripotent stem (iPS) cells. "They both had the same high level of non-CG methylation, which was lost when we forced them to differentiate," says Pelizzola.

Being able to create high resolutions maps of the human epigenome, Ecker's group will now begin to examine how it changes during normal development as well as examining a variety of disease states. "For the first time, we will be able to see the fine details of how DNA methylation changes in stem cells and other cells as they grow and develop into new cell types," he says. "We believe this knowledge will be extremely valuable for understanding diseases such as cancer and possibly even mental disorders. Right now we just don't know how the epigenome changes during the aging process or how the epigenome is impacted by our environment or diet."

*This work was supported in part by grants from the Mary K. Chapman Foundation, the NIH, the California Institute for Regenerative Medicine, the Australian Research Council Centre of Excellence Program and the Morgridge Institute for Research. Researchers who also contributed to the work include Robert H. Dowen and Joseph R. Nery in the Genomic Analysis Laboratory, Gary Hon, Leonard Lee, Zhen Ye, Que-Minh Ngo and Lee Edsall at the Ludwig Institute for Cancer Research at the University of California San Diego, Julian Tonti-Filippini and A. Harvey Millar at the ARC Center of Excellence in Plant Energy Biology in Crawley, Australia, Jessica Antosiewicz-Bourget, Ron Stewart, Victor Ruotti and James A. Thomson at the Morgridge Institute for Research and at the Genome Center of Wisconsin, both at the University of Wisconsin in Madison.*

## BCM scientists find 'molecular trigger' for sudden death in epilepsy

HOUSTON – The most common gene for a syndrome associated with abnormal heart rhythms and sudden death triggers epileptic seizures and could explain sudden unexplained death in epilepsy, said researchers from Baylor College of Medicine in a report that appears today in the journal Science Translational Medicine.

The identification of this particular potassium channel KvLQT in neurons of the central nervous system gives scientists a clue about which epilepsy patients face the greatest risk of dying unexpectedly, said Dr. Jeffrey Noebels, the study's senior author and director of the Blue Bird Circle Developmental Neurogenetics Laboratory at Baylor College of Medicine. The channel has been identified in heart muscle cells and now for the first time in brain or nerve cells.

"Idiopathic (unexplained) epilepsy is one of neurology's oldest mysteries. While most persons with epilepsy will have a normal lifespan, our finding now points the way to a simple and essential test to identify risk for sudden death in persons with seizures of unknown origin. In these patients, a routine cardiology evaluation consisting of an EKG, and if indicated, a genetic screening test for this family of genes can positively identify this new risk factor," said Noebels. "If the gene test is positive, there are effective treatments for the heart irregularity, including drugs known as beta blockers, as well as the use of a cardiac pacemaker to prevent lethal arrhythmias."

As many as 18 percent of deaths in epilepsy come suddenly without warning, devastating families.

"Living with epilepsy is difficult enough, but unexpectedly dying from it, as happens in young adults with the disorder, is one of the greatest fears a family must face," said Dr. Alica Goldman, assistant professor in the BCM department of neurology. Noebels is a professor in the departments of neurology, neuroscience and molecular and human genetics at BCM.

No one knew why young people with epilepsy died suddenly, but Goldman built on previous work in Noebels' lab that found that an ion channel gene thought to work only in the heart was active in the brain as well. She examined five ion channel genes linked to long QT syndrome, a disorder associated with heart rhythm disorders and sudden death. Long QT refers to an interval in electrocardiograms – the QT interval, which is prolonged in this disorder. An ion channel is a tiny pore in a membrane that controls the flow of ions such as calcium and potassium in and out of a cell.

Goldman found that mice with a mutation in the gene that encodes for the KvLQT1 ion channel had frequent epileptic seizes as well as life-threatening heart rhythm irregularities. 'This demonstrates the long-sought molecular link between heart and brain in epilepsy," said Noebels.

Goldman is now screening epilepsy patients to determine whether they have the same gene mutation.

*Others who took part in this work include Ed Glasscock, Jong Yoo, Tara Klassen and Tim Chen. Funding for the work came from the Dana Foundation, the National Institutes of Health, the American Heart Association, and Blue Bird Circle Foundation of Houston. When the embargo lifts, an abstract of the report will be available at http://stm.sciencemag.org/.*

## Gene blamed for immunological disorders shown to protect against breast cancer development

### *Researchers say the findings suggest drug therapy targeted against the gene's protein may be risky*

Washington, DC – Researchers at Georgetown University Medical Center (GUMC) are voicing alarm that drugs to treat a wide variety of allergies, asthma and autoimmune diseases now in human clinical trials may errantly spur development of breast tumors.

As the researchers report in the October 15 issue of PLoS ONE, the gene SYK and its protein product, Syk*, are crucial for prevention of breast cancer in the mice and human breast cells they studied. The research is the

most definitive yet to demonstrate the beneficial function of Syk as a tumor suppressor, but Syk is better known for its negative role in ramping up activity of the immune system, leading to a cornucopia of immunological disorders.

The concern the authors have is that agents for these conditions – which are now being tested in humans – might spur breast cancer development because they are designed to inhibit the activity of Syk. "Our study shows that in normal breast cells, Syk is needed to control growth and thus prevent breast cancer. So if people use a drug that stops Syk activity, they could be at risk for developing this cancer, particularly at a young age during breast development" says the study's senior author, Susette Mueller, PhD, professor of oncology at the Lombardi Comprehensive Cancer Center at GUMC.

"Years of research has led us to believe that Syk is important in breast cancer, but we still need to find out why and when some women lose Syk function," she says. "In the meantime, we can only voice concern that inhibiting the protein may have unfortunate consequences."

She adds that Syk is a complex gene product, and that researchers elsewhere have also shown that it can promote development of other types of cancer, such as head and neck and certain forms of leukemia. "As we are discovering more and more, proteins can have different functions in the human body, depending on the context in which they are used. Syk is a perfect example of this phenomenon," Mueller says.

Mueller and her collaborators have been studying Syk for about a decade, and have the largest body of work detailing how it functions in the breast. They first showed that Syk protein is present in normal breast cells and its absence correlated with invasion and metastasis in tumor cells and later found that as breast tumors progressed, more and more Syk protein was lost. Now, it is recognized that the amount of Syk present in a tumor is an indicator of risk of metastasis.

In this study, first author You Me Sung, PhD, a postdoctoral researcher in Mueller's lab, conducted mice studies in which one of two Syk alleles were genetically deleted. (Because Syk is believed to be important in embryonic development as well, deleting both will not sustain life.) The research team demonstrated that loss of the single allele led to "profoundly" increased proliferation and invasion of normal breast cells in the mouse mammary gland during puberty, resulting in development of breast cancer in adulthood. They then studied normal human breast cells in laboratory culture, and showed that knocking out Syk protein dramatically increased cell growth as well, and produced changes that would allow cells to invade through tissue-like barriers.

"Our findings in living mouse and in human breast cells mirrored each other," Mueller says. "All the data on Syk suggest it is very important in controlling growth as breast tissue develops indicating a potent role as tumor suppressor for breast cancer."

The researchers are now studying patients who have lost Syk function in order to pinpoint the reason why the gene no longer produces its protein. Ultimately, the goal is to identify the molecules that Syk negatively regulates in order to target them for breast cancer therapy.

*The study was funded by the National Institutes of Health and by a postdoctoral research fellowship from the Susan G. Komen Breast Cancer Fellowship. The authors declare no related financial interests.*

**Note to editor: When referring to the gene, SYK is written in all caps. The protein is written Syk.*

## Popular antidepressant associated with a dramatic increase in suicidal thoughts amongst men

Nortriptyline has been found to cause a ten-fold increase in suicidal thoughts in men when compared to its competitor escitalopram. These findings are published in the open access journal BMC Medicine.

The research was carried out by Dr. Nader Perroud from the Institute of Psychiatry, Kings College London, who headed up GENDEP, an international team. Dr Perroud said "Suicidal thoughts and behaviours during antidepressant treatment have prompted warnings by regulatory bodies". He continued "the aim of our study was to investigate the emergence and worsening of suicidal thoughts during treatment with two different types of antidepressant."

Both escitalopram and nortriptyline have their effect through the mood modulating neurotransmitter systems. The former is a selective serotonin reuptake inhibitor (SSRI), preventing serotonin from re-entering the cell and thereby prolonging its effect on nerve synapses. The latter is a tricyclic antidepressant that inhibits the reuptake of noradrenaline, and to a lesser extent, that of serotonin.

The study was carried out on 811 individuals with moderate to severe unipolar depression. Whilst an overall trend in reduction of suicidal thoughts was observed, men who took nortriptyline were found to have a 9.8-fold increase in emerging suicidal thoughts and a 2.4-fold increase in worsening suicidal thoughts compared to those who took escitalopram.

Perroud concludes, "Our findings that treatment-emerging and worsening suicidal thoughts may also be associated with psychomotor activation triggered by antidepressants needs to be investigated in future studies. The study also refutes the idea that newer antidepressants such as the SSRIs are worse than older medications in terms of increasing suicidal thoughts."

***Notes to Editors:****1. Suicidal ideation during treatment of depression with escitalopram and nortriptyline in Genome-Based Therapeutic Drugs for Depression (GENDEP): a clinical trial Nader Perroud, Rudolf Uher, Andrej Marusic, Marcella Rietschel, Ole Mors, Neven Henigsberg, Joanna Hauser, Wolfgang Maier, Daniel Souery, Anna Placentino, Aleksandra Szczepankiewicz, Lisbeth Jorgensen, Jana Strohmaier, Astrid Zobel, Caterina Giovannini, Amanda Elkin, Cerisse Gunasinghe, Joanna Gray, Desmond Campbell, Bhanu Gupta, Anne E Farmer, Peter McGuffin and Katherine J Aitchison BMC Medicine (in press)* ***During embargo, article available here***

## Virtual workforce found in Kenyan refugee camp

* 14 October 2009 **by Jim Giles**

THE very poorest people on the planet have benefited little from the digital economy, but a pilot project in African refugee camps has hinted at how that might change. Refugees at the Dadaab camps in Kenya have been able to dramatically increase their income by tapping into a global demand for unskilled digital labour.

The project uses CrowdFlower, a website that allows companies to quickly outsource routine tasks such as transcription and image-tagging to online workers. "We can generate an incredible amount of social impact through this technology," says Leila Chirayath Janah, founder of Samasource, the San Francisco-based charity behind the project.

Workers typically receive a few cents per task and companies can often get jobs done in minutes. CrowdFlower lets companies choose from several virtual pools of labour, including Amazon's "Mechanical Turk" service.

Thanks to Samasource's work, a group of over 150 refugees in the three camps at Dadaab will soon make up one of those pools. Over the last two months, a pilot group of 16 workers has been given access to computers and trained on a range of tasks, including a data-entry job for a mapping company. The firm uses software to identify roads in aerial images, but its software sometimes mistakenly tracks other features, such as lines of parked cars. The refugees check each image and decide whether the software has done its job.

After an unpaid trial period, the workers started taking paid tasks late last month. They have been earning around US$2 per hour; the typical income among the camps' 250,000 inhabitants is $50 per month. Lukas Biewald of San Francisco-based CrowdFlower, says that the 16 refugees have received $1200 so far. Samasource now has funding to train another 150 refugees and is also working with Kenyans outside the camps. Meanwhile, it is in talks regarding a second refugee-camp project, this time in northern India.

Biewald says that firms like the feel-good factor that comes with using the Dadaab workers. And the results can be more reliable than those from other labour pools. "The refugees have more interest in a long-term relationship," says Biewald.

CrowdFlower and Samasource have also released GiveWork, an iPhone application that lets users donate their labour: its users complete the same tasks as the Dadaab workers, but the fee for those jobs is paid to the Dadaab team instead.

Later this month, cellphone users in Kenya will be able to sign up to txteagle, another remote-working service that distributes translation and image tasks by cellphone. Nathan Eagle, a cellphone technology researcher at the Santa Fe Institute in New Mexico and the developer of txteagle, estimates that 15 million Kenyans will be interested in taking part.

## Affordable anti-rejection drug as effective as higher cost option

WINSTON-SALEM, N.C. – A newer, less expensive drug used to suppress the immune system and prevent organ rejection in kidney and pancreas transplant patients works just as well as its much more expensive counterpart, according to a new study by researchers at Wake Forest University Baptist Medical Center.

Such discoveries are vital in an era of skyrocketing health care costs and debate over health reform, said lead investigator Alan C. Farney, M.D., Ph.D., an associate professor of surgery in the Department of General Surgery, Transplantation Services. "I think it's very important that the public consider cost, and that they ask their doctors if there are alternatives for them that are less expensive," he said. "Why should we use one drug or intervention over another that is equally effective and a fraction of the cost?"

For the study, published recently in the journal Transplantation, researchers looked at the two most common drugs used for induction immunosuppression therapy with kidney and pancreas transplants:

* alemtuzumab, a newer drug that costs about $1,000 per single-dose treatment and is marketed under the name CampathTM; and

* rabbit antithymocyte globulin, which costs about four times more for its multidose treatment than alemtuzumab, and is marketed under the name ThymoglobulinTM.

Both drugs destroy the cells that cause organ rejection during induction immunosuppression therapy – a short-term, early treatment meant to rapidly lower the immune system to prevent rejection until the patient begins taking daily drugs to suppress the immune system.

Though more expensive, rabbit antithymocyte globulin has generally been more commonly prescribed than alemtuzumab at Wake Forest Baptist and other transplant centers because there has been a concern that the newer drug would suppress the immune system too much and lead to infections or cancer, Farney said.

"We want to avoid acute rejection, but we also don't want to pay a price when we're trying to do that by leaving the patient over-immunosuppressed," he said. "We were being cautious, but this study reveals that, through at least two years of follow up, both drugs are equally effective and safe."

In the study of 222 patients receiving either kidney transplants alone, simultaneous kidney-pancreas transplants, or pancreas-after-kidney transplants, researchers found that both drugs showed similar survival rates for the patients (96 percent), the transplanted kidneys (89 percent) and the transplanted pancreases (90 percent). The drugs also had similar infection rates.

From Feb. 1, 2005, to Sept. 1, 2007, transplant patients participating in the study received either alemtuzumab or rabbit antithymocyte globulin, followed by the same course of maintenance drugs. Both groups included patients who varied in age, race, gender and risk – a unique approach with clinical studies, which usually look at a group with similar characteristics.

The researchers wanted to design this study – one of the largest single-institution trials for transplantation drugs – to reflect the actual demographics of the Medical Center's transplant patients, Farney said. Transplantation Services at Wake Forest University Baptist Medical Center performs more than 150 kidney and pancreas transplants each year. "It represents who we really transplant at Wake Forest Baptist," Farney said. "Other trials are so exclusive that you don't know what the true results are for most people."

As a result of the study, the Wake Forest Baptist Transplant Program has adopted the newer drug as part of its standard anti-rejection protocol for kidney and pancreas transplantation, Farney said.

*Co-investigators, all from the Medical Center, are William Doares, Pharm.D., M.A.Ed., Jeffrey Rogers, M.D., Rajinder Singh, M.D., Erica Hartmann, M.D., Lois Hart, Elizabeth Ashcraft, Amber Reeves-Daniel, D.O., Michael Gautreaux, Ph.D., Samy S. Iskandar, M.BB.Ch., Ph.D., Phillip Moore, M.D., Patricia L. Adams, M.D., and Robert J. Stratta, M.D.*

*The researchers continue to track the study participants annually to determine the long-term outcomes for both drugs.*

## Fabled 'vegetable lamb' plant contains potential treatment for osteoporosis

The "vegetable lamb" plant — once believed to bear fruit that ripened into a living baby sheep - produces substances that show promise in laboratory experiments as new treatments for osteoporosis, the bone-thinning disease. That's the conclusion of a new study in ACS' monthly Journal of Natural Products.

Young Ho Kim and colleagues point out that osteoporosis is a global health problem, affecting up to 6 million women and 2 million men in the United States alone. Doctors know that the secret to strong bones involves a delicate balance between two types of bone cells: Osteoblasts, which build up bone, and osteoclasts, which break down bone.

Seeking potential medications that might tip the balance in favor of bone building, the researchers turned to the "vegetable lamb" plant as part of a larger study plants used in folk medicine in Vietnam. In the 16th and 17th centuries, some of the world's most celebrated scientists believed the plant (Cibotium barmoetz) fruited into a newly born lamb, which then grazed on nearby grass and weeds. Kim's group isolated compounds from C. barmoetz and showed that they blocked formation of bone-destroying osteoclasts formation in up to 97 percent of the cells in laboratory cultures without harmful effects on other cells. The substances "could be used in the development of therapeutic targets for osteoporosis," the article notes.

***This illustration from an 1887 book shows the fabled "Vegetable Lamb of Tartary," a plant once believed to ripen into a baby sheep. The plant now shows promise for treating osteoporosis.*** **Wikimedia Commons**

***Article For Immediate Release*** *"Inhibitors of Osteoclast Formation from Rhizomes of Cibotium barometz"*

***Download Full Text Article*** *http://pubs.acs.org/stoken/presspac/presspac/full/10.1021/np9004097*

## 'Magnetricity' observed for first time

* 21:28 14 October 2009 **by David Shiga**

The magnetic equivalent of electricity, dubbed "magnetricity", has been demonstrated experimentally for the first time. Just as the flow of electrons produces electrical current, individual north and south magnetic poles have been observed to roam freely, generating magnetic "current".

The result could lead to the development of "magnetronics", including nano-scale computer memory.

Magnets normally have two poles, north and south, that are inseparable. Cutting a magnet in half only results in each piece developing its own north and south pole. That is true even if one disassembles a magnet all the way down to its individual atoms, since each behaves as a tiny bar magnet with two poles.

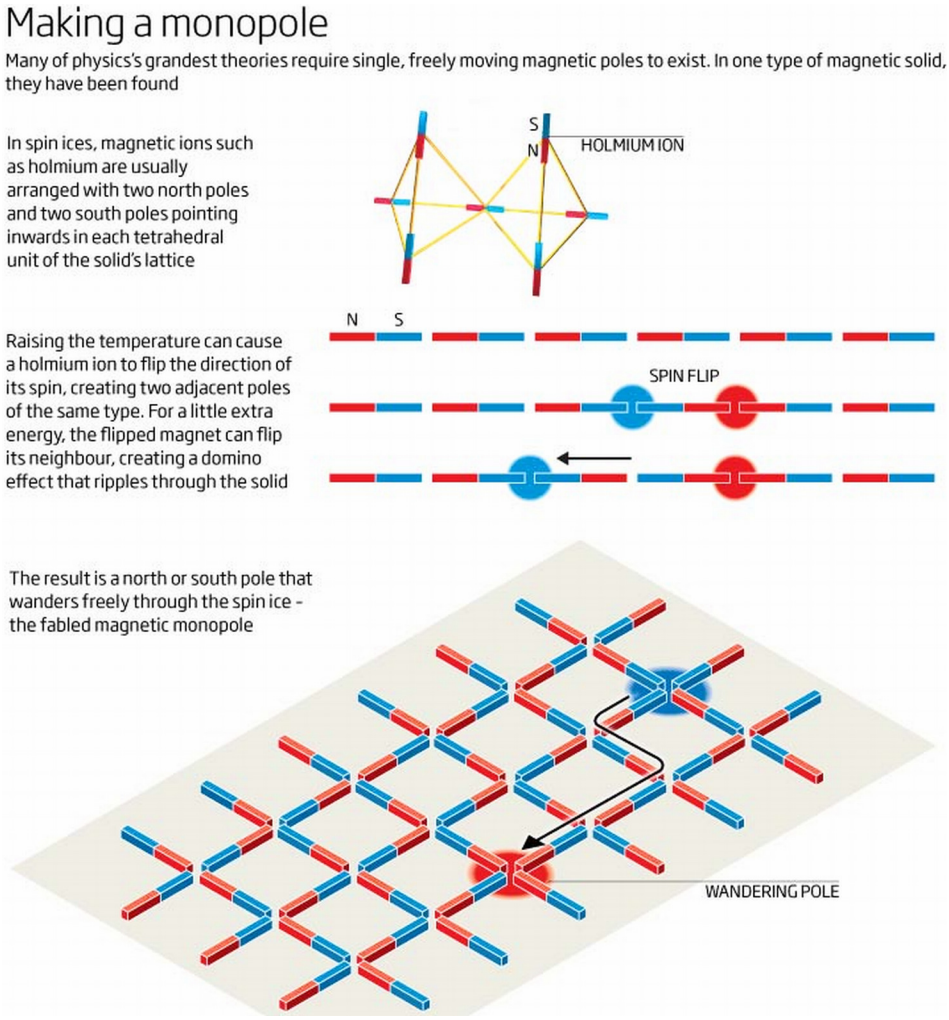
But physicists have theorised that magnetic monopoles – individual north and south poles that are not bound in pairs and can move independently of one another – could form inside a crystalline material called spin ice.

***Individual magnetic 'charges' - equivalent to the north and south poles of a magnet - have been observed inside a crystalline material called spin ice*** **(Image: STFC)**

**Changing patterns**

The individual atoms would still have both north and south poles. But patterns in their orientation would propagate through the material and look just like little magnetic poles roaming around (see illustration). These patterns would effectively be monopoles, as far as any measurements are concerned.

In September, two teams of physicists fired neutrons at spin ices made of titanium-containing compounds chilled close to absolute zero. The behaviour of the neutrons suggested that monopoles were present in the material. Now, another team has managed to measure the amount of magnetic "charge" on the monopoles and to measure magnetic analogues to electric current for the first time. The team calls the motion and interaction of monopoles "magnetricity".




The experiment, reported in Nature, was led by Steven Bramwell of the London Centre for Nanotechnology in the UK. Bramwell was a member of a team, led by Tom Fennell of the Laue-Langevin Institute in Grenoble, that reported neutron results in September.

**Magnetic 'charge'**

To get more detailed information on the monopoles than had previously been possible, Bramwell's team injected muons - short-lived cousins of electrons - into the spin ice. When the muons decayed, they emitted positrons in directions influenced by the magnetic field inside the spin ice.

***The first materials identified as spin ices were the pyrochlores Ho2Ti2O7, Dy2Ti2O7, and Ho2Sn2O7. Very recently, compelling evidence has been reported that Dy2Sn2O7 is also a spin ice.***

This revealed that the monopoles were not only present but were moving, producing a magnetic current. It also allowed the team to measure the amount of magnetic charge on the monopoles. It turned out to be about a 5 in the obscure units of Bohr magnetons per angstrom, in close agreement with theory, which predicted 4.6. Unlike the electric charge on electrons, which is fixed, the magnetic charge on monopoles varies with the temperature and pressure of the spin ice.

Shivaji Sondhi of Princeton University in New Jersey, a spin ice researcher who is not a member of Bramwell's team, called the new achievement "a triumph of a bold experimental foray" in an accompanying commentary in Nature. "The experiment itself and the determination of the charge of magnetic monopoles are striking."

**Shrinking memory**

Data is stored on computer hard discs by magnetising their surfaces in patterns that represent 1s and 0s. Bramwell speculates that monopoles could one day be used as a much more compact form of memory than anything available today, given that the monopoles are only about the size of an atom. “It is in the early stages, but who knows what the applications of magnetricity could be in 100 years time," he says.

The monopoles in the spin ice are not the same as cosmic monopoles, fundamental magnetic particles theorised to have been forged in the big bang that have never been observed.

*Journal reference: Nature (DOI: 10.1038/nature08500)*

## In shaping our immune systems, some 'friendly' bacteria may play inordinate role

Out of the trillions of "friendly" bacteria - representing hundreds of species -that make our intestines their home, new evidence in mice suggests that it may be a very select few that shape our immune responses. The findings detailed in two October 16th reports appearing in the journals Cell and Immunity, both Cell Press publications, offer new insight into the constant dialogue that goes on between intestinal microbes and the immune system, and point to a remarkably big role for a class of microbes known as segmented filamentous bacteria (SFB).

"It's the first example of a commensal bacteria that can induce accumulation in the gut of a highly specific branch of the immune system," said Dan Littman of the Howard Hughes Medical Institute and the New York University School of Medicine, who led the study reported in Cell. "We're headed into an exciting new area, and we hope more pieces of how the microbial-host interaction contributes to health will begin to fall into place."

"Our study provides the surprising result that among the hundreds of bacterial species composing the gut microbiota - only a very small number, the prototype of which is SFB - can efficiently stimulate the post-natal physiologic maturation of the immune barrier," added Valérie Gaboriau-Routhiau of INSERM in France, who led the Immunity report. "A unique feature of SFB appears to be its capacity to simultaneously stimulate a large spectrum of intestinal immune responses - innate and adaptive, pro-inflammatory and regulatory - which complete and balance each other."

Notably, those SFBs stimulate particular types of helper T cells, known as Th17 cells, the studies show.

In Littman's case, the findings by his group were something of an accidental discovery. They were studying T cells in the intestine and were getting some inconsistencies in their results. Those inconsistencies could be traced to differences in the gut floras of mice obtained from different sources, and specifically, they found, in the presence or absence of SFB.

Introduction of SFB, but not other bacteria, stimulated the production of Th17 cells in mice who were otherwise deficient in them, they show. The bacteria also set in motion a pro-inflammatory gene program. That SFB-induced immune response protected the mice from becoming ill with an intestinal pathogen, supporting a role for the SFBs in setting up the intestine's immunity barrier.

Gaboriau-Routhiau similarly found in studies of conventional and germ-free mice that colonization of the gut induced a broad spectrum of pro-inflammatory and T cell responses, including the emergence of Th17 cells. That occurred despite the fact that most bacteria, in combination or on their own, didn't lead to such a reaction. Rather, that function appeared limited to a restricted number of bacteria, her team reports, the prototype of which is the SFB. All on its own, SFB could largely recapitulate the coordinated maturation of T cell responses normally induced by the whole mouse microbiota.

Gaboriau-Routhiau suspects that SFBs may have some special attributes that explain their importance.

"For us, it was first a surprise to observe so little redundancy in the role of commensal bacteria on stimulating immune responses," Gaboriau-Routhiau said. "One striking feature of SFB, which makes it very different from the vast majority of the members of the microbiota, is its capacity to adhere to epithelial cells notably in the ileum, a property normally more the prerogative of pathogens." The ileum is the final section of the small intestine and is distinguished by many folds, giving it a very substantial surface area.

The findings also suggest how such commensal bacteria might sometimes go from beneficial inhabitants, helping to fend off nasty bugs, to ones that may tip the balance of the immune system toward the development of inflammatory, autoimmune disease, such as Crohn's disease, psoriasis and even arthritis, according to the researchers. Indeed, the Th17 cells observed in the new studies have been noted in recent years because of their importance in autoimmune diseases, Littman explained. Animals with defects in those Th17 cells generally don't develop autoimmune disease or develop disease that is less severe, earlier studies showed.

"Th17 cells make cytokines that can be highly protective in the case of infection," he said. "At the same time, in the wrong context or in the wrong amount [they can lead to disease]. You need to have the right balance."

Given the bacterial diversity found within our guts, the new results show how much there still is to learn about this important aspect of the immune system. While probiotic products on the market today don't have the

benefit of such a thorough understanding, says Littman, there is little doubt that down the road we may be able to manipulate our immune system in beneficial ways with microbes. Alternatively, he said, some of the molecular products of those bacteria - particular sugars or peptides, for instance - might ultimately serve as useful therapies on their own.

***Cell article:*** *The researchers include Ivaylo I. Ivanov, New York University School of Medicine, New York, NY; Koji Atarashi, Osaka University, Osaka, Japan, Nicolas Manel, New York University School of Medicine, New York, NY; Eoin L. Brodie, Lawrence Berkeley National Laboratory, Berkeley, CA, Tatsuichiro Shima, Yakult Central Institute for Microbiological Research, Kunitachi, Tokyo, Japan, Ulas Karaoz, Lawrence Berkeley National Laboratory, Berkeley, CA; Dongguang Wei, Carl Zeiss SMT, Inc., Nanotechnology Systems Division, Peabody, MA; Katherine C. Goldfarb, Lawrence Berkeley National Laboratory, Berkeley, CA; Clark A. Santee, Lawrence Berkeley National Laboratory, Berkeley, CA; Susan V. Lynch, University of California San Francisco, San Francisco, CA; Takeshi Tanoue, Osaka University, Osaka, Japan; Akemi Imaoka, Yakult Central Institute for Microbiological Research, Kunitachi, Tokyo, Japan; Kikuji Itoh, University of Tokyo, Tokyo, Japan; Kiyoshi Takeda, Osaka University, Osaka, Japan; Yoshinori Umesaki, Yakult Central Institute for Microbiological Research, Kunitachi, Tokyo, Japan; Kenya Honda, Osaka University, Osaka, Japan, Japan Science and Technology Agency, Saitama, Japan; and Dan R. Littman, New York University School of Medicine, New York, NY, Howard Hughes Medical Institute.*

***Immunity article:*** *The researchers include Vale´ rie Gaboriau-Routhiau, INRA, U910, Unite´ Ecologie et Physiologie du Syste`me Digestif, Domaine de Vilvert, Jouy-en-Josas, France, INSERM, Universite´ Paris, Paris, France; Sabine Rakotobe, INRA, U910, Unite´ Ecologie et Physiologie du Syste`me Digestif, Domaine de Vilvert, Jouy-en-Josas, France, INSERM, Universite´ Paris, Paris, France; Emelyne Le´ cuyer, INRA, U910, Unite´ Ecologie et Physiologie du Syste`me Digestif, Domaine de Vilvert, Jouy-en-Josas, France, INSERM, Universite´ Paris, Paris, France; Imke Mulder, University of Aberdeen, Aberdeen, UK; Annai¨g Lan, University of Aberdeen, Aberdeen, UK; Chantal Bridonneau, INRA, U910, Unite´ Ecologie et Physiologie du Syste`me Digestif, Domaine de Vilvert, Jouy-en-Josas, France; Violaine Rochet, INRA, U910, Unite´ Ecologie et Physiologie du Syste`me Digestif, Domaine de Vilvert, Jouy-en-Josas, France; Annamaria Pisi, University of Bologna, Bologna, Italy; Marianne De Paepe, INSERM, Universite´ Paris, Paris, France; Giovanni Brandi, Ge´ rard Eberl, University of Bologna, Bologna, Italy; Johannes Snel, NIZO Food Research, The Netherlands; Denise Kelly, University of Aberdeen, Aberdeen, UK; and Nadine Cerf-Bensussan, INSERM, Universite´ Paris, Paris, France.*

## It's official: Your bullying boss really is an idiot

* 14:28 15 October 2009 **by Ewen Callaway**

Got a bullying boss? Take solace in new research showing that leaders who feel incompetent really do lash out at others to temper their own inferiority.

"Power holders feel they need to be superior and competent. When they don't feel they can show that legitimately, they'll show it by taking people down a notch or two," says Nathanael Fast, a social psychologist at the University of Southern California in Los Angeles, who led a series of experiments to explore this effect.

In one, Fast and his colleague Serena Chen, who is at the University of California, Berkeley, asked 90 men and women who had jobs to complete online questionnaires about their aggressive tendencies and perceived competence. The most aggressive of the lot tended to have both high-power jobs and a chip on their shoulder, Fast and Chen found.

To see if a bruised ego can actually cause aggression, the researchers manipulated people's sense of power and self-worth by asking them to write about occasions when they felt either empowered or impotent and then either competent or incompetent. Previous research has suggested that such essays cause a short-term bump or drop in feelings of power and capability, Fast says.

**Feel-bad factor**

Next, Fast and Chen asked their volunteers to select a punishment to be given to university students for wrong answers in a hypothetical test of learning. Volunteers chose between horn sounds that ranged from 10 decibels to a deafening 130 decibels.

The volunteers who felt the most incompetent and empowered picked the loudest punishments – 71 decibels on average. Workers who felt up to their jobs, selected far quieter punishments, between 55 and 62 decibels, as did those primed to feel incompetent yet powerless.

Flattery seems to temper the aggressive urges of insecure leaders. When Fast and Chen coaxed the egos of these volunteers by praising their leadership skills, their aggressive tendencies all but disappeared. This is proof that leaders are aggressive because of a hurt ego, not simply a threat to their power, Fast says.

This might also explain why leaders of organisations both big and small surround themselves with yes-men and women, he says.

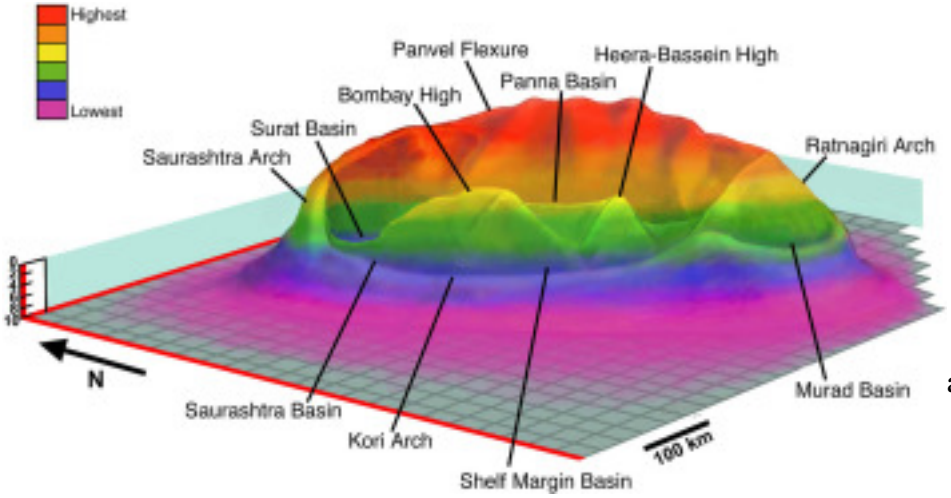
Blind flattery may not be the best solution for the 54 million US citizens estimated to have experienced workplace bullying (PDF). But easing leaders into new positions of power, or telling them that it's natural to feel daunted, could prevent future outbursts, says Adam Galinsky , a social psychologist at Northwestern University's Kellogg School of Management in Evanston, Illinois.

*Journal reference: Psychological Science, DOI: 10.1111/j.1467-9280.2009.02452.x*

## Giant Impact Near India -- Not Mexico -- May Have Doomed Dinosaurs

Boulder, CO, USA - A mysterious basin off the coast of India could be the largest, multi-ringed impact crater the world has ever seen. And if a new study is right, it may have been responsible for killing the dinosaurs off 65 million years ago.

Sankar Chatterjee of Texas Tech University and a team of researchers took a close look at the massive Shiva basin, a submerged depression west of India that is intensely mined for its oil and gas resources. Some complex craters are among the most productive hydrocarbon sites on the planet. Chatterjee will present his research this month's Annual Meeting of the Geological Society of America in Portland, Oregon.




***Three-dimensional reconstruction of the submerged Shiva crater (~500 km diameter) at the Mumbai Offshore Basin, western shelf of India from different cross-sectional and geophysical data. The overlying 4.3-mile-tick Cenozoic strata and water column were removed to show the morphology of the crater.***

"If we are right, this is the largest crater known on our planet," Chatterjee said. "A bolide of this size, perhaps 40 kilometers (25 miles) in diameter creates its own tectonics."

By contrast, the object that struck the Yucatan Peninsula, and is commonly thought to have killed the dinosaurs was between 8 and 10 kilometers (5 and 6.2 miles) wide.

It's hard to imagine such a cataclysm. But if the team is right, the Shiva impact vaporized Earth's crust at the point of collision, leaving nothing but ultra-hot mantle material to well up in its place. It is likely that the impact enhanced the nearby Deccan Traps volcanic eruptions that covered much of western India. What's more, the impact broke the Seychelles islands off of the Indian tectonic plate, and sent them drifting toward Africa.

The geological evidence is dramatic. Shiva's outer rim forms a rough, faulted ring some 500 kilometers in diameter, encircling the central peak, known as the Bombay High, which would be 3 miles tall from the ocean floor (about the height of Mount McKinley). Most of the crater lies submerged on India's continental shelf, but where it does come ashore it is marked by tall cliffs, active faults and hot springs. The impact appears to have sheared or destroyed much of the 30-mile-thick granite layer in the western coast of India.

The team hopes to go India later this year to examine rocks drill from the center of the putative crater for clues that would prove the strange basin was formed by a gigantic impact.

"Rocks from the bottom of the crater will tell us the telltale sign of the impact event from shattered and melted target rocks. And we want to see if there are breccias, shocked quartz, and an iridium anomaly," Chatterjee said. Asteroids are rich in iridium, and such anomalies are thought of as the fingerprint of an impact.

## Xenotropic murine leukemia virus-related virus may not be associated with human prostate cancer

The xenotropic murine leukemia virus-related virus (XMRV) which has previously been linked to prostate cancer has been found to have a dramatically lower prevalence among German prostate cancer patients, if any. Contrary to some reports, which have found XMRV in 40% of cases in patients in the US with familial prostate cancer, research published today in BioMed Central's open access journal, Retrovirology has found no link between the two conditions in a large study of German prostate cancer patients.

The experimental research was undertaken by a team from the Robert Koch Institute and the Charité in Berlin, Germany, led by Norbert Bannert and Reinhard Kurth. They used real-time PCR and nested PCR techniques to genotype the RNase L gene (an interferon regulated antiviral defence gene) and detect the presence of the XMRV virus in samples collected from 589 prostate cancer patients between the years 2000 and 2006. Some samples were also tested for the presence of Env antibodies directed against XMRV using an ELISA.

Knowledge relating to the genetic susceptibility and risk factors of prostate cancer increase the likelihood of early detection and successful treatment of the disease. Previously, the HPC1 locus (hereditary prostate cancer locus-1) has been identified as a hereditary factor associated with a predisposition to prostate cancer. The gene RNaseL is found within this locus. The RNase L gene codes for an endoribonuclease that is involved in the interferon-regulated antiviral defence pathway. Certain polymophisms in this gene in which the enzyme product

has reduced activity have been reported by others as being linked to increased risk of prostate cancer (presumptively due to XMRV-infection) in the US and Japan.

In the current study, from the 589 prostate tumor samples, 76 were found to be homozygous for the previously reported RNase L presumptively XMRV-susceptible Q (R462Q) genotype, however, neither DNA nor RNA fragments of XMRV were detected in samples collected from the prostate cancers. ELISA results show that none of the patients had antibodies directed against XMRV, suggesting that in German prostate cancer patients at least, there is no evidence for XMRV infection or XMRV-linked prostate cancer even in individuals with the RNase L XMRV-susceptible Q genotype. According to Bannert, "a possible geographical restriction of XMRV and its associations with cases of prostate cancer should be studied closely", adding that "the oncogenic potential of the virus must be thoroughly investigated in order to establish whether or not it can trigger the development of prostate cancer."

**Notes to Editors**

1. Article: ***Lack of evidence for xenotropic murine leukemia virus-related virus (XMRV) in German prostate cancer patients*** Oliver Hohn, Hans Krause, Pia Barbarotto, Lars Niederstadt, Nadine Beimforde, Joachim Denner, Kurt Miller, Reinhard Kurth and Norbert Bannert Retrovirology (in press)

## Sea anemone stings make a 'hypodermic' skin cream

* 15:03 15 October 2009 **by Colin Barras**

***Taking the sting out of their tail: Israeli company NanoCyte has found a way of harvesting sea anemone needles to painlessly inject drugs into people*** **(Image: NanoCyte)**

Mixing stinging cells from sea anemones into skin cream sounds like a bad practical joke. But this novel approach to painlessly injecting drugs could be a needle-free way to deliver insulin to diabetics.

The stinging cells, or cnidocysts, of sea anemones, jellyfish and other cnidarians contain a coiled hollow thread that unravels rapidly when triggered by physical contact – so rapidly that the pressure on the tip can theoretically reach nearly 7 gigapascals (PDF), higher than the pressure needed to form diamonds within the Earth's mantle. Unsurprisingly, the threads easily penetrate human skin and can even puncture fish scales.

The threads normally inject venom into the target of the animal's attack. But NanoCyte, a firm based in Or Akiva, Israel, is using them to inject drugs instead.

**Stinging harvest**

The firm uses needles "harvested" from the Mediterranean and Red Sea anemone Aiptasia diaphana, grown in aquariums.

"We use a particular stimulus that causes the release of filaments from the body of the anemone," says Yaron Daniely, president and CEO of NanoCyte. It's unclear why the animals release the filaments, which contain stinging cells, although Daniely does not think it's a stress response. Once the team has gathered up the filaments the animal is returned to its tank: "It's a bit like milking a cow," he says.

NanoCyte processes the stinging cells to denature the toxic proteins and extracts as much of them as possible – though this species of anemone is relatively non-toxic to humans to begin with. "Dermal toxicity protocols have been established to ensure that all batches display similar safety profiles," says Daniely.

Stinging cells isolated from the filaments are 60 micrometres long and 8 micrometres wide, and contain a hair-like needle 40 micrometres long (see an image of a stinging cell). "The key to our work is to be able to control these cells under an environment that doesn't make them trigger [and fire the needle during handling]," says Daniely. "The actual process we use is secret, but when you're familiar with the mechanisms of activation you can engineer a manufacturing environment that prevents them triggering."

**This won't hurt a bit**

The stinging cells are added to a cream which contains the active ingredient to be injected into the skin, some of which diffuses into the cells. Applying the cream to the skin triggers the stinging cells, possibly because of exposure to water on the skin and in the air.

One square centimetre of cream-coated skin can contain as many as a million tiny needles, and Daniely says that around one-third of the stinging cells in the cream end up pointing in the right direction to fire their needles into the skin – but because each is just a few micrometres thick, the process is painless.

Once discharged, each stinging cell acts as a tiny pump to deliver its content down the needle, also drawing in the active ingredient from the cream (see an image of a firing stinging cell).

The walls of stinging cells don't allow very large drug molecules to get through, however, says Daniely: "After years of trial and error, we have a clear idea about what types of molecule work well with our system."

**Dentists and diabetes**

Last week, NanoCyte concluded phase II clinical trials in the US of a cream containing lidocaine, a local anaesthetic used to relieve itching or to numb the mouth during dental work. The firm hopes to bring cosmetic products, such as "anti-ageing" treatments, to market in 2010. "We have several collaborations with some of the top 10 cosmetic companies in the world," says Daniely.

Preliminary work with mice suggests it is possible to use the approach to fire insulin through the skin to reach the bloodstream, he adds.

"It is exciting that this approach has reached phase II trials," says Mark Prausnitz at the Georgia Institute of Technology in Atlanta, who works on drug delivery methods. Using stinging cells is "very clever and innovative", he says, but he points out that pharmaceutical applications have more rigorous requirements than cosmetic ones. "There is a lot to learn before we can know its utility for drug delivery."

## Approaching footsteps boost seeing in the dark

* 18:00 15 October 2009 **by Michael Marshall**

There are footsteps behind you in the dark alley and they're getting closer. By the time you turn around to see who is following, your brain's vision circuits have already boosted their sensitivity, primed to pick out your pursuer in dim light.

That's the suggestion from a study of people's responses to "looming signals" – sounds that indicate that something is approaching rapidly. The changes in the visual cortex occur before people are even conscious of a looming sound, suggesting that the response is hard-wired in the brain.

Vincenzo Romei of the University of Glasgow, UK, and his colleagues played 15 volunteers a selection of sounds, some of which sounded like they were approaching, while others seemed to be receding or stationary.

At the same time, they used transcranial magnetic stimulation (TMS) to excite the visual cortex at the back of the brain (see How the human brain works).

TMS uses magnetic fields to generate weak electrical currents that excite brain cells. When used on the visual cortex, it can make people see illusory spots of light called phosphenes. The more sensitive the visual cortex is, the higher the chance of seeing phosphenes.

**Seeing sounds**

All the sounds made the volunteers more likely to see phosphenes during TMS, but the looming one had by far the strongest effect.

Volunteers saw phosphenes in 70 per cent of trials in which the looming sound was played, compared with 50 per cent when the sound was stationary, 45 per cent when it was receding and 36 per cent when no sound was played. Romei says, "The visual cortex is responding to non-visual stimuli."

Vincent Walsh of University College London, who was not involved in the study, says the results make sense.

"Auditory processing is faster than visual processing, so if the brain gets an auditory signal first, it will be likely to influence the interpretation of subsequent incoming stimuli," he says. "Think of how film music sets a scene's mood, even when the screen is dark."

**Brain links**

Making the visual cortex more sensitive when we hear something approaching could help us to spot threats more quickly in the dark, according to Romei. "It's important for our survival to respond as fast as possible to something that's approaching fast."

The looming sounds had an effect even when the volunteers did not know what they were. Bursts of looming sound just 80 milliseconds long, which the volunteers could not consciously identify as approaching rather than stationary, still made the visual cortex more sensitive.

Walsh suggests that the effect could be controlled by a part of the brain called the colliculus. He says, "The colliculus is the sprint winner: it responds very rapidly to looming. It is what makes you put up your hands defensively when a bird flies past, long before you know it is a bird."

*Journal reference: Current Biology, DOI: 10.1016/j.cub.2009.09.027*

## Super sticky barnacle glue cures like blood clots

Barnacles are a big problem for boats. Adhering to the undersides of vessels, carpets of the crustaceans can increase fuel consumption by as much as 25%. Ship owners would love to know how to stop these hitchhikers gluing on, but before you can learn how to disrupt an adhesive, you have to understand the curing process. Curious about many aspects of the crustacean's lifestyle, Dan Rittschof from Duke University decided to find out how barnacle adhesive polymerizes. 'The process must be related to something because glue isn't de novo,' says Rittschof, so he wondered what else coagulates under water and came up with two answers: blood and semen. With a colossal body of blood clotting literature to draw on, Rittschof decided to follow his evolutionarily inspired theory to see whether barnacle glue polymerization is really an extreme example of scab

formation and publishes his results on 16 October 2009 in the Journal of Experimental Biology at http://jeb.biologists.org.

Rittschof teamed up with Gary Dickinson and the first thing that Dickinson had to do was work out how to collect the unpolymerised glue and keep it fluid. Building on 30 years of Rittschof's experience and Beatriz Orihuela's expertise at growing and reattaching barnacles, Dickinson learned to gently lift polymerised glue away from the pores that secrete the adhesive and quickly collect the minute drops as they oozed from the shell. Working in the cold room to slow the polymerization process, Dickinson had only 5 minutes before each sample polymerized and the glue set solid.

Next the team had to convince themselves that the viscous secretion was glue and not some other body fluid. Dickinson found that the fluid polymerised rapidly and was packed full of protein, just like barnacle glue. Next Dickinson teamed up with Kathy Wahl to use atomic force microscopy to compare the molecular structures of naturally cured glue (from stuck-down barnacles) and his polymerized samples. The two samples were virtually indistinguishable and Dickinson could clearly see tangled webs of fibres in his glue drops, similar to the tangled fibres in blood clots.

But this evidence was still far from proving that barnacle glue cures by the same process as blood clots. Dickinson and Rittschof needed to identify the key proteins that polymerize the cement. Knowing that blood clots are formed when enzymes, known as trypsin-like serine proteases, trigger a cascade of events that culminates in the formation of the long fibres found in blood clots, Dickinson and Rittschof began searching for the protease in the unpolymerised glue. Separating the glue's components on a gel, Dickinson could see the tell-tale pattern of bands that suggested that a trypsin-like serine protease was present. And when Dickinson added an inhibitor, to inactivate the protease, to a fresh sample of glue, the sample didn't set.

Having convinced themselves that the glue contained a trypsin-like serine protease, the team began to search for other blood-clot-like proteins in the barnacle's secretions. Teaming up with Joseph Bonaventura and Irving Vega, Dickinson chopped each glue component into minute fragments, measured their sizes with mass spectrometry and matched the fragment pattern to known protein sequences. Amazingly, one of the glue proteins was remarkably similar to human factor XIII: a human blood clotting factor that cross-links clot fibres to form a scab. In fact, some regions of the human and barnacle proteins were completely identical. Dickinson and Rittschof had stumbled across the crucial protein that cross-links the glue fibres to cure barnacle cement and it was very similar to factor XIII, an essential human blood-clotting factor.

Rittschof admits that he is shocked that his hypothesis stands up to the tests. 'It seems likely that barnacle glue polymerization is a specialized form of wound healing,' he says and suspects that many other marine animals that rely on glue to get a grip may use the same polymerization mechanism.

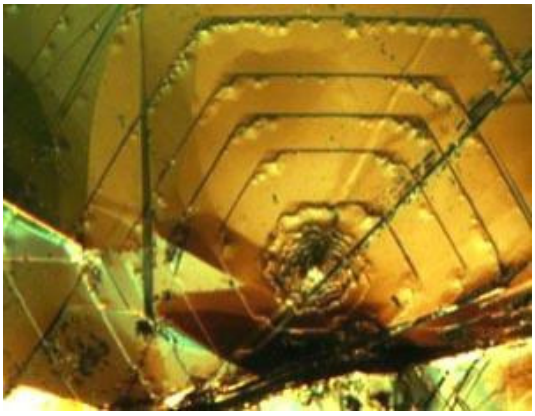
***REFERENCE:*** *Dickinson, G. H., Vega, I. E., Wahl, K. J., Orihuela, B., Beyley, V., Rodriguez, E. N., Everett, R. K., Bonaventura, J. and Rittschof, D. (2009). Barnacle cement: a polymerization model based on evolutionary concepts. J. Exp. Biol. 212, 3499-3510 http://jeb.biologists.org*

*Full text of the article is available ON REQUEST. To obtain a copy contact Kathryn Knight, the Journal Of Experimental Biology, Cambridge, UK. Tel: +44 (0)1223 425525 or email kathryn@biologists.com*

## Solving the crystal maze: The secrets of structure

* 16 October 2009 **by Stephen Battersby**

CRYSTALS are objects of true and profound mystery. That's not because they channel occult energies, or hold misty hints of the future in their limpid depths. Their puzzle is much less esoteric: why are they as they are?



***What makes graphite like this?*** **(Image: Walden)**

It is an incredibly basic question, yet physicists still struggle with it. Can we say why a given group of atoms prefers one particular arrangement over another? Can we predict how a crystal will be structured, and so deduce what properties it will have?

By and large, the answer is an embarrassing no. Or at least it used to be, if Chris Pickard of University College London is right. He has developed a surprisingly simple way of predicting crystal structures. His technique, along with another that has just emerged, might finally show us the way through the crystal maze.

There is more at stake here than the prettiness of some multifaceted amethyst. Crystals occur within most materials around us, be they metals, rocks or our own bones. Crystal structures determine crystal properties: the arrangement of atoms in a material makes it hard or soft, conducting or insulating. But theory alone has been

unable to work out what those structures should be. "We have to rely on experiment," says Pickard. "That always bugged me."

With good reason. Sometimes X-rays and other probes just don't reveal how a crystal is built, and materials in extreme situations such as other planetary cores are simply beyond the reach of experiment. Besides, if you could cook up crystals in a theoretical simulation, you might be able to discover new materials with remarkable properties.

Pickard's idea for breaking the impasse took a while to crystallise. In 1994, when he was a novice PhD student at the University of Cambridge, his supervisor Mike Payne had written a computer program called CASTEP to simulate what electrons and nuclei do within solids. "He said, take it and calculate anything you like," recalls Pickard.

Pickard chose to tackle carbon, an element that typifies crystal mystery: depending on how its atoms team up, it can form ultrahard transparent diamond, or soft grey graphite. He started off by tossing carbon atoms randomly into a box large enough to fit the basic "unit cell" of the crystal, and worked out the energy of the resulting structure. Knowing that nature always favours the lowest-energy arrangement, CASTEP could work out how the atoms could move to reduce their energy. By repeating this process until the energy could be reduced no more, the final structure should by rights be nature's crystal.

In fact, it was an almighty mess. The carbon atoms did not arrange themselves into the regular tetrahedral cage of a diamond crystal, or into the flat, honeycomb sheets that make up graphite. The structure had no obvious symmetry to it at all.

**Joining the dots**

Pickard had hit the same snag as many before him. Although electrical forces between electrons and nuclei will naturally pull randomly arranged atoms into a more stable, low-energy arrangement, they won't necessarily find the stablest, lowest-energy arrangement. It is like dropping a ball onto a complex landscape of hills and valleys. The ball will roll to the bottom of the nearest dip, but in the gnarled and forbidding energy landscape that represents the interactions of even just a few atoms, the chance is slim that the dip is the very bottom of the deepest valley - the home of nature's crystals.

Deterred, Pickard turned to other projects. In 2004, though, he was helping his PhD student Rachel Strong use a different method, known as graph theory, to chip away at the structures of diamond and other similar crystals. The idea was first to draw a cartoon crystal with simple dots marking the atomic nuclei, and lines representing the electron bonds between them. Graph theory calculates which ways of joining the dots satisfy the constraints imposed by chemical bonding, and so radically reduces the number of configurations admissible in any simulation.

The join-the-dots tactic was showing some promise, but was also frustratingly imperfect. It only worked with some types of bond, and even then only if you made assumptions about how many bonds each atom could form. That's not always obvious. In graphite, each carbon atom forms bonds with three neighbours; in diamond, it is four. On a whim, Pickard reran his calculations of 10 years before to compare them with the structures Strong was producing. Something remarkable happened. "I started to get sensible structures," he says.

What had changed? Computers had become faster, of course, and Pickard had helped to rewrite CASTEP to make it far easier to repeat simulations with atoms in different starting positions. That, it turned out, was the key. Most of the configurations that emerged were still random messes, but when Pickard ran the simulation many times some familiar-looking structures kept recurring - diamond and graphite. In mimicking nature, it seems that if at first you don't succeed, try and try again.

Pickard was initially sceptical that the result was more than a fluke, but when he showed his work to Richard Needs of the University of Cambridge, who studies the behaviour of electrons in solids, he got an enthusiastic response. The two soon unleashed the random structure search method on hydrogen.

Hydrogen is the simplest of atoms, consisting of just one proton circled by one electron, but in its solid state, it is a perplexing beast. Crude calculations suggest that solid hydrogen should become electrically conducting when squeezed to pressures of about 3 million atmospheres; in experiments, though, it remains insulating. Running the simulation with the pressure turned up, Pickard and Needs discovered a previously unsuspected form of solid hydrogen that was not only stable, but was indeed an insulator, with all its electrons bound to individual atoms rather than free to wander and carry an electrical current (Nature Physics, vol 3, p 473).

The duo weren't alone in their success. By the time they published the paper describing their method in 2006, other groups were starting to use rather different methods to predict crystal structures (see "Many ways through the crystal maze"). These predictive tools share the promise of revealing weird and wonderful new materials. Armed with such software, it should be possible to whip up any combination of atoms into a crystal and see what it's like. "You can see what the landscape gives you, then see what its properties are," says Pickard.

History cautions against excessive enthusiasm quite yet, however. A crystal prediction method must prove its worth on all sorts of structures - including, crucially, organic molecules, which Pickard has yet to take on. Nor is prediction the end of the story, as Pickard himself admits. "Say I stumble on a new crystal structure, and - wow! - it's the strongest material, it's a room-temperature superconductor, it cures cancer," he says. "Then the chemist says, 'But how do I make it?' I can't answer that yet."

Even discovering the possibility of some new ultrahard material or high-temperature superconductor would be a big step. Pickard and Needs are also looking for materials that efficiently pack a lot of hydrogen into a small space as a solid fuel for cars. They have already had one tantalising candidate: a mix of three hydrogen atoms to one aluminium atom that is solid at high pressures. Cranking the pressure in the simulation down, though, the structure did not survive.

A similar thing happens to mundane old nitrogen at very high pressures. At about 1 million atmospheres, it turns into a solid with a similar structure to diamond, but unlike diamond, it dissolves into a polymer mush when you take the pressure off. Even after it does so, it retains much of the energy stored in its bonds in the high-pressure state, potentially making it useful as a "green" explosive with no toxic residue, or as a fuel for stealth rockets that leave no chemical trace of their passage. Pickard is studying nitrogen right now, but he is a little cagey about why. "I can't say much about this," he says.

Together with his colleague Dominic Fortes, he is also looking into the properties of a mix of ammonia and water called ammonia monohydrate, whose behaviour could help answer whether there is a subsurface ocean on Jupiter's moon Ganymede and Saturn's moon Titan, and potentially explain the origin of watery volcanoes thought to exist on Titan. Here the appeal of simulations is obvious, given the difficulty of doing experiments in situ.

That said, experiments on Earth can at least match the pressures a few hundred kilometres under the crust of Titan, which reach several thousand atmospheres. Not so inside Jupiter, the solar system's weightiest planet, whose core pressure is thought to approach 100 million atmospheres. According to models of the solar system's formation, much of Jupiter's core is made of silicate rocks similar to those that make up the bulk of Earth. But is that a hard heart or a soft centre? At Jupiter's internal pressures no one knows whether silicates would be solid crystals or a liquid.

Experiments on Earth are unlikely to help. We can only create such extreme pressures in the lab for a split second, by sending shock waves through a sample - for example, using the lasers of the National Ignition Facility in Livermore, California. That's too brief to probe crystal structure. Researchers can compress matter less explosively using a device called a diamond anvil cell, but only up to about 3.5 million atmospheres - good enough to reproduce the heart of Earth, but not Jupiter.

Pickard's plan, now backed by a £1.3 million grant from a UK funding body, is that the simulations will boldly go there - and further. Beyond the solar system, planets even more massive than Jupiter are being discovered. What strange materials could lurk at their hearts? And what about some of the most extreme environments imaginable, the ultra-compressed crusts of neutron stars? Those would be some pretty far-out crystals. Unlocking their secrets, though, might not be so very far away.

**Many ways through the crystal maze**

Chris Pickard's random structure search (see main story) is not the only path that might lead to the heart of the crystal mystery. One early approach, called simulated annealing, involves loading model atoms into a computer simulation, then repeatedly raising the temperature and lowering it again. Given enough of this thermal jiggling, the atoms should eventually find the most stable, lowest-energy configuration. In practice, though, this approach needs an unfeasible amount of computer time.

A more effective rival to Pickard's method emerged around 2006 in the form of genetic algorithms rooted in ideas of sex and death. Such simulations start with a small population of different crystal structures that then reproduce, with only the fittest crystals surviving (Journal of Chemical Physics, vol 124, p 244704).

Artem Oganov of Stony Brook University, New York, is a leading exponent of this approach. "We throw out the highest-energy structures, in a rather cruel way," he explains. "From the rest we create children." Some children are made from different pieces of two parent structures. Others are mutated offspring of a single parent, randomly distorted or with different atoms swapped around.

One problem with early genetic algorithms was that the population often turned into an unchanging set of clones before it reached the fittest, most stable structure. Oganov found that he could avoid this stagnation by making the mutations more extreme. With his algorithm, he has been able to reproduce some of the more familiar crystals of nature, such as diamond, and also many exotic new materials. He found, for example, that pure sodium, when compressed to about 3 million atmospheres, suddenly turns from being a red metal into an

insulator that is clear as glass - and experiments have since confirmed this. He is now working on a project to find superhard materials.

Oganov and Pickard disagree on which of the two methods is the more efficient and powerful. It may just turn out that they are each better for different materials, says Pickard. "Maybe they will each find their niches and coexist." ***Stephen Battersby is a writer based in London***

## Promising novel treatment for human cancer -- Chrysanthemum indicum extract

A series of studies have demonstrated that Chrysanthemum indicum possesses antimicrobial, antiinflammatory, immunomodulatory, and neuroprotective effects. Recently, much attention has been devoted to the anticancer activity of Chrysanthemum indicum, especially in hepatocellular carcinoma (HCC). However, its anticancer mechanism of action is still not clear and needs further investigation.

A research article to be published on September 28, 2009 in the World Journal of Gastroenterology addresses this question. The research team, led by Prof. Zong-fang Li from the Second Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, investigated the effects of Chrysanthemum indicum extract (CIE) on inhibition of proliferation and on apoptosis, and the underlying mechanisms, in a human HCC MHCC97H cell line.

They examined viable rat hepatocytes and human endothelial ECV304 cells by trypan blue exclusion and MTT assay, respectively, as normal controls. The proliferation of MHCC97H cells was determined by MTT assay. The cellular morphology of MHCC97H cells was observed by phase contrast microscopy. Flow cytometry was performed to analyze cell apoptosis with annexin V/propidium iodide (PI), mitochondrial membrane potential with rhodamine 123 and cell cycle with PI in MHCC97H cells. Apoptotic proteins such as cytochrome C, caspase-9, caspase-3 and cell cycle proteins, including P21 and CDK4, were measured by Western blotting.

The results showed CIE inhibited proliferation of MHCC97H cells in a time- and dose-dependent manner without cytotoxicity in rat hepatocytes and human endothelial cells. CIE induced apoptosis of MHCC97H cells in a concentration-dependent manner, as determined by flow cytometry. The apoptosis was accompanied by a decrease in mitochondrial membrane potential, release of cytochrome C and activation of caspase-9 and caspase-3. CIE arrested the cell cycle in the S phase by increasing P21 and decreasing CDK4 protein expression.

The researchers drew a conclusion that CIE exerted a significant apoptotic effect through a mitochondrial pathway and arrested the cell cycle by regulation of cell cycle-related proteins in MHCC97H cells without an effect on normal cells. The cancer-specific selectivity shown in their study suggests that the plant extract could be a promising novel treatment for human cancer.

***Reference:*** *Li ZF, Wang ZD, Ji YY, Zhang S, Huang C, Li J, Xia XM. Induction of apoptosis and cell cycle arrest in human HCC MHCC97H cells with Chrysanthemum indicum extract. World J Gastroenterol 2009; 15(36): 4538-4546 http://www.wjgnet.com/1007-9327/15/4538.asp*

## Be overweight and live longer

Contrary to what was previously assumed, overweight is not increasing the overall death rate in the German population. Matthias Lenz of the Faculty of Mathematics, Computer Science, and Natural Sciences of the University of Hamburg and his co-authors present these and other results in the current issue of Deutsches Ärtzeblatt International (Dtsch Artzebl Int 2009; 106[40]: 641 ).

Most Germans are overweight, with a body mass index (BMI) between 25 and 29.9 kg/m2. About 20% are obese (BMI of 30 or over), with age- and gender-related differences. The authors systematically evaluated 42 studies of the relationships between weight, life expectancy, and disease.

The Süddeutsche Zeitung published an advance notice of the report, which shows that overweight does not increase death rates, although obesity does increase them by 20%. As people grow older, obesity makes less and less difference.

For coronary heart disease, overweight increases risk by about 20% and obesity increases it by about 50%. On the other hand, a larger BMI is associated with a lower risk of bone and hip fracture.

In relation to cancer, the overall death rate among extremely obese men (BMI above 40) is no higher than among those of normal weight. Men who are overweight even have a 7% lower death rate. No significant association was found in women.

According to the authors' analysis, overall mortality is unchanged by overweight, but increased by 20% by obesity, while extreme obesity raises it by up to 200%. *http://www.aerzteblatt.de/v4/archiv/pdf.asp?id=66217*

## TraDIS technique tackles typhoid

### *First high-throughput analysis of every Salmonella Typhi gene*

For the first time, researchers are able to look at the need for every gene in a bacterial cell in a single experiment. The new method will transform the study of gene activity and the search for weaknesses in bacterial armouries.

Using a newly developed, next-gen sequencing method, a team established which genes Salmonella Typhi needs to survive and which are more of a luxury. The results and the method will be a boon to scientists tackling bacterial disease, allowing them to capitalize on the abundance of genomic sequence data from next-generation sequencing technologies.

Every year 22 million people are infected and 220,000 die from infection with S. Typhi. It is a special threat in the developing world, in areas with poor sanitation or a lack of clean drinking water.

The team were able to look at almost all the genes in S. Typhi and showed that it needs only 356 genes for survival: 4162 genes were not essential. Knowing which genes are essential to the survival of pathogens, researchers can seek treatments to target those genes.

"We developed a new method that is ten times more powerful than any previous technique," says Sanger Institute graduate student Gemma Langridge, one of the first authors on the paper. "By combining transposon-induced mutagenesis – a method whereby small chunks of cut-and-paste DNA sequence are inserted into the genome effectively disabling individual genes – and high-throughput sequencing, we have been able to determine which genes are essential for the survival of S. Typhi and which are non-essential."

***Researchers have used next-generation sequencing to look at the need for every S. Typhi gene in a single experiment.***
**David Goulding, Wellcome Trust Sanger Institute**

"Crucially, our new method allows us to achieve all this in just a single experiment."

Using the novel method, which the team have named TraDIS (Transposon Directed Insertion site Sequencing), they inserted transposons into the S. Typhi genome to generate more than one million mutants. They then grew the bacteria and used next-generation sequencing to directly identify 370,000 insertion sites in the S. Typhi genome – an average of more than 80 insertion sites per gene. Previous methods produce only a few mutations per gene.

If a transposon inserts into an essential gene, the gene is silenced and that mutant cell will not grow and it - and the transposon insert – will be absent from the mutant pool. By sequencing DNA from the entire pool - approximately 1 million mutants in total – the team were able to identify genes in which no transposon insertions had been detected. In a single experiment using the TraDIS method, the team were able to determine whether or not 99.6% of the S. Typhi genes are essential to its survival.

"Sequencing centres such as ours can produce vast amounts of genomic data at a pace unimaginable just a few years ago," explains Professor Julian Parkhill, Director of Sequencing and head of Pathogen Genomics at the Sanger Institute. "One of our aims is to develop high-throughput research methods that can exploit this explosion of genetic data, to ensure these resources can be used effectively. We can now discover which of all the genes in an organism are essential to its survival or required for growth under special conditions, such as infection. Our new TraDIS method will make a dramatic difference to the ability to carry out such genome-wide research."

Importantly, the team applied the method to a clinical problem by looking at how S. Typhi might survive in humans. Typhoid can be spread by carriers who, without showing symptoms, act as reservoirs, storing the bacterium in the gallbladder and passing it to others. The most famous such carrier was Typhoid Mary, who worked in the food industry in the US and spread typhoid fever without exhibiting any symptoms herself.

But, bacteria cannot survive in the fairly hostile environment of the gall bladder unless they are tolerant to bile – the fatty fluid secreted by the gall bladder. Looking at genes involved in bile resistance, allows us to see which genes are essential for helping S. Typhi persist in a carrier.

"We grew the bacteria in ox bile to pick out genes required for bile tolerance," says Keith Turner, Sanger Institute investigator and a senior author on the paper. "We found 169 genes involved in bile tolerance - many of these had not been suspected before and more than 30 are genes not characterized at all.

"Using TraDIS, we have highlighted several possible new targets for treatment that would pick on S. Typhi's need to survive in the gall bladder."

For the first time, it is possible to paint a comprehensive picture of essential, advantageous or burdensome genes in many phases of the bacterial life cycle, to determine functions necessary to support them throughout their entire disease cycle. Such a picture is important for discovery of new targets for treatment.

This elegant new method exemplifies how high-throughput research allows scientists to determine systematically the function of or requirement for individual genes in a single experiment, opening the door for similar analyses of other pathogenic genomes in the future.

***Notes to Editors*** *Publication Details Langridge G C, Phan M-D, Turner D J et al. (2009)* ***Simultaneous assay of every Salmonella Typhi gene using one million transposon mutants. Genome Research***

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## Placebo effect caught in the act in spinal nerves

* 14:41 16 October 2009 **by Ewen Callaway**

The placebo effect is not only real; its ability to deaden pain has been pinpointed to cells in the spinal cord. That raises hopes for new ways of treating conditions such as chronic pain.

The researchers who made the discovery scanned the spinal cords of volunteers while applying painful heat to one arm. Then they rubbed a cream onto the arm and told the volunteers that it contained a painkiller – but in fact it had no active ingredient. Even so, the cream made spinal-cord neural activity linked to pain vanish.

"This type of mechanism has been envisioned for over 40 years for placebo analgesia," says Donald Price, a neuroscientist at the University of Florida in Gainesville, who was not involved in the new study. "This study provides the most direct test of this mechanism to date."

Indeed, the biggest obstacle to establishing the spinal cord's role in placebo pain relief was measuring its activity with fMRI scanning, says Falk Eippert, a neuroscientist at the University Medical Centre Hamburg-Eppendorf in Germany, who led the study.

**Squeezing a scan**

FMRI scanning has long been used to image the brain, but the part of the spinal cord that Eippert's team was interested in – the dorsal horn – is minuscule in comparison, and so is harder to image. It also swims around in cerebrospinal fluid, further complicating real-time measurement.

The team's first breakthrough was to squeeze an fMRI signal out of the spinal cord. Then they quickly adapted the technique to study placebo pain relief.

This meant telling 13 volunteers a white lie. They were told that the researchers were testing how effective a painkilling cream was, with an inactive cream as a control on the trial.

In fact, neither cream contained anaesthetic. However, when Eippert's team applied the alleged painkilling cream for the first time, they turned down the intensity of painful heat stimulation to 40 per cent of each volunteer's pain threshold – 46 °C on average. When the team tested the alleged control cream, they kept the temperature set at 80 per cent of the pain threshold – an average of 47 °C.

Because of this "fixing" of the temperatures, the volunteers would think, "'OK, this really seems to work, and it will work when I take it the next time,'" Eippert explains.

**Feeling the heat**

Later, with an fMRI scanner on, the researchers rubbed "control" and "painkiller" creams onto two different spots on each volunteer's left forearm and applied the same level of heat to each spot, 15 times.

The fake "painkiller" cream worked: volunteers said they experienced 26 per cent less pain on the "painkiller"-treated patch of their arm, compared with the "control"-treated area.

Meanwhile, the fMRI scanner witnessed the placebo effect. When skin treated with the "control" cream was heated, an area of the dorsal horn located on the left side of volunteers' lower necks lit up, suggesting increased neural activity there in response to pain. However, this signal disappeared in the "painkiller" trials.

Eippert's team didn't discover what caused this shift. He speculates that higher brain areas involved in buying into the bogus treatment trigger the release of endogenous opioids – chemicals our brain produces that work like opiates and may temper spinal cord activity.

Now that researchers know the neural hallmark of placebo pain relief, they could use it to develop treatments, cognitive or chemical, that take better advantage of belief, Eippert says.

*Journal reference: Science, DOI: 10.1126/science.1180142*

## Officials See a Shortage in Vaccine for Swine Flu

**By DENISE GRADY**

Health officials on Friday predicted a shortfall in the supply of swine flu vaccine, as the numbers of cases, hospitalizations and deaths grow to levels unprecedented for this time of year. Flu caused by the H1N1 virus is now widespread in 41 states, and flulike illnesses account for 6.1 percent of all doctor visits.

“That’s high for any time, particularly for October,” said Dr. Anne Schuchat, the director of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention.

Forty-three children have died from swine flu since Aug. 30 - about the same number that usually die in an entire flu season. Nineteen of the 43 who died were teenagers, and 16 were ages 5 to 11 years old; the rest were under 5. “These are very sobering statistics,” Dr. Schuchat said in a news briefing, “and unfortunately they are likely to increase.”

Fifteen percent to 20 percent of the patients who were hospitalized for the flu wound up in the intensive care unit, a rate comparable with that for seasonal flu. Although the disease continues to spread, its severity is not increasing. Projections of the supply of swine flu vaccine have widely varied. During the summer, health

officials said 120 million doses would be ready in October. They later dropped the estimate to 40 million doses by the end of the month.

Now, Dr. Schuchat said, they expect only 28 million to 30 million doses, adding that the exact numbers were impossible to predict and could change daily. She said vaccine manufacturers were reporting that production was behind schedule.

“I wish we could be more predictable, but this is how influenza vaccine goes,” Dr. Schuchat said. “Vaccine production for influenza is pretty complex,” she said in explaining the delay, “and the complex process this year is taking a bit longer than we had hoped. The yield of antigen is lower than they had hoped for.”

The antigen is the part of a virus included in vaccine to stimulate the body’s protective response. It is crucial; a vaccine will not work without it. Dr. Schuchat also said that once batches of vaccine were prepared, they had to be tested for potency and purity. “We are not cutting any corners,” she said. “It’s important to us that this process be done carefully and safely.” She acknowledged that some people were having trouble obtaining vaccinations, saying, “I’m sorry it’s a difficult time in terms of looking for vaccine.”

As of Wednesday, Dr. Schuchat said, 11.4 million doses of the H1N1 vaccine were available, with more being shipped. She predicted that by early November, there would be widespread vaccine availability and information on where people should go for it.

Explaining how just 30 million doses could translate into widespread availability, a spokesman for the disease centers, Tom Skinner, said: “ ‘Widespread’ means it’s going to be in a lot of places. It doesn’t mean that a lot is going to be in a lot of places. It just means it’s going to be out there.”

Dr. Schuchat acknowledged that some people had fears about the H1N1 vaccine, but she emphasized that it was safe and urged pregnant women to be vaccinated because they were especially prone to severe complications and had accounted for a disproportionate number of deaths.

Studies of the swine flu vaccine are being conducted in pregnant women. But, Dr. Schuchat said, “if I were pregnant, I would not wait for the results of those trials; the risk in pregnancy has been very striking.”

On the seasonal flu, Dr. Schuchat said 82 million doses of vaccine had been distributed, out of an expected total of 114 million.

But the vaccine has been running low in some areas. Dr. Schuchat urged the public to “keep looking” and emphasized that there was time because seasonal flu did not usually take hold until December. Virtually all cases now are the H1N1 swine flu, she said.

## Swedes divided over bunny biofuel

**By Helena Merriman** BBC News

***Bodies of thousands of rabbits are reportedly fuelling a heating plant***

Residents in Stockholm are divided over reports that rabbits are being used to make biofuel. The bodies of thousands of rabbits are fuelling a heating plant in central Sweden, local newspapers say.

The city of Stockholm has an annual cull of thousands of rabbits to protect the capital's parks and green spaces.

The rabbits, not native to Sweden, are mainly the offspring of pets released by owners, and are said to be destroying parks in the capital.

Since they have no natural predators, the city administration of Stockholm employs hunters to kill the rabbits.

Tommy Tuvunger, one of the hunters, told Germany's Spiegel website that 6,000 rabbits were culled last year, and another 3,000 this year. "They are a very big problem," he said. "Once culled, the rabbits are frozen and when we have enough, a contractor comes and takes them away."

The frozen rabbits are then taken to a heating plant in Karlskoga which incinerates them to heat homes.

**Bunny boilers**

Leo Virta, the Managing Director of Konvex - the plant's suppliers - told the BBC that Konvex has developed a new way of processing animal waste with funding from the EU as part of the Biomal project.

He says that with this new method, raw animal material is crushed, ground and then pumped to a boiler where it is burned together with wood chips, peat or waste to produce renewable heat. "It is a good system as it solves the problem of dealing with animal waste and it provides heat," said Mr Virta.

Reaction in Sweden has been divided, said James Savage, managing editor of The Local - an online news service covering Sweden. "In the town where they are burning them the reaction of the residents is quite relaxed," Mr Savage told the BBC World Service. "But in Stockholm there's the big city attitude of the rabbits being cute.

"That's amongst some people, particularly among some animal rights activists who think this is not a good way to treat rabbits."