SIRT1 takes down tumors

New study identifies another anti-cancer effect of the 'longevity' protein SIRT1

Yuan et al. have identified another anti-cancer effect of the "longevity" protein SIRT1. By speeding the destruction of the tumor promoter c-Myc, SIRT1 curbs cell division. The study will be published online April 13 (www.jcb.org) and will appear in the April 20 print issue of the Journal of Cell Biology.

The yeast and nematode equivalents of SIRT1 are fountains of youth that stretch lifespan. Whether SIRT1 slows aging in mammals isn't certain, but it's beneficial in other ways. The protein tunes up metabolism, reducing blood levels of glucose and insulin, and might forestall neurodegenerative illnesses such as Alzheimer's disease and ALS. Given its pro-life credentials, you might expect SIRT1 to inhibit cancer. And several studies suggest that it does. But other work indicates that the protein aids tumors. For example, SIRT1 chops off acetyl groups, which can inactivate the tumor suppressor p53.

Yuan et al. determined SIRT1's effect on the transcription factor c-Myc, whose expression surges in many breast, colon, and liver cancers. The two proteins are tangled in a regulatory loop, the team found. c-Myc latched onto SIRT1's promoter, spurring cells to manufacture more SIRT1. In turn, SIRT1 detached acetyl groups from c-Myc, hastening its breakdown. To test SIRT1's effects on tumor growth, the researchers implanted cancerous cells expressing c-Myc into nude mice that lack immune defenses. Boosting production of SIRT1 blocked tumor formation.

How deacetylation of c-Myc sparks its destruction is still a mystery. The researchers say that the results don't necessarily conflict with studies suggesting that SIRT1 is pro-tumor. Whether SIRT1 promotes or prevents cancer probably depends on the situation.

Study Finds Link Between Facebook Use, Lower Grades In College

SAN DIEGO - College students who use Facebook spend less time studying and have lower grade point averages than students who have not signed up for the social networking website, according to a pilot study at one university.

However, more than three-quarters of Facebook users claimed that their use of the social networking site didn’t interfere with their studies.

“We can’t say that use of Facebook leads to lower grades and less studying – but we did find a relationship there,” said Aryn Karpinski, co-author of the study and a doctoral student in education at Ohio State University.

“There’s a disconnect between students’ claim that Facebook use doesn’t impact their studies, and our finding showing they had lower grades and spent less time studying.”

While this was a relatively small, exploratory study, it is one of the first to find a relationship between college students’ use of Facebook and their academic achievement.

Typically, Facebook users in the study had GPAs between 3.0 and 3.5, while non-users had GPAs between 3.5 and 4.0.

In addition, users said they averaged one to five hours a week studying, while non-users studied 11 to 15 hours per week.

Karpinski conducted the study with Adam Duberstein of Ohio Dominican University. They presented their research April 16 in San Diego at the annual meeting of the American Education Research Association.

The researchers surveyed 219 students at Ohio State, including 102 undergraduate students and 117 graduate students. Of the participants, 148 said they had a Facebook account.

The study found that 85 percent of undergraduates were Facebook users, while only 52 percent of graduate students had accounts.

Students who spent more time working at paid jobs were less likely to use Facebook, while students who were more involved in extracurricular activities at school were more likely to use Facebook.

Science, technology, engineering, math (STEM) and business majors were more likely to use Facebook than were students majoring in the humanities and social sciences.

“Other research had indicated that STEM majors spend more time on the Internet than do other students, so that may be one reason why they are more likely to use Facebook,” Karpinski said.

There were no differences in Facebook use between different members of racial and ethnic groups that were part of the study, or between men and women.

Younger and full-time students were more likely to be Facebook users.

Findings showed that 79 percent of Facebook users claimed it did not have an impact on their academic performance. In open-ended questions on the survey, users claimed they didn’t use Facebook frequently enough to notice an impact, and emphasized that academics were a priority for them.

Karpinski emphasized that the results don’t necessarily mean that Facebook use leads to lower grades.

“There may be other factors involved, such as personality traits, that link Facebook use and lower grades,” she said.

“It may be that if it wasn’t for Facebook, some students would still find other ways to avoid studying, and would still get lower grades. But perhaps the lower GPAs could actually be because students are spending too much time socializing online.”

Karpinski said it was significant that the link between lower grades and Facebook use was found even in graduate students. She said that graduate students generally have GPAs above 3.5, so the fact that even they had lower grades when they used Facebook -- and spent less time studying – was an amazing finding.

The popularity of Facebook is evident in college lecture halls, Karpinski said. Faculty members who allow students to use laptops in class have told her they often see students on the Facebook site during class.

“It’s not going away anytime soon, and we need to learn more about how Facebook use is affecting students,” she said.

As for herself, Karpinski said she doesn’t have a Facebook account, although her co-author does.

“For me, I think Facebook is a huge distraction,” she said.

Review identifies dietary factors associated with heart disease risk

A review of previously published studies suggests that vegetable and nut intake and a Mediterranean dietary pattern appear to be associated with a lower risk for heart disease, according to a report published in the April 13 issue of Archives of Internal Medicine, one of the JAMA/Archives journals. However, intake of trans-fatty acids and foods with a high glycemic index may be harmful to heart health.

"The relationship between dietary factors and coronary heart disease has been a major focus of health research for almost half a century," the authors write as background information in the article. Although "a wealth of literature" has been published on the topic, "the strength of the evidence supporting valid associations has not been evaluated systematically in a single investigation."

Andrew Mente, Ph.D., of the Population Health Research Institute, and colleagues conducted a systematic search for articles investigating dietary factors in relation to heart disease published between 1950 and June 2007. A total of 146 prospective cohort studies (looking back on the habits of a particular group of individuals) and 43 randomized controlled trials (where participants are randomly assigned to a dietary intervention or a control group) were identified and included in the systematic review.

When the researchers pooled the study results and applied a predefined algorithm, "we identified strong evidence of a causal relationship for protective factors, including intake of vegetables, nuts and monounsaturated fatty acids and Mediterranean, prudent and high-quality dietary patterns, and harmful factors, including intake of trans–fatty acids and foods with a high glycemic index or load and a western dietary pattern," they write. "Among these dietary exposures, however, only a Mediterranean dietary pattern has been studied in randomized controlled trials and significantly associated with coronary heart disease."

In addition, modest relationships were found supporting a causal relationship between intake of several other foods and vitamins and heart disease risk, including fish, omega-3 fatty acids from marine sources, folate, whole grains, alcohol, fruits, fiber and dietary vitamins E and C and beta carotene. Weak evidence also supported causal relationships between vitamin E and ascorbic acid supplements, saturated and polyunsaturated fatty acids and total fats, alpha-linoleic acid, meat, eggs and milk.

"The modest or weak evidence of these dietary exposures is mostly consistent with the findings of randomized controlled trials, although randomized controlled trials have yet to be conducted for several factors," the authors write. "Taken together, these findings support a causal relationship between only a few dietary exposures and coronary heart disease, whereas the evidence for most individual nutrients or foods is too modest to be conclusive."

"Although investigations of dietary components may help to shed light on mechanisms behind the benefits of dietary patterns, it is unlikely that modifying the intake of a few nutrients or foods would substantially influence coronary outcomes," they conclude. "Our findings support the strategy of investigating dietary patterns in cohort studies and randomized controlled trials for common and complex chronic diseases such as coronary heart disease."

(Arch Intern Med. 2009;169[7]:659-669. Available pre-embargo to the media at www.jamamedia.org.)

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Many clinicians unaware of federally funded research on alternative therapies

Approximately one in four practicing clinicians appear to be aware of two major federally funded clinical trials of alternative therapies, and many do not express confidence in their ability to interpret research results, according to a report in the April 13 issue of Archives of Internal Medicine, one of the JAMA/Archives journals.

Complementary and alternative (CAM) therapies are widely used, but until recently few rigorous studies of their safety and effectiveness have been conducted, according to background information in the article. The National Institutes of Health (NIH) has invested more than $2 billion into this type of scientific research in the past decade. "For this investment to achieve its anticipated social value, clinical research must be translated into improvements in clinical and public health practice—a process fraught with obstacles," the authors write.

"For evidence from clinical research to have an impact on medical practice, health care professionals must first be aware of the research. Once aware, health care professionals must be able to interpret these findings, judging both their validity and their implications. Finally, they must apply the scientific evidence to their own practices," they continue. To assess this translation process surrounding CAM research, Jon C. Tilburt, M.D., M.P.H., of the NIH, Bethesda, Md., and Mayo Clinic, Rochester, Minn., and colleagues surveyed 2,400 practicing acupuncturists, naturopaths, internists and rheumatologists about their awareness of and attitudes toward CAM research.

A total of 1,561 clinicians (65 percent) completed the survey. Of those, 59 percent were aware of at least one of two major clinical trials recently published on CAM therapies for osteoarthritis of the knee (on assessing acupuncture and the other about the supplement glucosamine); only 23 percent were aware of both trials. Acupuncturists (46 percent) and rheumatologists (49 percent) were more likely to be aware of the acupuncture study than naturopaths (30 percent) and general internists (22 percent), whereas for the glucosamine trial, internists (59 percent) and rheumatologists (88 percent) were more aware than acupuncturists (20 percent) and naturopaths (39 percent).

A minority of clinicians in all groups said they were "very confident" in their ability to critically interpret research literature (20 percent of acupuncturists, 25 percent of naturopaths, 17 percent of internists and 33 percent of rheumatologists); more described themselves as "moderately confident" (59 percent of acupuncturists, 64 percent of naturopaths, 67 percent of internists and 59 percent of rheumatologists)

"Compared with those who were not aware of CAM trials, clinicians who were aware of CAM trials were much more likely to be rheumatologists, to be practicing in an institutional or academic setting, to have some research experience, to express greater ability to interpret evidence and to report greater acceptance of evidence," the authors write.

The results suggest that the translation of CAM trial results into clinical practice may vary widely based on the training, attitudes and experiences of the clinicians who might apply them, they continue. "For clinical research in CAM (and conventional medicine) to achieve its potential social value, concerted efforts must be undertaken that more deliberately train clinicians in critical appraisal, biostatistics and use of evidence-based resources, as well as expanded research opportunities, dedicated training experiences and improved dissemination of research results," the authors conclude.

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Editorial: Evidence-Based Medicine Goes Beyond Research Results

"If we are to teach more evidence-based medicine to physicians, we need to broaden and deepen our understanding of what counts as 'evidence' and which types of evidence are best used to inform differing aspects of clinical decision making," writes Wayne B. Jonas, M.D., of the Samueli Institute, Alexandria, Va., in an accompanying editorial.

"Rather than imposing an academic, hierarchical structure on medical decision making, evidence-based medicine should seek to inform the processes practitioners actually use in making clinical decisions to more effectively incorporate science into practice," Dr. Jonas writes. "That is, physicians need to know how to use a complete 'evidence house' and not just the 'evidence hierarchy' currently dominating evidence-based medicine in both conventional and complementary medicine."

"As with any skill, sufficient time and supervised application is needed before evidence-based medicine can become a habit in daily practice. Thus, both CAM and conventional practitioners should each seek to fill their respective gaps in knowledge and skills to make practices both more patient relevant and scientifically rigorous."

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Erectile dysfunction treatments do not appear to damage vision over 6 months

Two medications used to treat erectile dysfunction in men (tadalafil and sildenafil) do not appear to have visual side effects when taken daily for six months, despite concerns about eye-related complications, according to a report in the April issue of Archives of Ophthalmology, one of the JAMA/Archives journals.

The advent of the medications sildenafil citrate (sold as Viagra), tadalafil (sold as Cialis) and verdenafil hydrochloride (sold as Levitra) has profoundly changed the treatment of erectile dysfunction, according to background information in the article. These medications are known as selective phodiesterase type 5 (PDE5) inhibitors because they treat erectile dysfunction by interfering with the action of the compound PDE5 on the blood vessels in the penis. However, PDE5 inhibitors may also act on similar compounds in the retina, the part of the eye that receives and transmits images. Mild and transient blurred vision, blue-tinged vision and altered light perception have been reported by men taking these drugs, and some visual complications of long-term use have been suggested.

William H. Cordell, M.D., of Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, and colleagues conducted a randomized placebo-controlled study to assess changes in the retina among men taking tadalafil or sildenafil. A total of 244 healthy men, some with mild erectile dysfunction, age 30 to 65 were recruited. Of these, 85 were randomly assigned to take 5 milligrams of tadalafil, 77 to take 50 milligrams of sildenafil and 82 to take a placebo daily for six months. The men underwent comprehensive ophthalmologic examinations including electroretinography (a test to measure the electrical response of the light-sensitive rods and cones in the eye, used to detect diseases of the retina) before, during and after treatment.

Among the 194 men (79.5 percent) who completed the study, no significant differences were found between treatment and placebo groups on electroretinography, visual function tests, measurements of intraocular pressure (pressure within the eyeball) or assessments of the anatomy of the eye. Nine participants (two in the placebo group, one in the tadalafil group and six in the sildenafil group) discontinued the study because of an adverse event, but only one of those was an ophthalmologic event (in the placebo group). No abnormalities that would be suggestive of drug toxicity were observed in any of the participants.

"There are several reasons ophthalmologists need to be acquainted with the pharmacologic profiles of PDE5 inhibitors and their potential side effects," the authors write. "The frequency of erectile dysfunction, which is a form of peripheral vascular disease that impairs men's abilities to achieve and maintain an erection, increases dramatically with age and in the presence of cardiovascular risk factors. Therefore, many men who take PDE5 inhibitors to treat their erectile dysfunction will also be followed up by ophthalmologists for ocular disorders such as diabetic retinopathy, macular degeneration and ocular vascular disease."

"Furthermore, PDE5 inhibitors can exert direct effects on the retina, and such effects probably account for many of the visual side effects such as blue-tinged vision and light sensitivity that have been reported," they conclude. However, "our results indicate that there is no cumulative damage or effect of clinical significance for either 5 milligrams of tadalafil or 50 milligrams of sildenafil taken daily for six months."

(Arch Ophthalmol. 2009;127[4]:367-373. Available pre-embargo to the media at www.jamamedia.org.)

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University of Toronto chemists uncover green catalysts

Promising for cheaper drug production

A University of Toronto research team from the Department of Chemistry has discovered useful "green" catalysts made from iron that might replace the much more expensive and toxic platinum metals typically used in industrial chemical processes to produce drugs, fragrances and flavours.

The synthesis of drugs usually relies on the use of catalysts and the expense of the catalysts influences the ultimate cost of the drug. If the catalyst is toxic, as it usually is when platinum-metals such as ruthenium, rhodium and palladium are used, then it must be removed completely from the synthesized product using costly purification techniques.

"With a cheaper and less toxic catalyst, like iron, these drawbacks are avoided," says Professor Robert Morris. The study appeared online in Chemistry - A European Journal on April 9.

The successful use of iron as a catalyst in place of the more commonly used ruthenium is surprising since iron has been considered to be a "base metal" of low catalytic activity. The successful trick was to prepare a complex of iron with a structure similar to the most active ruthenium catalyst, says Morris.

Chemical catalysts are generally known for their ability to speed up a reaction but they can also influence the structure of the chemical that is produced in that reaction, says Morris. Catalysts used in the synthesis of a chemical used as a drug or fragrance are most valuable when they cause the production of the chemical in one structural form and not the mirror image of that form (i.e. producing a left-handed form and not the right-handed one).

The catalyst was made by attaching to iron, in its "ferrous" state, an organic molecule that contains carbon, hydrogen, phosphorus and nitrogen with the atoms arranged in exclusively a right-handed structural form. The catalyst is used in small amounts to convert a large amount of inexpensive ketone to a large amount of the valuable alcohol product in just the left-handed form. This process is called asymmetric transfer hydrogenation.

Their research was funded by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Petroleum Research Fund, administered by the American Chemical Society. The team leader and principal author is Professor Robert Morris. Other team members are Nils Meyer and Alan Lough. The group, which also includes Alexandre Mikhailine and Friederike Freutel, has applied for a patent to protect the invention through the University of Toronto's Innovation Group.

UQ research reclaims the power of speech

A UQ researcher has revealed a new treatment for a speech disorder that commonly affects those who have suffered a stroke or brain injury.

PhD graduate Dr Rachel Wenke has shown in a recent study that the Lee Silverman Voice Treatment® may be an effective option for dysarthria patients suffering from stroke and traumatic brain injury (TBI).

Dysarthria is a speech disorder which negatively affects a person's ability to communicate as they can be difficult to understand and may sound like they have slurred or unclear speech. The disorder affects 75% of individuals with Parkinson's disease, up to 30% of those who have experienced a stroke and about 60% of individuals with TBI.

The program was originally designed to assist Parkinson's patients, and Dr Wenke is the first to trial the method's effectiveness in a group study involving other neurological conditions.

"This research will also help to provide speech pathologists evidence for treatments for the disorder, which may also encourage further research in the area," she said.

In the study, the effectiveness of the treatment was compared with traditional dysarthria therapy for 26 participants ranging from 18 to 88 years who had experienced stroke and TBI.

The findings revealed that participants who received the treatment demonstrated positive effects of a louder and clearer voice and slower rate of speech. Many participants also reported increased confidence in their ability to communicate which significantly improved their quality of life and well-being.

"For instance, after receiving the treatment, one participant reported that the quality of his relationship with his wife had actually improved because his wife could now understand him, whereas before treatment, they would hardly communicate," Dr Wenke said. "My findings have also shown that people who lived with dysarthria for up to 21 years were able to make improvements following treatment, therefore the mindset of not treating patients who have not improved in one or two years should be challenged."

The LSVT® program is an intensive therapy administered one hour a day, four days a week for 4 weeks. The patients are trained to use loud speech in progressively more difficult speech tasks.

Dr Wenke's research will be published in Brain Injury and the International Journal of Language and Communication Disorders.

Scientists discover way to jumpstart bone's healing process

In-body stem cell therapy has enormous potential for bone injuries

Rarely will physicians use the word "miraculous" when discussing patient recoveries. But that's the very phrase orthopaedic physicians and scientists are using in upstate New York to describe their emerging stem cell research that could have a profound impact on the treatment of bone injuries. Results from preliminary work being released today show patients confined to wheelchairs were able to walk or live independently again because their broken bones finally healed.

At the heart of the research is the drug teriparatide, or Forteo, which was approved by the FDA in 2002 for the treatment of osteoporosis. Astute observations led a team of clinicians and researchers to uncover how this drug can also boost our bodies' bone stem cell production to the point that adults' bones appear to have the ability to heal at a rate typically seen when they were young kids.

Baseline research presented in February at the Orthopaedic Research Society meeting revealed that of 145 patients who had an unhealed bone fracture – half of them for six months or longer – 93 percent showed significant healing and pain control after being on teriparatide for only eight to 12 weeks. These findings were enough to convince the National Institutes of Health to fund a clinical trial underway in Rochester, and if the

preliminary data are any indication, researchers may have discovered a new, in-the-body stem cell therapy that can jumpstart the body's natural healing process in bones.

The clinical implication is significant, as orthopaedists can soon have a new tool at their disposable to deal with many common, painful bone ailments including the tens of thousands of painful fractures for which there is no treatment (pelvic fractures, vertebral compression fractures, clavicle fractures), fractures that won't heal, fractures in patients that are either too sick to have surgery or chose not to have surgery, and even reduce the size of a incision in some surgeries.

Aging Bones Heal Slower

Of the estimated six million fractures in the United States each year, approximately five percent will have slow or incomplete healing. According to J. Edward Puzas, Ph.D., who heads up orthopaedic bone research at the University of Rochester Medical Center and is the principal investigator of the clinical trial, a large portion of non-healing fractures tend to occur in older adults.

"In many people, as they get older, their skeleton loses the ability to heal fractures and repair itself," Puzas said. "With careful application of teriparatide, we believe we've found a way to turn back the clock on fracture healing through a simple, in-body stem cell therapy."

Those especially hard hit are the nearly 60,000 Americans suffering from pelvic fractures, where bracing and immobilization are not an option for an injury that leaves people immobile and in pain before the bone fuses.

"It takes three to four months for a typical pelvic fracture to heal. But during those three months, patients can be in excruciating pain, because there are no medical devices or other treatments that can provide relief to the patient," said Susan V. Bukata, M.D., medical director of the Center for Bone Health at the University of Rochester Medical Center Bukata. "Imagine if we can give patients a way to cut the time of their pain and immobility in half? That's what teriparatide did in our initial research."

Bukata said much more was at stake then just comfort and pain relief. Patients who would ordinarily be confined to nursing homes or require additional medical attention because of non-healing fractures might be able to live an independent life. Bukata and Puzas estimate that if this drug saved just one week in a nursing home, it would pay for itself – and beyond.

"Many people don't realize that pelvic fracture carries with them the same mortality as hip fractures – in one year, approximately one-quarter of all older women with pelvic fractures will die from complications," Bukata said. "And during that year of recovery, a patient typically puts a greater strain on our health care system, not to mention their pain and suffering."

Translational Research at Work

The impetus for the research began in Bukata's clinic, where she saw painful bone fractures in osteoporotic patients quickly heal within a few months of taking teriparatide. At the time, Bukata also served on a research team at the University's Center for Musculoskeletal Research, and she began to advocate that the team direct its efforts in an entirely new direction based on the results she was seeing with patients who were taking teriparatide.

"I had patients with severe osteoporosis, in tremendous pain from multiple fractures throughout their spine and pelvis, who I would put on teriparatide," said Bukata. "When they would come back for their follow-up visits three months later, it was amazing to see not just the significant healing in their fractures, but to realize they were pain-free – a new and welcome experience for many of these patients."

Puzas and Bukata developed a plan to focus attention in both the lab and clinic to understand if her observations were a fluke or if there was an underlying scientific process producing such life-changing results for patients.

"While we had come to understand how teriparatide builds bone more robustly than the body can on its own, up to that point, we had no clue how the drug would or could help with fracture healing," Puzas said.

Bukata began prescribing teriparatide to patients with non-healing fractures, and was amazed at her findings: 93 percent showed significant healing and pain control after being on teriparatide for only eight to 12 weeks. And in the lab, Puzas began to understand how teriparatide stimulates bone stem cells into action.

Closing the Gap

When a fracture occurs, a bone becomes unstable and can move back and forth creating a painful phenomenon known as micromotion. As the bone begins healing it must progress through specific, well-defined stages. First, osteoclasts – cells that can break down bone – clean up any fragments or debris produced during the break. Next, a layer of cartilage – called a callus – forms around the fracture that ultimately calcifies, preventing the bony ends from moving, providing relief from the significant pain brought on by micromotion.

Only after the callus is calcified do the bone forming cells – osteoblasts – begin their work. They replace the cartilage with true bone, and eventually reform the fracture to match the shape and structure of the bone into what it was before the break.

According to Puzas, teriparatide significantly speeds up fracture healing by changing the behavior and number of the cartilage and the bone stem cells involved in the process.

"Teriparatide dramatically stimulates the bone's stem cells into action," Puzas said. "As a result, the callus forms quicker and stronger. Osteoblasts form more bone and the micromotion associated with the fracture is more rapidly eliminated. All of this activity explains why people with non-healing fractures can now return to normal function sooner."

"The decreased healing time is significant, especially when fractures are in hard-to-heal areas like the pelvis and the spine, where you can't easily immobilize the bone – and stop the pain," Bukata added. "Typically, a pelvic fracture will take months to heal, and people are in extreme pain for the first eight to 12 weeks. This time was more than cut in half; we saw complete pain relief, callus formation, and stability of the fracture in people who had fractures that up to that point had not healed."

The new clinical research will study post-menopausal women and men over 50 who come to the Emergency Department at Strong Memorial Hospital with a low-energy pelvic fracture. Patients will be divided into two groups - one offered teriparatide, the other a placebo - and followed for 16 weeks to measure the fracture healing process in a variety of ways: pain levels, microscopic bone growth determined through CT scans and functional testing of bone strength, among others.

Eli Lily, manufacturers of Forteo, are providing the medication for the clinical trial. Both Drs. Puzas and Bukata are members of Eli Lily's speaker bureau.

Male circumcision reduces HIV risk: No further evidence needed

Three recent African trials support male circumcision for reducing the risk of contracting HIV in heterosexual men. After including new data from these trials in their review, Cochrane Researchers have changed their previous conclusions that there was insufficient evidence to recommend circumcision as an intervention to prevent HIV infection in heterosexual men.

"Research on the effectiveness of male circumcision for preventing HIV in heterosexual men is conclusive. No further trials are required to establish that HIV infection rates are reduced in heterosexual men for at least the first two years after circumcision," says lead researcher Nandi Siegfried, Co-director of the South African Cochrane Centre at the South African Medical Research Council. "Policy makers can consider implementing circumcision as an additional measure into HIV prevention programmes."

Circumcision may help to protect against HIV by removing cells in the foreskin to which the virus is specifically attracted. Called Langerhans cells, they display receptors that enable HIV entry. Previous non-randomised studies investigated the association between circumcision and HIV, but until now, Cochrane researchers have been unable to make strong recommendations for the intervention due to a lack of high quality evidence gained from randomised clinical trials.

The clinical trials included in the review took place in South Africa, Uganda, and Kenya between 2002 and 2006, and included a total of 11,054 men. The results show that circumcision in heterosexual men significantly reduces their risk of acquiring HIV by 54% over a two year period, compared with uncircumcised men. This reduced risk is the best estimate of the average effect and the researchers report that the true risk will be reduced by between 38 to 66%. Further research, however, is required to establish whether male circumcision offers any benefit to women partners of circumcised men and homosexual men.

The researchers warn that policy makers also need to think about the culture and environment in which circumcision is carried out. "In many countries, male circumcision is practiced as part of the rites of initiation by traditional healers who are not trained in aseptic surgical techniques. So adverse events following traditional circumcisions can be high," says Siegfried.

Energy drinks work -- in mysterious ways!

Runners clutching bottles of energy drink are a common sight, and it has long been known that sugary drinks and sweets can significantly improve athletes' performance in endurance events. The question is how?

Clearly, 'sports' drinks and tablets contain calories. But this alone is not enough to explain the boost, and the benefits are felt even if the drink is spat out rather than swallowed. Nor does the sugary taste solve the riddle, as artificial sweeteners do not boost performance even when they are indistinguishable from real sugars.

Writing in the latest issue of The Journal of Physiology, Ed Chambers and colleagues not only show that sugary drinks can significantly boost performance in an endurance event without being ingested, but so can a tasteless carbohydrate – and they do so in unexpected ways.

The researchers prepared drinks that contained either glucose (a sugar), maltodextrin (a tasteless carbohydrate) or neither, then carefully laced them with artificial sweeteners until they tasted identical. They asked endurance-trained athletes to complete a challenging time-trial, during which they rinsed their mouths with one of the three concoctions.

The results were striking. Athletes given the glucose or maltodextrin drinks outperformed those on 'disguised' water by 2 - 3% and sustained a higher average power output and pulse rate, even though didn't feel they were working any harder. The authors conclude that as-yet unidentified receptors in the mouth independent from the usual 'sweet' taste buds must be responsible. "Much of the benefit from carbohydrate in sports drinks is provided by signalling directly from mouth to brain rather than providing energy for the working muscles," explained Dr Chambers.

The team then used a neuro-imaging technique known as fMRI to monitor the athletes' brain activity shortly after giving them one of the three compounds. They found that both glucose and maltodextrin triggered specific areas of the brain associated with reward or pleasure, while the artificial sweetener did not. This acts to reduce the athletes' perception of their workload, suggest the authors, and hence enables them to sustain a higher average output.

Their findings support the emerging 'central governor hypothesis' – the theory that it is not the muscles, heart or lungs that ultimately limit performance, but the brain itself, based on the information it receives from the body. Stimulating the brain in certain ways – such as swilling sugary drinks – can boost output, perhaps giving athletes that all-important edge over their rivals.

The role of inbreeding in the extinction of the Spanish Habsburg dynasty

The powerful Habsburg dynasty ruled Spain and its empire from 1516 to 1700 but when King Charles II died in 1700 without any children from his two marriages, the male line died out and the French Bourbon dynasty came to power in Spain. Reporting in the open-access, peer-reviewed journal PLoS ONE, April 15, Gonzalo Alvarez and colleagues at the University of Santiago de Compostela, Spain, provide genetic evidence to support the historical evidence that the high frequency of inbreeding (mating between closely related individuals) within the dynasty was a major cause for the extinction of its male line.

Using the genealogical information for Charles II and 3,000 of his relatives and ancestors across 16 generations, the researchers calculated the inbreeding coefficient (F) for each individual; this value indicates the probability that an individual receives, at a given locus, two genes identical by descent due to the common ancestry of its parents. They found that F increased considerably down the generations—from 0.025 for Philip I, the founder of the dynasty, to 0.254 for Charles II—as the Habsburg kings tended to marry close relatives more frequently in order to preserve their heritage. Several members of the dynasty had inbreeding coefficients higher than 0.20, which means that more than 20% of the genome is expected to be homozygous in these individuals.

The authors cite three lines of evidence to support the theory that inbreeding was a major factor in the extinction of the male Habsburg line, on the death of Charles II.

Firstly, there was a very high level of marriage between biological relatives (consanguineous marriage) within the Habsburg dynasty: nine of the 11 marriages over 200 years were consanguineous, including two uncle-niece marriages, one double-first-cousin marriage and one first-cousin marriage.

The two individuals with the highest inbreeding coefficient were Charles II and his grandfather Philip III. Although both were the sons of uncle-niece marriages, their F values were almost as high as the expected value for the offspring of an incestuous (parent-child or brother-sister) marriage. The researchers explain that this is likely to be due to multiple remote ancestors of these individuals (remote inbreeding), on top of the high degree of relatedness of their parents.

Secondly, there was a high rate of infant and child mortality in the Habsburg families with only half of the children born in the dynasty during the years studied surviving to age one, compared to about 80% in Spanish villages of the time. Alvarez and colleagues calculated that inbreeding at the level of first cousin (F = 0.0625) exerted an adverse effect on the survival to age 10 of offspring of 17.8 % ± 12.3, which could explain the high levels of infant and child mortality.

Thirdly, Charles II, dubbed El Hechizado ("The Hexed"), suffered from many different disorders and illnesses, some of which may result from the consanguineous marriage of his parents. According to contemporary writings he was short and weak and suffered from intestinal problems and sporadic hematuria Children of closely consanguineous couples often have an increased incidence of detrimental health effects due to rare deleterious recessive alleles inherited from common ancestors, although this will depend on how inbred their pedigree is already.

Charles II

Based on this clinical genetic knowledge and on information gathered by historians on the health of Charles II, Alvarez and colleagues speculate that the simultaneous occurrence of two different genetic disorders (combined pituitary hormone deficiency and distal renal tubular acidosis), determined by recessive alleles at two unlinked loci, could explain much of the complex clinical profile of this king, including his impotence/infertility, which led to the extinction of the dynasty.

Citation: Alvarez G, Ceballos FC, Quinteiro C (2009) The Role of Inbreeding in the Extinction of a European Royal Dynasty. PLoS ONE 4(4): e5174. doi:10.1371/journal.pone.0005174
http://dx.plos.org/10.1371/journal.pone.0005174

Savant skills may be widespread in people with autism

* 12:15 14 April 2009 **by Celeste Biever**

Savant-like skills, such as astounding memory, perfect pitch or the ability to multiply very high numbers together, may be much more common among people with autism than previously thought.

A new study of about 100 adults with autism shows that one third have skills that stand out, both in comparison with their other abilities and with the skills of the general population. Previous studies put the prevalence of savantism in autistic people as around 1 in 10.

"People often focus on the things people with autism can't do," says Patricia Howlin of the Institute of Psychiatry at King's College in London, who led the study. "One of the things our study illustrates is that these are people who do have special skills but they are not being used."

The notion of the savant – someone who has a skill that is exceptional both compared to the general population and to that person's other skills – has long captured the imagination of cognitive scientists and the general public alike. But despite this fascination, the connection between autism and savantism remains mysterious.

Some studies indicate that there are more savants within the autistic population than among the general population and among the populations of people with other mental difficulties. Putting an exact figure on the prevalence of such special skills among people with autism, however, has proved difficult.

Outstanding skills

In an attempt to quantify this, Howlin's team looked at two different measures of exceptional ability in a group of people with autism – all now adults – who the team have been studying periodically since they were first diagnosed between 1950 and 1985. They found that 39 met criteria for either what they call a "savant skill" or an "exceptional cognitive skill".

To identify savant skills, the researchers sent the parents of the autistic adults a questionnaire asking them to identify and describe, using specific examples, any outstanding skills and talents that were present "at a level that would be unusual even for normal people".

Of almost 100 parents who replied, about half (45) claimed that their child had a special skill. But only 24 met the researchers' tough criteria for what constitutes a savant skill: both exceptional in terms of population norms and above the individual's overall level of ability.

Relying on parents' anecdotal reports of skills could be risky. However, Francesca Happe, also at the Institute of Psychiatry but not involved in the study, says that the team's criteria were "pretty strict": "They didn't count anything that could conceivably be considered a normal skill. I don't think the parental reports are inflated."

Searching for savants

Among those skills considered at the savant level were: being able to name the elevation of both the sun and the moon at any time of day, on any specified date; being able to name the day of the week for any date in the distant past or future (a fairly common savant ability known as calendrical calculation); perfect pitch; and the ability to say, from a single chord, which piece of music it came from.

To identify exceptional cognitive ability, Howlin's team also examined the volunteers' scores on standard intelligence tests consisting of a range of subtests aimed at different aspects of IQ, such as arithmetic, spatial and motor skills and memory span. They found that 23 had an ability on at least one of these subtests that was well above the general population's average score on that subtest.

Eight of these 23 had also been identified as a mathematical or calendrical savant according to the first criteria, and the team concludes that overall 28.5% – or almost one third – of their volunteers had either a savant skill or an exceptional cognitive ability.

"I think it is a surprisingly high number, but believable," says Happe. She says that the study opens a window into the mind of a child with autism and recommends using these isolated, exceptional abilities as a way to motivate people with autism to learn other skills – such as social or communication ones – that might not come as easily.

One in ten?

Darold Treffert, a psychiatrist based in Fond du Lac, Wisconsin who studies savants, says that he sticks by an earlier estimate of the prevalence of savantism as being one in ten among people with autism. This is based on previous studies and backed up by his own observations.

He says this is partly because he is mistrustful of parental reports, and partly because he does not think that the peak ability in the intelligence subtests qualifies someone as a savant. "Some autistic savants do well on IQ subtests, but not all autistic persons who do well on IQ subtests are savant."

But he says the study is interesting, because it underscores the failings of IQ tests to measure overall intelligence. "We are all made up of a series of intelligences, especially the savant, and IQ measures one component," he says. "Savants starkly challenge our definition of 'intelligence' and require us to look for ways to measure other 'intelligences'."

"We need a more reliable definition of savant syndrome, and a more reliable definition of intelligence," he adds.

Journal reference: Philosophical Transactions of the Royal Society B, DOI: 10.1098/rstb.2008.0328

Study confirms 3 Neanderthal sub-groups

The Neanderthals inhabited a vast geographical area extending from Europe to western Asia and the Middle East 30,000 to 100,000 years ago. Now, a group of researchers are questioning whether or not the Neanderthals constituted a homogenous group or separate sub-groups (between which slight differences could be observed). A new study published April 15 in the online, open-access, peer-reviewed journal PLoS ONE may provide some answers.

Paleoanthropological studies based on morphological skeletal evidence have offered some support for the existence of three different sub-groups: one in Western Europe, one in southern Europe and another in the Levant.

Researchers Virginie Fabre, Silvana Condemi and Anna Degioanni from the CNRS Laboratory of Anthropology (UMR 6578) at the University of Marseille, France, have given further consideration to the question of diversity of Neanderthals by studying the genetic structure of the mitochondrial DNA (mtDNA) and by analyzing the genetic variability, modeling different scenarios. The study was possible thanks to the publication, since 1997, of 15 mitochondrial DNA (mtDNA) sequences (the mtDNa is maternally transmitted) that originated from 12 Neanderthals.

The new study confirms the presence of three separate sub-groups and suggests the existence of a fourth group in western Asia. According to the authors, the size of the Neanderthal population was not constant over time and a certain amount of migration occurred among the sub-groups. The variability among the Neanderthal population is interpreted to be an indirect consequence of the particular climatic conditions on their territorial extension during the entire middle Pleistocene time period.

Degioanni and colleagues obtained this result by using a new methodology derived from different biocomputational models based on data from genetics, demography and paleoanthropology. The adequacy of each model was measured by comparing the simulated results obtained using BayesianSSC software with those predicted based on nucleotide sequences.

The researchers hope that one day this methodology might be applied to questions concerning Neanderthal cultural diversity (for example the lithic industry) and to the availability of natural resources in the territory. This could provide new insights into the history and extinction of the Neanderthals.

***Citation**: Fabre V, Condemi S, Degioanni A (2009) Genetic Evidence of Geographical Groups among Neanderthals. PLoS ONE 4(4): e5151. doi:10.1371/journal.pone.0005151*
http://dx.plos.org/10.1371/journal.pone.0005151

Signals from stroking have direct route to brain

Nerve signals that tell the brain that we are being slowly stroked on the skin have their own specialised nerve fibres in the skin. This is shown by a new study from the Sahlgrenska Academy. The discovery may explain why touching the skin can relieve pain.

The specialised nerve fibres in the skin are called CT nerves (C-tactile) and they travel directly to the areas in the brain that are important in the emergence of feelings.

Basically the signals that tell the brain that we are being stroked on the skin have their own direct route to the brain, and are not blocked even if the brain is receiving pain impulses from the same area. In fact it's more the opposite, that the stroking impulses are able to deaden the pain impulses," says Line Löken, postgraduate student in neurophysiology at the Sahlgrenska Academy.

The results are being published in the distinguished scientific journal, Nature Neuroscience. The research group examined a group of healthy subjects using a technique called microneurography.

By inserting a thin electrode into a nerve in the forearm we can listen in on the nerve and pick up signals from one of the thousands of nerve fibres that make up a nerve," explains Associate Professor Håkan Olausson, who is leading the research group behind the discovery, together with Johan Wessberg.

Each individual nerve fibre is responsible for touch signals from roughly a square centimetre of skin. The research team used a specially-designed robot, which brushed over the exact area of skin for which a particular nerve fibre is responsible. The subjects were also asked to rate how pleasant or unpleasant they found the brushing.

"As the nerve signals that were sent in the CT nerves became more frequent, the subjects reported the experience as being increasingly pleasant. Of the skin nerves that we studied, it was only the CT nerves that had this strong link between the frequency of the signals and how pleasant it felt," says researcher Johan Wessberg.

***Source**: Nature Neuroscience Coding of pleasant touch by unmyelinated afferents in humans*
Authors: Line S. Löken, Johan Wessberg, India Morrisson, Francis McGlone, Håkan Olausson
The full text article is available on Nature Neuroscience's web page:
http://www.nature.com/neuro/journal/vaop/ncurrent/abs/nn.2312.html

Largemouth bass vulnerability to being caught by anglers a heritable trait

URBANA - In an experiment spanning over 20 years, researchers at the University of Illinois have found that vulnerability to being caught by anglers is a heritable trait in largemouth bass.

The study began in 1975 with the resident population of bass in Ridge Lake, an experimental study lake in Fox Ridge State Park in Charleston. The fishing was controlled. For example, anglers had to reserve times, and every fish that was caught was put into a live well on the boat. The fish were measured and tagged to keep track of how many times each fish had been caught. All fish were then released.

"We kept track over four years of all of the angling that went on, and we have a total record – there were thousands of captures," said David Philipp, ecology and conservation researcher at U of I. "Many fish were caught more than once. One fish was caught three times in the first two days, and another was caught 16 times in one year."

After four years, the pond was drained, and more than 1,700 fish were collected. "Interestingly, about 200 of those fish had never been caught, even though they had been in the lake the entire four years," Philipp said.

Males and females from the group that had never been caught were designated Low Vulnerability (LV) parents. To produce a line of LV offspring, these parents were allowed to spawn with each other in university research ponds. Similarly, males and females that had been caught four or more times in the study were designated High Vulnerability (HV) parents that were spawned in different ponds to produce a line of HV offspring. The two lines were then marked and raised in common ponds until they were big enough to be fished.

"Controlled fishing experiments clearly showed that the HV offspring were more vulnerable to angling than the LV offspring," said Philipp.

This selection process was repeated for several generations over the course of the 20 year experiment.

"As we had predicted, vulnerability was a heritable trait," he said. Philipp went on to explain that with each generation, the difference between lines in angling vulnerability grew even larger.

"Most of the selection is occurring on the LV fish – that is, for the most part, the process is making that line of fish less vulnerable to angling. We actually saw only a small increase in angling vulnerability in the HV line," Philipp said.

Male bass are the sole caregiver for the offspring. Females lay eggs and leave. The male guards the nest against brood predators for about three to four days before the eggs hatch and another eight to 10 days after they hatch, before they become free-swimming. Even after the baby bass start to swim, the dads stay with them for another three weeks while they feed and grow, protecting them from predators.

Philipp explained that the experiment sped up what's actually happening in nature. "In the wild, the more vulnerable fish are being preferentially harvested, and as a result the bass population is being directionally selected to become less vulnerable. We selected over three generations, but in the wild the selection is occurring in every generation.

"We've known for 50 years that commercial fishing exerts selection on wild populations," he said. "We take the biggest fish, and that has changed life histories and growth patterns in many populations of commercially harvested species. Because there is no commercial fishing for bass, we were assessing the evolutionary impacts of recreational fishing."

Philipp explained that the perception among anglers is that catch-and-release has no negative impact on the population. During the spawning season, however, if bass are angled and held off of their nests for more than a few minutes, when they are returned to the lake, it's too late; other fish have found the nest and are quickly eating the babies.

Philipp recommends that to preserve bass populations across North America, management agencies need to protect the nesting males during the spawning season. "There should be no harvesting bass during the reproductive period. That makes sense for all wildlife populations. You don't remove the adults during reproduction.

"One of the big issues for concern is the explosion of tournaments. Lots of bass tournaments are held during the springtime because there are lots of big fish available. In tournaments you put fish into live wells, and yes, they're released, but they could be held for up to 8 hours first. They're brought back to the dock, miles from their nest. So, basically, if a fish is caught in a tournament and brought into the boat and put into a live well, his nest is destroyed."

Philipp recommended that if fishing tournaments were held during the spawning season, then regulations should require that there be immediate catch-and-release, eliminating the use of tournament weigh-ins.

Philipp urges management agencies to go even further and suggests that a portion of each lake could be set aside as a bass spawning sanctuary, where all fishing would be prohibited until after bass reproduction is complete. In the rest of the lake, mandatory catch-and-release regulations could be put into place during that same reproductive period. In Illinois, the bass reproduction period is from about April 1 through June 15. Philipp said that in that way, anglers could help protect the long-term future of the resource without completely restricting fishing.

"The potential for angling to have long-term evolutionary impacts on bass populations is real. If we truly want to protect this valuable resource into the future, then we need to understand that and adjust our management strategies," Philipp said.

Others on the University of Illinois research team include Steven Cooke, Julie Claussen, Jeffrey Koppelman, Cory Suski, and Dale Burkett. Selection for Vulnerability to Angling in Largemouth Bass was published in Transactions of the American Fisheries Society 138:189-199, 2009.

Study: Herbs added to 5,100-year-old Egyptian wine

RON TODT The Associated Press

PHILADELPHIA - Herbs have been detected in wine from the tomb of one of ancient Egypt's first rulers, many centuries before the civilization's known use of herbal remedies in alcoholic beverages, according to a study published Monday.

The findings from a wine jar dated to 5100 B.C. provide concrete evidence of ancient Egyptian organic medicine, which had only been ambiguously referred to in later papyrus documents, said Patrick McGovern of the University of Pennsylvania Museum of Archaeology and Anthropology, one of the researchers.

Tests on one of 700 jars buried with Scorpion I in his tomb at Abydos about 3100 B.C. confirmed that the vessel contained wine, according to the paper published in the Proceedings of the National Academy of Sciences. The tests also detected tree resin, which was used as a preservative and for medical purposes, and other chemicals that make up various herbs.

"There were a lot of additives in this wine, and it fits very well with the later Egyptian pharmacology texts, the medical papyri that describe similar kinds of alcoholic beverages with herbs in them," McGovern said.

"So the assumption is that, although we're 1500 years before the earliest medical papyrus, in fact we're looking at medicinal wine," he said.

Medical papyri, texts which describe ancient Egyptian medical procedures and practices, show that resins and herbs were added to wine, beer and water for use as pain relievers, laxatives, diuretics, or aphrodisiacs. Many of the ingredients are still part of the herbal medical tradition of the country, researchers said.

Herbs from the eastern Mediterranean that fit the chemicals found in the wine are coriander, balm, mint, sage, senna, germander, savory and thyme, McGovern said.

The researchers cannot positively identify herb or herb combinations found because unique biomarkers for them have not been identified. And although prescriptions recorded on papyrus give a detailed picture of the ancient Egyptian drug cabinet, more than 80 percent of the 160 plant names listed have yet to be translated.

"Our contention is that plant additives, including various herbs and tree resins, were already being dispensed via alcoholic beverages millennia earlier" than temple inscriptions had indicated, the paper concludes.

Robert K. Ritner, Professor of Egyptology at the Oriental Institute of the University of Chicago, said Friday herbs and spices were also added for taste as well as health.

"I would not limit it specifically to medicinal uses; it certainly could have that, but there's no reason these wouldn't be spiced for flavor, like modern mulled wine," Ritner said.

Low glycemic breakfast may increase benefits of working out

The benefits of physical activity and a balanced diet are well documented and form the basis of many public health recommendations. This is because each of these factors can independently influence risks for many

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

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

To access full text of the study visit: http://www.nutrition.org/media/publications/JNMay109.pdf

McGovern said medical benefits of herbal wines seemed the most likely explanation. "You can't exclude the taste side of it, but we're at a time when people need to have some way to protect themselves from disease, cure themselves, and this was the primary way it was done," he said.

Q & A

Heartfelt Changes

By C. CLAIBORNE RAY

Victoria Roberts

Q. If, after many years of a high-fat, high-cholesterol, low-fiber/fruit/vegetable diet, one shifts to a healthy diet, can one repair some of the damage presumably done to blood vessels? If so, how much?

A. While diet is not the only factor in cardiovascular health, some studies have found that a very low-fat diet that is also high in fiber, fruits and vegetables can repair the damage to narrowed blood vessels, in at least a limited but measurable amount. But such improvements were found only in conjunction with other changes in the subjects' overall lifestyle, like regular exercise and stress reduction and such changes are difficult to maintain over a long period.

A widely publicized study published in 1990 in the British journal The Lancet, led by Dr. Dean Ornish, was the first controlled study to find such a benefit. The changes studied included a low-fat vegetarian diet, cessation of smoking, stress management training and moderate exercise.

In the 22 patients who followed this regimen for a year, images of blood vessels made after a dye was injected found that, on average, the narrowing of damaged coronary arteries was reduced to 37.8 percent of the vessel from 40 percent; in the control group of 19 patients, the narrowing of the vessel increased, to 46.1 percent from 42.7 percent. Some later studies have found similar results.

I feel like a different person

Study suggests link between how we feel, our culture and how we behave

Scientists have long been interested in the interplay of emotions and identity, and some have recently focused on cultural identity. One's heritage would seem to be especially stable and impervious to change, simply because it's been passed down generation after generation and is deeply ingrained in the collective psyche. But how deeply, exactly? Psychologists Claire Ashton-James of the University of British Columbia, William W. Maddux from INSEAD, Adam Galinsky of Northwestern University, and Tanya Chartrand from Duke University decided to explore this intriguing question in the laboratory, to see if even something as potent as culture might be tied to normal mood swings. European cultures are known to value independence and individuality, whereas Asian cultures prize community and harmony. This fundamental East-West cultural difference is well established, and so offered the researchers an ideal test.

The volunteers consisted of students hailing from a number of different countries and the researchers unconsciously raised or lowered their moods via two different methods. In one study, the volunteers listened to some upbeat Mozart on the stereo to lift their moods, or some Rachmaninov to bring them down. In another study, the volunteers held pens in their mouths: Some held the pen with their teeth, which basically forces the face into a smile, which improves mood. Others held the pen with their lips, forcing a frown. Then the volunteers completed a variety of tests, each designed to measure the strength of their values. In one test, the volunteers were offered a choice of five pens, four blue and one red. In keeping with cultural values, Asians typically pick from the more common blue pens in this test — to be part of the group — while Westerners usually take the one red pen. In another test, the volunteers thought about the questions "Who am I?" and listed 20 answers. The lists were analyzed to see if they reflected predominantly individualistic or predominantly group values.

The results, published in Psychological Science, a journal of the Association for Psychological Science, were consistent for all of the tests: Feeling good did indeed encourage the volunteers — both European and Asian — to explore values that are inconsistent with their cultural norms. And elevated mood even shaped behavior, allowing volunteers to act "out of character." These findings suggest that people in an upbeat mood are more exploratory and daring in attitude — and therefore more apt to break from cultural stereotype. That is, Asians act more independently than usual, and Europeans are more cooperative. Feeling bad did the opposite: It reinforced traditional cultural stereotypes and constrained both Western and Eastern thinking about the world.

The researchers note these results suggest that emotions may serve an important social purpose. They surmise that positive feelings may send a signal that it's safe to broaden one's view of the world — and to explore novel notions of one's self. The researchers go on to indicate that negative feelings may do the opposite: They may send a signal that it's time to circle the wagons and stick with the "tried and true." They conclude that the findings also suggest that the "self" may not be as robust and static as we like to believe and that the self may be dynamic, constructed again and again from one's situation, heritage and mood.

For more information about this study, please contact: Claire Ashton-James (cajames@psych.ubc.ca)
Wray Herbert discusses this study in his blog, "We're Only Human..." (http://www.psychologicalscience.org/onlyhuman/)

MSU researcher develops vaccine for E. coli diarrheal diseases that kill up to 3 million children annually

EAST LANSING, Mich. — A Michigan State University researcher has developed a working vaccine for a strain of E. coli that kills 2 million to 3 million children each year in the developing world.

Enterotoxigenic E. Coli, which is responsible for 60 percent to 70 percent of all E. coli diarrheal disease, also causes health problems for U.S. troops serving overseas and is responsible for what is commonly called traveler's diarrhea.

A. Mahdi Saeed, professor of epidemiology and infectious disease in MSU's colleges of Veterinary Medicine and Human Medicine, has applied for a patent for his discovery and has made contact with pharmaceutical companies for commercial production. Negotiations with several firms are ongoing.

"This strain of E. coli is an international health challenge that has a huge impact on humanity," said Saeed, who has devoted four years to develop a working vaccine at MSU's National Food Safety and Toxicology Center. "By creating a vaccine, we can save untold lives. The implications are massive."

ETEC affects millions of adults and children across the globe, mainly in southern hemisphere countries throughout Africa and South America. It also poses a risk to U.S. troops serving in southern Asia and the Middle East.

Saeed's breakthrough was discovering a way to overcome the miniscule molecular size of one of the illness-inducing toxins produced by the E. coli bug. Since the toxin was so small, it did not prompt the body's defense system to develop immunity, allowing the same individual to repeatedly get sick, often with more severe health implications.

Saeed created a biological carrier to attach to the toxin that once introduced into the body induces a strong immune response. This was done by mapping the toxin's biology and structure during the design of the vaccine. Saeed's work was funded in part by a $510,000 grant from the National Institutes of Health.

After creating the carrier in a lab at MSU, Saeed and his team tested it on mice and found the biological activity of the toxin was enhanced by more than 40 percent, leading to its recognition by the body's immune system. After immunizing a group of 10 rabbits, the vaccine led to the production of the highest neutralizing antibody ever reported for this type of the toxin.

Saeed hopes that human clinical trials could begin late in the year.

There also are several other human health implications for the vaccine, besides providing immunity against most E. coli disease, according to Saeed. Many patients who undergo anesthesia during a medical procedure

surgery suffer from post-operative paralytic ileus, or an inability to have a bowel movement. A small oral dosage of the vaccine could act as a laxative, which often aren't prescribed after a surgery for fear of side effects, Saeed said. A small dose also could help with urinary retention.

The vaccine will be available for animals as well, Saeed added. He pointed out the E. coli bug also is a major cause of sickness and death for newborn animals such as calves and piglets, which in the United States alone causes $300 million in loss of agricultural products each year.

Tentacles of venom: new study reveals all octopuses are venomous.

Once thought to be only the realm of the blue-ringed octopus, researchers have now shown that all octopuses and cuttlefish, and some squid are venomous. The work indicates that they all share a common, ancient venomous ancestor and highlights new avenues for drug discovery.

Conducted by scientists from the University of Melbourne, University of Brussels and Museum Victoria, the study was published in the Journal of Molecular Evolution.

Dr Bryan Fry from the Department of Biochemistry at the Bio21 Institute, University of Melbourne said that while the blue-ringed octopus species remain the only group that are dangerous to humans, the other species have been quietly using their venom for predation, such as paralysing a clam into opening its shell.

"Venoms are toxic proteins with specialised functions such as paralysing the nervous system" he said.

"We hope that by understanding the structure and mode of action of venom proteins we can benefit drug design for a range of conditions such as pain management, allergies and cancer."

While many creatures have been examined as a basis for drug development, cephalopods (octopuses, cuttlefish and squid) remain an untapped resource and their venom may represent a unique class of compounds.

Dr Fry obtained tissue samples from cephalopods ranging from Hong Kong, the Coral Sea, the Great Barrier Reef and Antarctica. The team then analysed the genes for venom production from the different species and found that a venomous ancestor produced one set of venom proteins, but over time additional proteins were added to the chemical arsenal.

The origin of these genes also sheds light on the fundamentals of evolution, presenting a prime example of convergent evolution where species independently develop similar traits.

The team will now work on understanding why very different types of venomous animals seem to consistently settle on the similar venom protein composition, and which physical or chemical properties make them predisposed to be useful as toxin.

"Not only will this allow us to understand how these animals have assembled their arsenals, but it will also allow us to better exploit them in the development of new drugs from venoms," said Dr Fry.

"It does not seem a coincidence that some of the same protein types have been recruited for use as toxins across the animal kingdom."

Neurodegenerative diseases target healthy brain's intrinsic networks

New research suggests that neurodegenerative diseases are neither diffuse nor random but specifically target large-scale functional networks in the human brain. The study, published by Cell Press in the April 16 issue of the journal Neuron, may drive a new generation of network-based strategies for diagnosing and monitoring neurodegenerative diseases.

Brain imaging studies have revealed the architecture of intrinsic functional networks in the human brain. These networks involve multiple functionally related groups of neurons that exhibit spontaneous synchronous baseline activity during task-free conditions. Previous work has established that connectivity within these networks can influence task performance, but it has remained unclear how fluctuations in neural network activity are correlated with brain structure in health and disease.

"Although some studies suggested that Alzheimer's disease may attack a specific large-scale network, we hypothesized that all neurodegenerative diseases target a distinct signature network," says lead study author Dr. William W. Seeley from the University of California, San Francisco. "If demonstrated as a class-wide phenomenon, this network degeneration framework could have major mechanistic significance, predicting that spatial patterning of disease relates to some structural, metabolic, or physiological aspect of neural network biology."

To examine whether large-scale neural networks are targeted by disease in living humans, Dr. Seeley and colleagues used neuroimaging to study patients with five distinct neurodegenerative syndromes and two healthy control groups. The researchers found that each of the neurodegenerative syndromes featured a distinct regional vulnerability pattern within one of five specific healthy human intrinsic networks.

Additionally, the authors found a direct link between intrinsic connectivity and normal brain structure. In the healthy individuals, nodes within each functional network exhibited tightly correlated gray matter tissue

volumes. "These results provide a new, structure-based window into network organization," says Dr. Seeley. "It appears that regions that fire together also grow (in health) or atrophy (in disease) together."

These results provide strong support for the network degeneration hypothesis. "Our findings show that functional and structural network mapping approaches yield robust, convergent, anatomically predictable networks, and that specific neurodegenerative diseases target these patterned brain systems," says Dr. Seeley. "Future studies may clarify how these complex systems are assembled during development and undermined by disease."

The researchers include William W. Seeley, University of California, San Francisco, San Francisco, CA; Richard K. Crawford, University of California, San Francisco, San Francisco, CA; Juan Zhou, University of California, San Francisco, San Francisco, CA; Bruce L. Miller, University of California, San Francisco, San Francisco, CA; and Michael D. Greicius, Stanford University School of Medicine, Stanford, CA.

Op-Ed Contributor

Boldly Going Nowhere

By SETH SHOSTAK Mountain View, Calif.

IT'S a birthright proffered by science and prophesied by "Star Trek," "Battlestar Galactica" and a thousand other space operas: We're destined to go to the stars. Our descendants will spread beyond this nondescript solar system and seek adventure and bumpy-headed pals in the stellar realms.

Well, cool your warp jets, Mr. Scott, because we're not about to breach the final frontier. Piling into a starship and barreling into deep space may long remain — like perfect children or effort-free bathroom cleaners — a pipe dream.

The fastest rocket ever launched, NASA's New Horizons probe to Pluto, roared off its pad in 2006 at 10 miles per second. That pace would be impressive in the morning commute, and it's passably adequate for traversing the solar system, something we've done and will continue to do. Combustion rockets, like New Horizons, can deliver you to the Moon in a matter of days, Mars in a matter of months, and the outer planets in a matter of years. But a trip to Proxima Centauri, the nearest star beyond the Sun and 100 million times farther from us than the Moon, would consume a tedious 800 centuries or so. You'll want to upgrade.

Maxwell Loren Holyoke-Hirsch

We'll build faster spacecraft, of course. Many have been designed, including ion beam rockets that shoot particles from their nozzles rather than hot gas, and nuclear-powered models. The former made their debut in NASA's Deep Space 1 mission to investigate asteroids and could conceivably cruise at 50 miles per second. Atomic rockets, whose development was halted by test-ban treaties in the '60s, had a target velocity 20 times greater. Alas, despite these snappier speeds, such craft are still untenable for manned journeys to the stars, taking at least a dozen lifetimes to reach the nearest.

Carting humans into deep space requires technology akin to wormhole rockets or matter-antimatter engines, the standard transports of science fiction. Wormhole travel, which takes shortcuts to the stars by warping space, looks appealing on blackboards, but physicists can't yet say whether it would ever work in practice. Matter-antimatter engines use the enormous energy released when ordinary atoms encounter their exotic, opposite numbers, demanding the creation and storage of large amounts of hard-to-contain antimatter — a Sisyphean task, to put it gently.

In addition, such sci-fi crafts would get embarrassingly bad mileage. The energy required to reach even the nearest stars in a decade or less with a very modest-size starship (say, the tonnage of the 17th-century Mayflower) equals the total energy consumed in the United States last year. At 10 cents per kilowatt-hour, that's a fuel bill of $5 trillion.

The pace of improvement in rocketry is languid. It will be a decade before NASA's new Orion spacecraft allows humans to revisit the Moon, a short cosmic hop. And while today's launching vehicles are more powerful than their predecessors, the speeds are hardly impressive. The New Horizons probe cleared the pad at a clip barely twice that of the Atlas rocket that hoisted John Glenn into orbit at the dawn of the space age.

So while there's little doubt that humanity will soon explore and eventually colonize the Moon, Mars and the satellites and asteroids of the outer solar system, sending humans beyond that is impractical for the foreseeable future.

But there's another technology that's developing at a breakneck clip, and with which our grandchildren could make virtual trips to other solar systems. It's called telepresence — a collection of technologies that extends vision, hearing and touch far beyond the corporeal confines of our nervous system.

Consider that in 1965 the Mariner 4 spacecraft made the first fuzzy photos of Mars with a black-and-white TV camera boasting 40,000 pixels. The HiRISE camera now operating onboard NASA's Mars Reconnaissance Orbiter sports 200 million pixels. It can snap photos of objects just three feet across.

That's resolution comparable to what's on Google Earth, which many people use to examine remote parts of the globe or inspect cities known only from the nightly news. Google Mars takes advantage of the high-quality imagery being collected by our robotic orbiters, enabling armchair astronauts to peruse the red planet in considerable detail without the angst of transporting their delicate protoplasm 34 million miles into space.

Photography from the Mars Exploration Rover is so good that the data have been interpreted in an IMAX film, giving audiences a near-lifelike experience in strolling the red planet's rusty, dusty desert. The Phoenix Mars lander has sent back pictures of individual sand grains. In other words, it's already possible for anyone to make a rigorous reconnaissance of another planet — even though not a single human has yet stomped his boots in the Martian dust.

This is not merely the tired argument over manned versus unmanned space missions. Sending humans to the stars is simply not in the offing. But this is how we could survey other worlds, around other suns. We fling data-collecting, robotic craft to the stars. These proxy explorers can be very small, and consequently can be shot spaceward at tremendous speed even with the types of rockets now available. Robot probes don't require life support systems, don't get sick or claustrophobic and don't insist on round-trip tickets.

A plausible solution would be to re-energize NASA's development of nuclear-powered rockets, with the intention of building a craft able to send clusters of micro-bots into deep space at velocities of, say, one-tenth light speed. Depending on financing and our ability to garner international cooperation, these probes could be sent off before the 21st century starts to wane. By the middle of the following century, on-the-scene data from Epsilon Eridani, the nearest known planetary system, could be in our hands.

These microbots would supply the information that, fed to computers, would allow us to explore alien planets in the same way that we navigate the virtual spaces of video games or wander through online environments like Second Life. High-tech masks and data gloves, sartorial accessories considerably more comfortable than a spacesuit, would permit you to see the landscape, touch objects and even smell the air.

Our desire to walk a landscape that basks in the light of another star, to hear the whistle of an alien planet's wind and feel its sting on our faces, will not — any century soon — be sated by hurling massive, human-filled starships into space. Instead, we will extend our senses light-years beyond Earth with these telepresence proxies and data collectors. That's a far more realistic version of the "Star Trek" future: to explore distant worlds, under alien suns, without leaving the familiar surroundings of our terrestrial home.

Seth Shostak, an astronomer at the SETI Institute, is the author of "Confessions of an Alien Hunter: A Scientist's Search for Extraterrestrial Intelligence."

Fishing fleets squander half their catches

* 00:01 15 April 2009 **by Andy Coghlan**

Huge volumes of captured fish go to waste either because they're non-target species or because fishing fleets make no effort to record and manage non-target species sustainably.

That's the conclusion of an international study (pdf) by WWF, which estimates how much of the fish harvest goes to waste as bycatch, the species thrown back dead into the sea or used for other purposes, such as feed for aquaculture.

WWF says the study reinforces the need for a complete paradigm shift in how fisheries are managed, so that everything taken from the sea is accounted for. What's also needed is a clear and consistent new definition of bycatch to avoid existing disparities in how "waste" fish is recorded and accounted for.

"We want to see everything taken out to be managed in some way to make sure we are fishing within the limits of what's sustainable," says study author, Robin Davies of WWF International.

Davies suggests that from now on, bycatches should include fish that are either unused and thrown back, or fish that are caught but are not currently monitored to check for any species in danger.

Mass waste

Two earlier landmark studies cited by Davies estimated that between 7 and 27 million tonnes of fish go to waste as bycatch.

Davies new study estimates that 38 million tonnes go to waste, some 40 per cent of the total tonnage landed.

"If 40 per cent of the global catch is unused or unmanaged, how can we make sure it's fished sustainably?" says Davies, whose study will appear in Marine Policy later this month.

Davies arrived at the estimates by analysing public fisheries data from 2000 to 2003, covering 44 countries, two oceanic regions (the northeast Atlantic, and the Mediterranean and Black Sea) and global tuna and sharkfin fisheries.

The waste was greatest in sharkfin fisheries, which typically discarded 92 per cent of non-target species.

There were also disparities in what counted as bycatch. In some parts of the world, non-target fish were still utilised. In prawn fisheries in Asia, for example, owners paid their deck-hands in bycatch fish.

Davies also found that the use of technology to allow non-target fish to escape – such as in the prawn fisheries of Europe – was patchy on a global basis.

Monitor system

Equally, there were big differences in how and whether independent observers were allowed on boats to keep records of the species caught, and their fate.

Such a system has been operating in Europe for at least 20 years, and WWF argues that the latest estimates justify installing such systems everywhere. Even in Europe, for example, too many skates and rays are caught and discarded but not recorded.

"Monitors are so important, to show that fisheries are implementing technologies they should, and to get accurate data on bycatch," says Giles Bartlett, fisheries policy officer at WWF-UK. "The key is that they're in place, and part of overall fisheries management plans everywhere," he said. Otherwise, fisheries will continue to collapse.

Mark Tasker, head of marine advice at the Joint Nature Conservation Committee, which advises the UK government on nature management, says the new study is useful and sound. "It keeps the spotlight on the major environmental impact of fisheries, and it's a reasonable attempt to make bycatch estimates with good conclusions," he says.

"We know that 40 to 50 per cent of catches are being killed by being thrown back, and that's not a good thing," says Tasker.

He applauds the attempt to re-define bycatch, but wonders whether management of stocks will itself be difficult to define and implement. "I agree recording of total catch is a good thing, and then you could think about preserving rarer fish caught by accident," he said. "And we all agree that unused fish count as bycatch."

Play's the Thing - Study Shows "Free Play" Is Highly Important to Human Social Development

Boston College Researcher: Modern Focus On Competition, Drive To Win May Have Contributed To Economic Woes

CHESTNUT HILL, MA -- A new theory about early human adaptation suggests that our ancestors capitalized on their capacities for play to enable the development of a highly cooperative way of life.

Peter Gray Writing in the current edition of the interdisciplinary American Journal of Play, Boston College developmental psychologist Peter Gray suggests that use of play helped early humans to overcome the innate tendencies toward aggression and dominance which would have made a cooperative society impossible.

"Play and humor were not just means of adding fun to their lives," according to Gray. "They were means of maintaining the band's existence - means of promoting actively the egalitarian attitude, intense sharing, and relative peacefulness for which hunter-gatherers are justly famous and upon which they depended for survival."

This theory has implications for human development in today's world, said Gray, who explains that social play counteracts tendencies toward greed and arrogance, and promotes concern for the feelings and wellbeing of others. "It may not be too much of a stretch," says Gray, "to suggest that the selfish actions that led to the recent economic collapse are, in part, symptoms of a society that has forgotten how to play."

Interest in play is very much on the upswing among psychologists, educators, and the general public, according to Gray. "People are beginning to realize that we have gone too far in the direction of teaching children to compete," he said. "We have been depriving children of the normal, noncompetitive forms of social play that are essential for developing a sense of equality, connectedness, and concern for others."

Gray stressed that the kind of "play" that helped hunter-gatherer children develop into cooperative adults is similar to the sort of play that at one time characterized American children's summers and after-school hours in contemporary culture. This play is freely chosen, age-mixed, and, because it is not adult-organized, non-competitive, he said. This "free play" is distinct from leisure pursuits such as video games, watching TV, or structured extracurricular activities and sports.

"Even when children are playing nominally competitive games, such as pickup baseball or card games, there is usually relatively little concern for winning," said Gray. "Striving to do well, as individuals or teams, and helping others do well, is all part of the fun. It is the presence of adult supervisors and observers that pushes play in a competitive direction--and if it gets pushed too far in that direction it is no longer truly play."

The most important skill for social life, Gray said, is how to please other people while still fulfilling one's own needs and desires. In self-organized play, he contends, children learn to get along with diverse others, to compromise, and to anticipate and meet others' needs. "To play well," he said, "and to keep others interested in continuing to play with you, you must be able to see the world from the other players' points of view.

"Children and teenagers in hunter-gatherer cultures played in this way more or less constantly," he said, "and they developed into extraordinarily cooperative, egalitarian adults. My observations - published in previous articles - indicate that age-mixed free play in our culture, in those places where it can still be found, has all of these qualities."

Gray's article addresses not just children's play, but also play as a fundamental component of adult human nature, which allowed humans to develop as intensely social and cooperative beings. Through the course of his research, he said, it became increasingly apparent that play and humor lay at the core of hunter-gatherer social structures and mores.

Hunter-gatherers used humor, deliberately, to maintain equality and stop quarrels, according to Gray, and their means of sharing had game-like qualities. Their religious beliefs and ceremonies were playful, founded on assumptions of equality, humor, and capriciousness among the deities. They maintained playful attitudes in their hunting, gathering, and other sustenance activities, partly by allowing each person to choose when, how, and how much they would engage in such activities.

"Professor Gray's novel insight sheds new light on the question of how such societies can maintain social harmony and cooperation while emphasizing the autonomy of individuals," said Kirk M. Endicott, a leading anthropologist and hunter-gatherer expert at Dartmouth College. "Conversely, his demonstration of the wide-ranging role of play in hunter-gatherer societies focuses attention on the importance of play in the evolutionary success of the human species."

Peter Gray has been a professor of psychology at Boston College for more than 35 years. In 2002 he retired from the position of full professor and assumed the position of research professor. He is the author of "Psychology," a widely-used psychology textbook now in its 5th edition, and has published a number of scholarly articles on the role of play in education. In addition, he writes a regular blog for Psychology Today magazine, "Freedom to Learn" (http://blogs.psychologytoday.com/blog/freedom-learn).

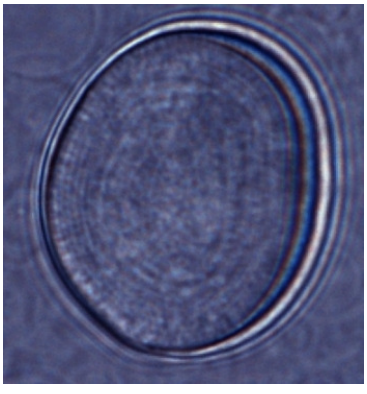
Long-lasting Nerve Block Could Change Pain Management

Injectable local anesthetic shows promise for prolonged pain relief without toxicity

Boston, Mass. -- Researchers at Children's Hospital Boston have developed a slow-release anesthetic drug-delivery system that could potentially revolutionize treatment of pain during and after surgery, and may also have a large impact on chronic pain management.

In NIH-funded work, they used specially designed fat-based particles called liposomes to package saxitoxin, a potent anesthetic, and produced long-lasting local anesthesia in rats without apparent toxicity to nerve or muscle cells. The research will be published online on April 13 by the Proceedings of the National Academy of Sciences.

"The idea was to have a single injection that could produce a nerve block lasting days, weeks, maybe even months," explains Daniel Kohane, MD, PhD, of the Division of Critical Care Medicine in the Department of Anesthesiology at Children's, and the report's senior author. "It would be useful for conditions like chronic pain where, rather than use narcotics, which are systemic and pose a risk of addiction, you could just put that piece of the body to sleep, so to speak."



Multilamellar liposome containing local anesthetics

Previous attempts to develop slow-release anesthetics have not been successful due to the tendency for conventional anesthetics to cause toxicity to surrounding tissue. Indeed, drug packaging materials have themselves been shown to cause tissue damage. Now, Kohane and colleagues report that if saxitoxin is packaged within liposomes, it is able to block nerve transmission of pain without causing significant nerve or muscle damage.

In lab experiments, the researchers evaluated various formulations--various types of liposomes containing saxitoxin with or without dexamethasone, a potent steroid known to augment the action of encapsulated anesthetics. The best liposomes produced nerve blocks lasting two days if they contained saxitoxin alone and seven days if combined with dexamethasone.

Cell culture experiments and tissue analysis confirmed that the formulations were not toxic to muscle or nerve cells. Furthermore, when the team examined expression of four genes known to be associated with nerve injury, they found no up-regulation.

"If these long-acting, low-toxicity formulations of local anesthetics are shown to be effective in humans, they could have a major impact on the treatment of acute and chronic pain," says Alison Cole, PhD, of the NIH's National Institute of General Medical Sciences, which partially funded the work. "This slow-release technology may also have broader applications in drug delivery for the treatment of a variety of diseases."

Kohane is currently optimizing the formulation to make it last even longer, while avoiding local and systemic toxicity. "It is conceivable we could have a formulation that is suitable for clinical trials before too long," he says.

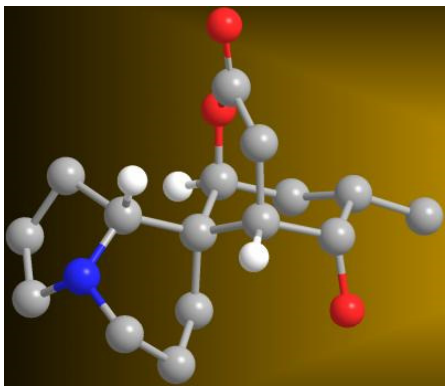
The study was supported by the National Institute of General Medical Sciences. Hila Epstein-Barash, PhD, was first author on the paper.

Chemists synthesize herbal alkaloid

The club moss Lycopodium serratum is a creeping, flowerless plant used in homeopathic medicine to treat a wide variety of ailments. It contains a potent brew of alkaloids that have attracted considerable scientific and medical interest. However, the plant makes many of these compounds in extremely low amounts, hindering efforts to test their therapeutic value.

That is no longer a problem for what is arguably the most complex of these alkaloids, a compound called Serratezomine A: an alkaloid that could have anti-cancer properties and may combat memory loss. A team of synthetic chemists at Vanderbilt University report in the March 18 issue of the Journal of the American Chemical Society that they have created an efficient way to make this molecule from scratch.

A 3-D model of the alkaloid serratezomine A shows the molecule's complex ring structure. **Johnston Group**



It took six years to develop the process because the researchers had to invent some entirely new chemical methods to complete the synthesis. These methods should make it easier to synthesize other Lycopodium alkaloids as well as other natural compounds with therapeutic potential.

In addition to their therapeutic possibilities, the Vanderbilt chemists were attracted to these compounds because they are among the most intricately structured and functionally dense of all the small molecules produced by living organisms. The compounds consist of carbon and nitrogen atoms assembled in unique ring structures.

"This was a challenging problem," says Professor of Chemistry Jeffrey Johnston, who led the research effort. 'It takes years to develop a new chemical reaction and then apply it to the natural product target. So, once we start, we don't stop."

In the world of total synthesis chemistry, it is not enough to figure out a way to synthesize a naturally occurring molecule. The process has to produce large enough quantities of the molecule that it can be tested for biological activity. That means that the number of sequential steps in the process – what chemists refer to as the longest linear sequence – should be as small as possible to maximize production. For example, if a sequence has 30 steps and each step has an 80 percent yield, the overall yield of the sequence is about one-tenth of a percent. At the same time, one low-yield step will knock a process out of contention.

The longest linear sequence in the Serratezomine A synthesis is 15 steps and it has an overall yield of 1.7 percent, Johnston says. That is an average yield of 77 percent per step. The chemists kept the sequence this short by using a strategy called convergence. They prepared one of the key fragments in the synthesis in parallel to the main sequence.

Johnston has handed over the Serratezomine A that his group has produced to Vanderbilt's drug discovery program, which identifies novel agents suitable for preclinical testing, in order to evaluate its therapeutic value.

Members of Johnston's research team are doctoral student Aroop Chandra; Julie A. Pigza, who is now a post-doctoral associate at the University of California, San Diego; Jeong-Seok Han, who now works at CJ Pharmaceuticals in South Korea; and Daniel Mutnick, who is now an associate scientist at Novartis in San Diego. The research was supported by grants from the National Institute of General Medical Sciences and Eli Lilly and Company and by a Pfizer Diversity Fellowship.

[Note: A multimedia version of this story is available on Exploration, Vanderbilt's online research magazine, at http://www.vanderbilt.edu/exploration/stories/lycopodium.html]

Why some people sneeze when the sun comes out

* 15 April 2009 **by Richard Webb**

I WAS rounding the corner to the bus stop when it hit me - a bright shaft of sunlight smack between the eyes. My reaction was immediate: an unpleasant prickling in my nose, a quickening of my breath, an uncontrollable watering of my eyes. Then, almost as quickly as the sensation came, relief, blessed relief. Aaaaa-tisshoo! A sneeze.

It wasn't the first time. In fact, the same thing happens every time I go into the sun. For a long time, I thought it was a quirk all of my own. Then a friend mentioned she was similarly afflicted. Next my mother came out of

the closet. With a bit of digging around I came to a startling realisation: not only am I not alone, but the "photic sneeze reflex" is actually common. Quite how common, no one knows exactly - but anything between 1 in 10 and 1 in 3 of us might be affected.

The more I looked, the more mysterious things became. Sunlight is the most widespread, but by no means the only, odd stimulus that sets off sneezing. Thinking about sex, eyebrow tweezing, eating chocolate or a mint, or drinking a glass of wine - all these activities can leave us groping around for handkerchiefs. Members of one Kuwaiti family were even reported to sneeze whenever they had a full stomach - a phenomenon dubbed "snatiation". Then there was the case of the medical student who sneezed with almost clockwork precision around 8.20 every morning.

All these oddities are faithfully recorded in the medical literature, almost always accompanied by an earnest call for further investigation. But a teensy problem has always stood in the way. Despite the fact that everyone does it, we still don't fully understand the way the nervous system coordinates a normal sneeze, let alone a photic sneeze.

A sneeze, one of the most violent actions your body will ever perform, should be triggered by an irritant in the mucus-producing membranes of our nostrils. This stimulates the endings of the trigeminal or fifth cranial nerve, which mediates sensory inputs from all over our face. The result is a cascade of reactions throughout our body: mucus production in the nose, a momentary closing of the eyes, and a wave of motor impulses down into our torsos to generate an explosive expulsion of air at up to 150 kilometres an hour - an extremely localised personal hurricane if you like.

The forces are considerable. Instances of whiplash through sneezing are not unknown, and a sneezing fit in 2004 threw Chicago Cubs baseball legend Sammy Sosa's back into spasm, knocking him out of the game for two weeks. I once gave myself a hernia during a pollen-induced sneezing fit in the bath.

Coordinating such a ferocious manoeuvre - together with the mucus production and blink reflex - is no mean feat. Sneezes are orchestrated by the parasympathetic nervous system, that part of our subconscious control hardware that regulates reflex housekeeping activities from producing tears and saliva to moving the waste products of digestion down the gut to our bowels.

The nerves within the parasympathetic nervous system that coordinate sneezing feed into a part of our brainstem known as the medulla oblongata. A series of experiments conducted by researchers from Asahikawa Medical College, Japan, in 1990 showed this was the case for cats (Brain Research, vol 511, p 265), and it seems to be true for humans too since some people with damaged medullas lose the ability to sneeze (Neurology, vol 56, p 138).

Unfortunately, current brain imaging techniques are not sensitive enough to pin down exactly which neurons within the medulla control the sneeze response. It is within this elusive "sneeze centre" of the brain that the mystery of photic sneezing lies.

This mystery has a long history. In the 4th century BC, Aristotle asked why the heat of the sun prompts us to sneeze, whereas the heat of the fire does not. A partial answer came two millennia later, when the English natural philosopher Francis Bacon showed that his photic sneeze had nothing to do with heat at all: if he closed his eyes when going into the sun, he didn't sneeze even though the heat was still there. While Bacon's application of the scientific method was beyond reproach, his conclusions are distinctly iffy to a modern nose. "The cause is not the heating of the nostrils," he asserted, "but the drawing down of the moisture of the brain."

It took a long time, however, before modern science could better that explanation. Henry Everett, a consultant psychiatrist at the Johns Hopkins University Hospital in Baltimore, Maryland, was the first to make a systematic attempt to understand the condition. Noting in 1964 that six of the 18 junior psychiatric doctors at Johns Hopkins were photic sneezers, he questioned 75 of his patients and 169 of his students in detail about their sneezing habits (Neurology, vol 14, p 483).

In the group of patients, 18 per cent reported a photic sneeze reflex; among the students, it was 24 per cent. Small sample sizes in this study and subsequent research have made it difficult to work out with any certainty how common the condition is. About 35 per cent of my colleagues at New Scientist turned out to be photic sneezers, which is significantly higher than Everett's findings but seems to fit the upper bound set by studies since.

Everett also thought to ask his volunteers about photic sneezing among their nearest and dearest. Whereas 80 per cent of sneezers reported other sneezers among their close relatives, only 20 per cent of non-sneezers did. As Everett perceptively observed, the results were likely to be skewed. People with the condition tend to be attuned to other people's sneezing (apart from me, that is), whereas those without it often don't notice when other members of their family are sneezers.

Nevertheless, the correlation was too significant to ignore, suggesting photic sneezing is an inherited rather than acquired response to environmental conditions, as had previously been assumed. Subsequent studies have borne out that hunch, with patterns of inheritance suggesting that it is carried on a dominant gene (Birth Defects, vol 14, p 361), so anyone with just one copy would be afflicted. This is known as autosomal dominant transmission, giving scientists the unmissable opportunity to rename the condition "autosomal-dominant compelling helio-ophthalmic outburst" - ACHOO for short.

So it seems I can blame my genes for my photic sneeze. I don't have to look far for the culprit: my mother, caught red-handkerchiefed.

But that was only half the answer. Now I wanted to know what exactly this aberrant gene was doing. How come it made both my mother and me sneeze when our eyes, not our noses, were stimulated?

Curious conditions

Clues might lie, I thought, in some of the other curious conditions. So I phoned Mahmood Bhutta of Wexham Park Hospital in Slough, UK. Together with his colleague Harold Maxwell, he caused a stir in December last year with his description of patients who sneezed at orgasm or even in response to having sexual thoughts (Journal of the Royal Society of Medicine, vol 101, p 587).

The connection between sex and sneezing is not a new observation. As far back as 1875, scientists had an inkling that the root cause was the erectile tissues common to both the nether regions and the glands of the nasal cavity. The theory was that nitric oxide released during arousal to dilate blood vessels in the genitals could diffuse through the body and excite the erectile tissue in the nasal cavity, triggering a sneeze.

Bhutta doesn't have much time for this explanation - the diffusion would take far too long to explain the rapidity of symptoms, he says. "The speed and involuntary nature of the response means the cause is likely to be neurological." That chimed with something I had read in Everett's paper, where he proposed a series of possible neurological explanations for photic sneezing.

It might be, for example, the result of confused signalling from a hyperactive trigeminal nerve as it gathers tactile information from across the face. Somewhere along the nerve the impulses from different nerve endings around the eye and in the nose may become scrambled, confusing the brain about the origin of the different signals. That seemed plausible enough, and since the nerve endings in the eyebrows also belong to the trigeminal, something similar might also account for sneezing when tweezing.

Alternatively, Everett suggested, the photic sneeze could be explained by a special connection between trigeminal and optic nerves. That was attractive, since it might also lie behind the mysterious phenomenon of sun-induced head-shaking in horses.

There was still something vaguely unsatisfactory about these explanations, though, since none can explain all those different types of sneezing at one fell swoop. What about orgasmic sneezing and snatiation, for example?

The answer to that, Bhutta suggests, might lie in another one of Everett's hypotheses: that the confusion arises in the way the medulla regulates our reflex actions. Everett originally proposed this idea to explain just photic sneezing, but Bhutta thinks it could explain all the strange sneezing conditions, since all of the triggers involve stimulation of a parasympathetic nerve response controlled by the medulla. When bright sunlight hits our eyes, our pupils contract involuntarily - a parasympathetic response. When our stomachs are full, the parasympathetic system kicks in to start our gastric juices flowing. When we think of sex, parasympathetic action stimulates blood flow to our genitals.

All these nerve responses flow to and from regions of the medulla close to where the sneeze centre is located. This suggests that far from being a neat system of discrete responses to individual stimuli, our reflex systems at their base in the medulla are often a tangled web of cross-talking nerve wires. Sometimes when bright sunlight hits our eyes, the parasympathetic system responds appropriately and our pupils constrict. But for certain people whose medullas are wired differently, sunlight triggers a different reflex response, such as a sneeze.

Nervous overkill is no deal breaker in the survival stakes as long as the right reflexes are also stimulated at the right time, so aberrant genes that cause confused reflexes in some individuals would have been conserved by evolution. "It's a mess," says Bhutta, "because it's never had to be anything else."

All this is just a hypothesis, not established fact, Bhutta emphasises, and is likely to remain so until we fashion better tools for studying the activity of individual nerve pathways in living humans. This is a sentiment echoed by Louis Ptácek, a neurogeneticist at the University of California, San Francisco. "People speak as if they know what the hell's going on," he says. "In reality, we don't."

That doesn't make Ptácek any less interested in the photic sneeze. On the contrary, he hopes work on the disorder could shed light on far more serious conditions, such as migraines and epilepsy, which are also caused by crossed wires in the nervous system. These disorders are diverse and often bizarre. In a condition called paroxysmal dyskinesia, for example, a startle or sudden voluntary movement can induce dance-like involuntary

movements lasting for minutes on end; and there are instances of epilepsy induced by listening to music or reading.

Certain parallels between these conditions and photic sneezing are obvious. "We know, for example, that some people with epilepsy have seizures if you flash strobe lights at them," says Ptácek. "But measure the brain waves of an epileptic with no strobe response when a strobe is switched on, and you still see sudden spikes in brain activity." That looks rather like just a more generalised version of photic sneezers' over-the-top response to a light stimulus.

The fact that photic sneezing is so common and is almost certainly also an inherited trait could provide an unparalleled opportunity to get to grips with these neurological confusions. Ptácek is hoping someone will study the condition in detail and pin down its pathology once and for all (see "Are you a sneezer?"). "It would be just the thing for some ambitious young doc to make his or her mark with," he says.

The photic sneeze has long been overlooked because its effects are generally less than serious. The US military once studied it as a risk factor for fighter pilots, true, but otherwise reports have concentrated on more esoteric concerns such as its potential "to disrupt outdoor group photographs".

Ptácek thinks the connection to the kind of disorders he studies means that a change of perception is long overdue. "Sometimes to discover things that make you go 'wow' in science," he says, "you have to follow your nose."

From a darkened room I'll say "bless you" to that.

Are you a photic sneezer? Take the questionnaire and find out

Are you a sneezer?

Part of the problem in pinpointing the prevalence of the photic sneeze, says Louis Ptácek, a neurogeneticist at the University of California, San Francisco, is the question of degree. Many people will happily look into a bright artificial light to complete a sneeze, but are not necessarily true photic sneezers. Below are certain factors that he says are cast-iron indicators.

A Predictable Response Photic sneezers almost always sneeze a set, unchanging number of times on exposure to light: most commonly just once, but sometimes twice or more.

The Threshold Effect The sneeze depends on light contrast - only a sudden, sharp exposure, such as when entering bright sunlight from a darkened space, or when the sun moves out from behind a cloud, will do.

The Latency Effect The sneeze takes time to "recharge" - if you go back into a darkened space and then re-enter bright light within a certain time, you will not sneeze again.

The Genetic Effect If you can pinpoint a close family member with the sneeze - a parent, sibling or child - you are on to a winner.

Sneezing: fact and myth

When You Sneeze Your Eyes Can Pop Out False. The fluid bath around our eyes comfortably absorbs the considerable air pressure built up during a sneeze, and for added safety the blink reflex prevents our eyes from extruding.

You Should Never Stifle A Sneeze Partially true. While reports that a stifled sneeze can rupture blood vessels in the brain seem exaggerated, holding both your nose and mouth shut while sneezing forces the air to find another escape route - via the Eustachian tube to the ear, where its force can easily rupture an eardrum.

Some People Never Stop Sneezing Not quite: reflex sneeze responses lasting for days and weeks have been recorded. The record seems to lie with a 12-year-old English girl called Donna Griffiths, who sneezed every few minutes for 977 days between January 1981 and August 1983.

There's Actually No Point In Sneezing Possibly, at least the way adult humans do it. Unlike our young, we develop the habit of sneezing almost entirely through our mouths - meaning it is less successful at clearing our nasal passages.

Iguanas Are Great Sneezers True, but then in common with many other lizards they sneeze for quite a different reason - to expel excess salt stored in nasal salt glands. ***Richard Webb is a feature editor at New Scientist***

Microbes thrive in harsh, isolated water under Antarctic glacier

Newfound iron-breathing species have lived in cold isolation for millions of years

CAMBRIDGE, Mass. -- A reservoir of briny liquid buried deep beneath an Antarctic glacier supports hardy microbes that have lived in isolation for millions of years, researchers report this week in the journal Science.

The discovery of life in a place where cold, darkness, and lack of oxygen would previously have led scientists to believe nothing could survive comes from a team led by researchers at Harvard University and Dartmouth College. Their work was funded by the National Science Foundation, NASA, and Harvard's Microbial Sciences Initiative.

Despite their profound isolation, the microbes are remarkably similar to species found in modern marine environments, suggesting that the organisms now under the glacier are the remnants of a larger population that once occupied an open fjord or sea.

"It's a bit like finding a forest that nobody has seen for 1.5 million years," says Ann Pearson, Thomas D. Cabot Associate Professor of Earth and Planetary Sciences in Harvard's Faculty of Arts and Sciences. "Intriguingly, the species living there are similar to contemporary organisms, and yet quite different -- a result, no doubt, of having lived in such an inhospitable environment for so long."

"This briny pond is a unique sort of time capsule from a period in Earth's history," says lead author Jill Mikucki, now a research associate in the Department of Earth Sciences at Dartmouth and visiting fellow at Dartmouth's Dickey Center for International Understanding and its Institute of Arctic Studies. "I don't know of any other environment quite like this on Earth."

Analysing DNA fragments from the "blood falls" has revealed that the bacteria survive on organic compounds trapped with them all those years ago that will eventually run out. **Ralph Maestas/Science**

Chemical analysis of effluent from the inaccessible subglacial pool suggests that its inhabitants have eked out a living by breathing iron leached from bedrock with the help of a sulfur catalyst. Lacking any light to support photosynthesis, the microbes have presumably survived by feeding on the organic matter trapped with them when the massive Taylor Glacier sealed off their habitat an estimated 1.5 to 2 million years ago.

Mikucki, Pearson, and colleagues based their analysis on samples taken at Antarctica's Blood Falls, a frozen waterfall-like feature at the edge of the Taylor Glacier whose striking red appearance first drew early explorers' attention in 1911. Those "Heroic Age" adventurers speculated that red algae might have been responsible for the bright color, but scientists later confirmed that the coloration was due to rust, which the new research shows was likely liberated from subglacial bedrock by microorganisms.

Because water flows unpredictably from below the glacier at Blood Falls, it took Mikucki a number of years to obtain the samples needed to conduct an analysis. Finally, in the right place at the right time, she was able to capture some of the subglacial brine as it flowed out of a crack in the glacial wall, obtaining a sample of an extremely salty, cold, and clear liquid for analysis.

"When I started running the chemical analysis on it, there was no oxygen," she says. "That was when this got really interesting. It was a real 'Eureka!' moment."

The fluid is rich in sulfur, a geochemical signature of marine environments, reinforcing suspicions that the ancestors of the microbes now beneath the Taylor Glacier probably lived in an ocean long ago. When sea level fell more than 1.5 million years ago, they hypothesize, a pool of seawater was likely trapped and eventually capped by the advancing glacier.

The exact size of the subglacial pool remains a mystery, but it is thought to rest under 400 meters of ice some four kilometers from its tiny outlet at Blood Falls.

Mikucki's analysis showed that the sulfur below the glacier had been uniquely reworked by microbes and provides insight into how these organisms have been able to survive in isolation for so long.

The research answers some questions while raising others about the persistence of life in such extreme environments. Life below the Taylor Glacier may help address questions about "Snowball Earth," the period of geological time when large ice sheets covered Earth's surface. But it could also be a rich laboratory for studying life in other hostile environments, and perhaps even on Mars and its ice-covered moon, Europa.

Mikucki and Pearson's co-authors are David T. Johnston and Daniel P. Schrag at Harvard, Alexandra V. Turchyn at the University of Cambridge, James Farquhar at the University of Maryland, Ariel D. Anbar at Arizona State University, John C. Priscu at Montana State University, and Peter A. Lee at the College of Charleston.

Study points to disruption of copper regulation as key to prion diseases

SANTA CRUZ, CA--An investigation of a rare, inherited form of Creutzfeldt-Jakob disease suggests that disrupted regulation of copper ions in the brain may be a key factor in this and other prion diseases.

Researchers at the University of California, Santa Cruz, discovered a striking relationship between changes in the copper-binding properties of abnormal prion proteins and the clinical features of prion disease in patients with certain rare, genetic mutations. They described their findings in a paper published by PLoS Pathogens on April 17.

"The loss of copper regulation may play a very important role in prion disease progression," said Glenn Millhauser, professor of chemistry and biochemistry at UCSC and corresponding author of the paper.

Prion diseases are fatal neurodegenerative brain disorders caused by a misfolded form of the normal cellular prion protein. Human prion diseases include classic and variant types of Creutzfeldt-Jakob disease (CJD). The

vast majority of CJD cases are sporadic, meaning they are thought to arise from spontaneous misfolding of the prion protein. Infectious transmission of the prion accounts for a very small percentage of cases, while about 10 percent of cases are caused by inherited defects in the structure of the prion protein.

Millhauser and his coauthors studied the effects of insertional mutations that cause extra sequences of eight amino acids (known as the octarepeat sequence) to be incorporated into the prion protein. Whereas the normal prion protein has four octarepeat segments, insertional mutations can result in as many as nine additional octarepeats. The extra octarepeats change the properties of the prion protein and eventually lead to the progressive brain damage characteristic of CJD.

These insertional mutations are known from a small number of cases reported in the literature, involving about 30 families and 108 individuals. Reviews of these cases have suggested that higher numbers of inserts are associated with earlier-age onset of the disease.

The octarepeat domain takes up copper ions, which are essential for the proper functioning of neurons. Millhauser's lab looked at the effects of insertional mutations on the prion protein's ability to bind copper. Graduate student Daniel Stevens, lead author of the paper, and postdoctoral researcher Eric Walter performed experiments using magnetic resonance spectroscopy to study how prion proteins with different numbers of octarepeats interact with copper.

The normal prion protein responds dynamically to varying concentrations of copper by changing the way it binds the metal, allowing it to soak up more copper ions at higher concentrations. When the researchers studied proteins with octarepeat inserts, however, they found that the protein loses this ability to switch binding modes as the number of inserts increases beyond four.

"We got excited when we saw that the threshold in the effects on copper binding corresponds to the threshold for age of onset that was seen in the clinical studies," Millhauser said.

The average age of onset is 64 years for patients with one to four extra repeats, but for patients with five to nine inserts the average age of onset drops to 38 years. Similarly, Millhauser's group found a transition in the copper-binding properties of the protein that occurred between four and five inserts, the same threshold observed for early-onset disease.

For the statistical analysis of clinical cases, Millhauser enlisted the help of statisticians David Draper and Abel Rodriguez, professors of applied mathematics and statistics in the Jack Baskin School of Engineering at UCSC. Draper and Rodriguez used several approaches to analyze the pooled data from case studies in the literature. Their results are consistent with the existence of two groups of patients: a group with one to four extra octarepeats and late-onset disease, and a group with five or more inserts and early-onset disease.
The normal function of the prion protein remains uncertain, but the new findings support the idea that it plays a role in the regulation of copper ions in the brain, Millhauser said. The prion protein is anchored to the outside of the cell membranes of neurons and is concentrated at the synapses, the junctions between neurons where signals are transmitted. The concentration of copper in the synapses is dynamic, and as the copper concentration goes up and down the prion protein switches from one copper-binding mode to another. Millhauser suspects that the prion protein soaks up excess copper ions to protect brain cells from harmful reactions.

"The prion protein goes into a neuroprotective mode at higher levels of copper, and that mode gets lost when extra octarepeats are added to the protein structure," he said.

While changes in copper binding begin to appear with four or more extra octarepeats, other changes in the molecular properties of the prion protein occur with as few as one insert. These changes include an increased propensity to clump together and form protein deposits in brain tissue.

Research on prion diseases has tended to focus on these aggregates and deposits, which are thought to have toxic effects on brain cells. But the strong relationship between changes in copper binding and clinical progression of the disease suggests that more attention should be given to the normal function of the prion protein, Millhauser said.

"The fundamental issue may be the loss of copper regulation, and excess copper may be what causes the cytotoxicity," he said.

In addition to Millhauser, Stevens, Walter, Rodriguez, and Draper, the coauthors of the PLoS Pathogens paper include Paul Davies and David Brown of the University of Bath.

New nucleotide could revolutionize epigenetics

The discovery of a new nucleotide in the mouse brain opens the door to a new domain of epigenetic DNA modification

Anyone who studied a little genetics in high school has heard of adenine, thymine, guanine and cytosine – the A,T,G and C that make up the DNA code. But those are not the whole story. The rise of epigenetics in the past decade has drawn attention to a fifth nucleotide, 5-methylcytosine (5-mC), that sometimes replaces

cytosine in the famous DNA double helix to regulate which genes are expressed. And now there's a sixth. In experiments to be published online Thursday by Science, researchers reveal an additional character in the mammalian DNA code, opening an entirely new front in epigenetic research.

The work, conducted in Nathaniel Heintz's Laboratory of Molecular Biology at The Rockefeller University, suggests that a new layer of complexity exists between our basic genetic blueprints and the creatures that grow out of them. "This is another mechanism for regulation of gene expression and nuclear structure that no one has had any insight into," says Heintz, who is also a Howard Hughes Medical Institute investigator. "The results are discrete and crystalline and clear; there is no uncertainty. I think this finding will electrify the field of epigenetics."

Genes alone cannot explain the vast differences in complexity among worms, mice, monkeys and humans, all of which have roughly the same amount of genetic material. Scientists have found that these differences arise in part from the dynamic regulation of gene expression rather than the genes themselves. Epigenetics, a relatively young and very hot field in biology, is the study of nongenetic factors that manage this regulation.

One key epigenetic player is DNA methylation, which targets sites where cytosine precedes guanine in the DNA code. An enzyme called DNA methyltransferase affixes a methyl group to cytosine, creating a different but stable nucleotide called 5-methylcytosine. This modification in the promoter region of a gene results in gene silencing.

Some regional DNA methylation occurs in the earliest stages of life, influencing differentiation of embryonic stem cells into the different cell types that constitute the diverse organs, tissues and systems of the body. Recent research has shown, however, that environmental factors and experiences, such as the type of care a rat pup receives from its mother, can also result in methylation patterns and corresponding behaviors that are heritable for several generations. Thousands upon thousands of scientific papers have focused on the role of 5-methylcytosine in development.

The discovery of a new nucleotide may make biologists rethink their approaches to investigating DNA methylation. Ironically, the latest addition to the DNA vocabulary was found by chance during investigations of the level of 5-methylcytosine in the very large nuclei of Purkinje cells, says Skirmantas Kriaucionis, a postdoctoral associate in the Heintz lab, who did the research. "We didn't go looking for this modification," he says. "We just found it."

Kriaucionis was working to compare the levels of 5-methylcytosine in two very different but connected neurons in the mouse brain — Purkinje cells, the largest brain cells, and granule cells, the most numerous and among the smallest. Together, these two types of cells coordinate motor function in the cerebellum. After developing a new method to separate the nuclei of individual cell types from one another, Kriaucionis was analyzing the epigenetic makeup of the cells when he came across substantial amounts of an unexpected and anomalous nucleotide, which he labeled 'x.'

It accounted for roughly 40 percent of the methylated cytosine in Purkinje cells and 10 percent in granule neurons. He then performed a series of tests on 'x,' including mass spectrometry, which determines the elemental components of molecules by breaking them down into their constituent parts, charging the particles and measuring their mass-to-charge ratio. He repeated the experiments more than 10 times and came up with the same result: x was 5-hydroxymethylcytosine, a stable nucleotide previously observed only in the simplest of life forms, bacterial viruses. A number of other tests showed that 'x' could not be a byproduct of age, DNA damage during the cell-type isolation procedure or RNA contamination. "It's stable and it's abundant in the mouse and human brain," Kriaucionis says. "It's really exciting."

What this nucleotide does is not yet clear. Initial tests suggested that it may play a role in demethylating DNA, but Kriaucionis and Heintz believe it may have a positive role in regulating gene expression as well. The reason that this nucleotide had not been seen before, the researchers say, is because of the methodologies used in most epigenetic experiments. Typically, scientists use a procedure called bisulfite sequencing to identify the sites of DNA methylation. But this test cannot distinguish between 5-hydroxymethylcytosine and 5-methylcytosine, a shortcoming that has kept the newly discovered nucleotide hidden for years, the researchers say. Its discovery may force investigators to revisit earlier work. The Human Epigenome Project, for example, is in the process of mapping all of the sites of methylation using bisulfite sequencing. "If it turns out in the future that (5-hydroxymethylcytosine and 5-methylcytosine) have different stable biological meanings, which we believe very likely, then epigenome mapping experiments will have to be repeated with the help of new tools that would distinguish the two," says Kriaucionis.

Providing further evidence for their case that 5-hydroxymethylcytosine is a serious epigenetic player, a second paper to be published in Science by an independent group at Harvard reveals the discovery of genes that produce enzymes that specifically convert 5-methylcytosine into 5-hydroxymethylcytosine. These enzymes

may work in a way analogous to DNA methyltransferase, suggesting a dynamic system for regulating gene expression through 5-hydroxymethylcytosine. Kriaucionis and Heintz did not know of the other group's work, led by Anjana Rao, until earlier this month. "You look at our result, and the beautiful studies of the enzymology by Dr. Rao's group, and realize that you are at the tip of an iceberg of interesting biology and experimentation," says Heintz, a neuroscientist whose research has not focused on epigenetics in the past. "This finding of an enzyme that can convert 5-methylcytosine to 5-hydroxymethylcytosine establishes this new epigenetic mark as a central player in the field."

Kriaucionis is now mapping the sites where 5-hydroxymethylcytosine is present in the genome, and the researchers plan to genetically modify mice to under- or overexpress the newfound nucleotide in specific cell types in order to study its effects. "This is a major discovery in the field, and it is certain to be tied to neural function in a way that we can decipher," Heintz says.

Inexpensive drug appears to relieve fibromyalgia pain in Stanford pilot study

STANFORD, Calif. — For Tara Campbell, the onset of her fibromyalgia began slowly with repeated sore throats, fevers and fatigue. By the time she was diagnosed, a year later, she had become so debilitated by flulike symptoms and exhaustion that she often couldn't get off the couch all day.

"Fall, a year ago, I hit my very, very worst," said Campbell, 39, of Walnut Creek, Calif. "I felt overall pain to the point that even when my children or husband just touched me it hurt."

Campbell's symptoms still linger, but since taking part in a Stanford University School of Medicine clinical trial in the spring of 2008, she's improved enough that she's gone back to working again as an interior decorator and even headed up the fundraising auction at her daughters' school.

"I am really, really good," Campbell said. "Having said that, I'm still not 100 percent. I'm still not that person I was before."

Campbell was one of 10 women with fibromyalgia to take part in a small pilot study at Stanford over a 14-week period to test the new use of a low dose of a drug called naltrexone for the treatment of chronic pain. The drug, which has been used clinically for more than 30 years to treat opioid addiction, was found to reduce symptoms of pain and fatigue an average of 30 percent over placebo, according to the results of the study to be published April 17 online in the journal Pain Medicine.

"Patients' reactions were really quite profound," said senior author Sean Mackey, MD, PhD, associate professor of anesthesia and chief of the pain management division at Stanford University Medical Center. "Some people decided to come off other medications. Some people went back to work really improving their quality of life."

Still, Mackey and his colleagues remain cautious about recommending the drug this early on in the research process. "People need to understand that while we're excited about preliminary results, they are still preliminary, and we need to do longer studies with more patients. There is still a significant amount of work to be done." The researchers are moving ahead with a second, longer-term trial of 30 patients who will be tested during a 16-week period.

The drug is particularly promising, the study states, because of the few treatment options available for fibromyalgia patients, its low cost of about $40 a month and its limited side effects. Vivid dreams were reported by a few participants.

Still considered a controversial diagnosis, fibromyalgia is a disorder classified by chronic widespread pain, debilitating fatigue, sleep disturbance and joint disorder. Advocates and doctors who treat the disorder, estimate it affects as much as 4 percent of the population. "The symptoms of fibromyalgia are commonly seen in a number of other diseases, and there is no well-established and objective blood test to confirm the diagnosis," said Jarred Younger, PhD, the study's lead author and an instructor in anesthesia and pain management at Stanford. "In the meantime, new treatments that work particularly well for fibromyalgia go a long way toward validating the usefulness of the diagnosis."

The idea to explore the use of a low-dose of naltrexone as a treatment for fibromyalgia began about two years ago when Younger began searching for relief for patients with the disorder. "I was asking patients, 'Does anything work for you?'" he recalled. "A lot of people in support groups were saying, 'Yeah, I tried naltrexone and it works for me.' It just kept coming up."

The use of naltrexone to treat pain at first seems counterintuitive, Younger said, because at normal doses the drug actually blocks the body's pain relief systems. However, naltrexone appears to have the opposite effect when given at a lower dose. Naltrexone, at these lower doses, is thought to work by modulating glial cells in the nervous system, Mackey said. Glial cells provide support and protection for neurons and act as a link between the neuronal and inflammatory systems.

"We're learning more and more that maybe by modulating these glial cells we can impact the abnormal processing of pain in these patients," Mackey said.

During the study, the women used a handheld electronic device to capture their symptoms on a daily basis. They took a placebo for two weeks and then the drug for eight weeks, but they weren't told when they were taking the drug or the placebo.

Some of the women, including Campbell, have continued to take the drug after the end of the study because the results were so positive, Younger said.

"Even after the study, it just got better and better and better," Campbell said. "I think my improvement was about 40 percent during the study. When you're not capable of doing much of anything, that's a lot. I still have localized pain, but I don't have the overall body pain. I can live with that if I don't have the fatigue and flulike symptoms. I'm much more back to normal."

Researchers reported no financial ties to the drug. More information is available at: http://paincenter.stanford.edu/.

"ANTEDRUGS": A Safer Approach To Drug Therapy

One lab's groundbreaking approach to tailoring drugs that meet only a specific target within the body has focused on anti-inflammatory, anti-AIDS and anti-cancer drugs since 1982

NEW ORLEANS—Corticosteroids are powerful drugs used to treat inflammatory conditions such as asthma and other chronic diseases which has made them among the most widely prescribed drugs. Although the anti-inflammatory drugs offer swift relief to the patient, they can carry with them serious side effects. For example, the inflammatory steroids used to treat a child's asthma, but can stunt the child's growth over time. Similarly, adult treatment of Addison's disease, which President John F. Kennedy endured, can lead to the development of diabetes and hypertension.

For more than 20 years, one research team has been working to develop a safer approach that would eliminate inflammation without causing damage to the body. Such drugs, called "antedrugs" have been developed in a lab at Florida A&M's College of Pharmacy. The efforts have been spearheaded by Dr. Henry J. Lee who has led antedrug research in anti-inflammatory, anti-AIDS and anti-cancer drugs for nearly 30 years.

A New Study

Lee and his team have recently completed a new study entitled, Anti-Inflammatory Activities of New Steroidal Antedrugs Isoxazoline Derivatives. It was conducted by Drs. Henry J. Lee, Younes J. Errahali, LeeShawn D. Thomas, Brenda G. Arnold and Glory B. Brown, all of the Florida Agricultural and Mechanical University, College of Pharmacy and Pharmaceutical Sciences, Tallahassee, Florida. The researchers will discuss their work at the 122nd Annual Meeting of the American Physiological Society (APS; www.the-APS.org/press) which is part of the Experimental Biology 2009 scientific conference. The meeting will be held April 18-22, 2009 in New Orleans.

The Study

Antedrug design is a new approach to create safer drugs that attack a problem such as inflammation then quickly become inactive before they can cause damage. The primary objective of this study was to synthesize a new group of corticosteroids that have anti-asthmatic and anti-inflammatory properties without adverse side effects.

The researchers synthesized new antedrugs, isoxazoline derivatives, from prednisolone. They then tested the derivatives in a test tube and found that antedrugs effectively reduced inflammation. In fact, they found isoxazoline derivatives were five times more potent than prednisolone in binding affinities to the cell corticosteroids receptors and reducing inflammation.

The researchers also studied the isoxazoline derivatives in the lung and liver cells of rats and found that the antedrugs significantly reduced the cell inflammation. In addition, the rat plasma began metabolizing rapidly the antedrugs to an inactive form with the half lives less than five minutes and more than 95% of prednisolone remained unchanged even after 100 min incubation.

Results

These results suggest that isoxazoline derivatives compared to conventional steroids improve topical anti-inflammatory activity without causing systemic damage. "This is a very promising outcome," according to Dr. Lee. Additional studies are currently underway, using a new group of corticosteroids in the treatment of asthma exacerbation and chronic pulmonary inflammation without systemic side effects such as body weight and hypothalamic-pituitary-adrenal axis change.

This project research described was supported by the National Institutes of Health, 5S06GM008111-36 NIGMS/MBRS and 2G12RR03020-24 / NCRR/RCMI. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCRR, NIGMS or the NIH.

Fossils suggest earlier land-water transition of tetrapod

DURHAM, N.C. -- New evidence gleaned from CT scans of fossils locked inside rocks may flip the order in which two kinds of four-limbed animals with backbones were known to have moved from fish to landlubber.

Both extinct species, known as Ichthyostega and Acanthostega, lived an estimated 360-370 million years ago in what is now Greenland. Acanthostega was thought to have been the most primitive tetrapod, that is, the first vertebrate animal to possess limbs with digits rather than fish fins.

But the latest evidence from a Duke graduate student's research indicates that Ichthyostega may have been closer to the first tetrapod. In fact, Acanthostega may have had a terrestrial ancestor and then returned full time to the water, said Viviane Callier, who is the first author of a report on the findings to be published in today's issue of the journal Science. "If there is one take-home message, it is that the evolutionary relationship between these early tetrapods is not well resolved," Callier said.

Co-author Jennifer Clack of the University Museum of Zoology in Cambridge, England -- where she supervised Callier's work for a master's degree -- found the fossils embedded in rocks collected from East Greenland.

Rather than trying to remove them -- an action that would have destroyed much of the evidence -- the researchers studied the fossils inside the stone with computed tomography (CT) scanning. Callier "reconstructed" the animals using imaging software (Amira and Mimics) to analyze the CT scans, focusing on the shapes of the two species' upper arm bones, or humeri.

The CT slices revealed that Clack had found the first juvenile forms of Ichthyostega. Previously known fossils of Ichthyostega had come from adults.

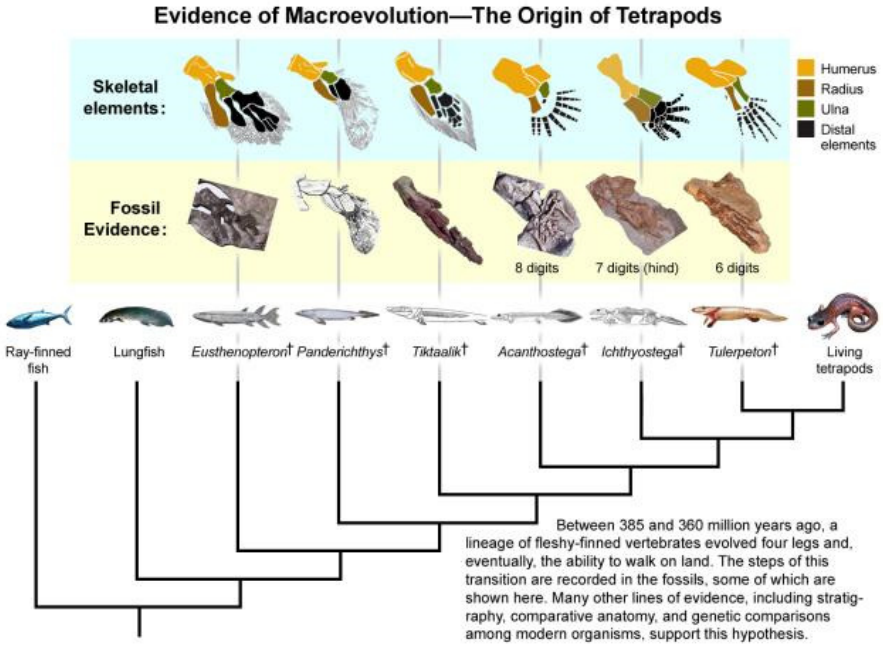
Anatomies can morph as animals move towards adulthood, Callier said. And such shifts can help scientists deduce when in development the animal acquired the terrestrial habit. The fossils suggest that Ichthyostega juveniles were aquatically adapted, and that the terrestrial habit was acquired relatively late in development. The fossils bore evidence that the muscle arrangement in adults was better suited to weight-bearing, terrestrial locomotion than the juvenile morphology. It is possible that Ichthyostega came out of the water only as a fully mature adult.

In contrast, in Acanthostega "there is less change from the juvenile to the adult. Although Acanthostega appears to be aquatically adapted throughout the recorded developmental span, its humerus exhibits subtle traits that make it more similar to the later, fully terrestrial tetrapods," Callier said

Because the shapes of its adult limbs seemed the most fin-like, scientists had previously concluded that Acanthostega was "more primitive," Callier said. "But now, if we look at the details of the humeri, Ichthyostega's are actually more similar to earlier fishes."

Ironically, the shape of Acanthostega's limbs, in both adult and the newly-discovered juvenile forms, is more "paddle-like" than Ichthyostega's, Callier said. "They would have been really good swimmers. So, although Acanthostega had limbs with digits, we don't think it was really terrestrial. We think even the adults were aquatic."

"If Ichthyostega is actually more primitive than Acanthostega, then maybe animals evolved towards a terrestrial existence a lot earlier than originally believed," she said. "Maybe Acanthostega was actually derived from a terrestrial ancestor, and then, went back to an aquatic lifestyle."



Per Ahlberg, a Swedish paleontologist who was previously Clack's graduate student, also joined Clack in a comparative analysis of other more fish-like species living at about the same time as Ichthyostega and Acanthostega.

Those include Tiktaalik, another animal that has made the news because of scientists' deductions that it was in transition from water to land.

"It seems like there were different species evolving the same or similar traits independently -- evidence of parallel evolution," Callier said. "The terrestrial environment posed new challenges like feeding and moving on

land and breathing air, to which the first tetrapods had to evolve solutions. Sometimes different lineages stumbled upon similar solutions."

Ahlberg, now professor at the University of Uppsala in Sweden, is corresponding author of the new Science report. The research was funded by the Winston Churchill Foundation and the Swedish Research Council.

Increasing carbon dioxide and decreasing oxygen in the oceans
will make it harder for deep-sea animals to "breathe"

Owlfish in the oxygen minimum zone of Monterey Bay

New calculations made by marine chemists from the Monterey Bay Aquarium Research Institute (MBARI) suggest that low-oxygen "dead zones" in the ocean could expand significantly over the next century. These predictions are based on the fact that, as more and more carbon dioxide dissolves from the atmosphere into the ocean, marine animals will need more oxygen to survive.

Concentrations of carbon dioxide are increasing rapidly in the Earth's atmosphere, primarily because of human activities. About one third of the carbon dioxide that humans produce by burning fossil fuels is being absorbed by the world's oceans, gradually causing seawater to become more acidic.

However, such "ocean acidification" is not the only way that carbon dioxide can harm marine animals. In a "Perspective" published today in the journal Science, Peter Brewer and Edward Peltzer combine published data on rising levels of carbon dioxide and declining levels of oxygen in the ocean in a set of new and thermodynamically rigorous calculations. They show that increases in carbon dioxide can make marine animals more susceptible to low concentrations of oxygen, and thus exacerbate the effects of low-oxygen "dead zones" in the ocean.

Brewer and Peltzer's calculations also show that the partial pressure of dissolved carbon dioxide gas (pCO2) in low-oxygen zones will rise much higher than previously thought. This could have significant consequences for marine life in these zones.

For over a decade, Brewer and Peltzer have been working with marine biologists to study the effects of carbon dioxide on marine organisms. High concentrations of carbon dioxide make it harder for marine animals to respire (to extract oxygen from seawater). This, in turn, makes it harder for these animals to find food, avoid predators, and reproduce. Low concentrations of oxygen can have similar effects.

Currently, deep-sea life is threatened by a combination of increasing carbon dioxide and decreasing oxygen concentrations. The amount of dissolved carbon dioxide is increasing because the oceans are taking up more and more carbon dioxide from the atmosphere. At the same time, ocean surface waters are warming and becoming more stable, which allows less oxygen to be carried from the surface down into the depths.

In trying to quantify the impacts of this "double whammy" on marine organisms, Brewer and Peltzer came up with the concept of a "respiration index." This index is based on the ratio of oxygen and carbon dioxide gas in a given sample of seawater. The lower the respiration index, the harder it is for marine animals to respire.

Brewer provides the following analogy, "Animals facing declining oxygen levels and rising CO2 levels will suffer in much the same way that humans in a damaged submarine would suffer, once the concentrations of these gasses reach critical levels. Our work helps define those critical levels for marine animals, and will enable the emerging risk to be quantified and mapped."

In the past, marine biologists have defined "dead zones" based solely on low concentrations of dissolved oxygen. Brewer and Peltzer hope that their respiration index will provide a more precise and quantitative way for oceanographers to identify such areas. Tracking changes in the respiration index could also help marine biologists understand and predict which ocean waters are at risk of becoming dead zones in the future.

A new study by marine chemists at MBARI suggests that deep-ocean animals such as this owlfish (Bathylagus milleri) may suffer as carbon dioxide increases and oxygen concentrations decline in the deep sea
Image: © 2001 MBARI

To estimate such effects in the open ocean, the MBARI researchers calculated the respiration index at various ocean depths, for several different forecasted concentrations of atmospheric carbon dioxide. They found that the most severe effects would take place in what are known as "oxygen minimum zones." These are depths, typically 300 to 1,000 meters below the surface, where oxygen concentrations are already quite low in many parts of the world's oceans.

Previously, marine biologists have assumed that the effects of increasing carbon dioxide in the oceans would be greatest at the sea surface, where most of the gas enters the ocean. Such studies have predicted a doubling of

pCO2 (from about 280 to 560 micro-atmospheres) at the sea surface over the next 100 years. Brewer and Peltzer's calculations suggest that the partial pressure of carbon dioxide will increase even faster in the deep oxygen minimum zones, with pCO2 increasing by 2.5 times, from 1,000 to about 2,500 micro-atmospheres.

Previous studies have indicated that such oxygen minimum zones may expand over the next century. Brewer and Peltzer's research suggests that the effects of this expansion will be even more severe than previously forecast.

According to coauthor Peltzer, "The bottom line is that we think it's important to look at both oxygen and carbon dioxide in the oceans, rather than just one or the other." The impact of these chemical changes may be minimal in well-oxygenated ocean areas, but as the authors point out in their paper, "We may anticipate a very large expansion of the oceanic dead zones." *For more information or images relating to this news release, please contact: Kim Fulton-Bennett: (831) 775-1835, kfb@mbari.org*

Research paper: P. G. Brewer, E. T. Peltzer. Limits to marine life. Science. 2009. Vol 324, Issue 5925. April 17, 2009

Autopsy Study Links Prostate Cancer to Singe Rogue Cell

One cell…one initial set of genetic changes – that's all it takes to begin a series of events that lead to metastatic cancer. Now, Johns Hopkins experts have tracked how the cancer process began in 33 men with prostate cancer who died of the disease. Culling information from autopsies, their study points to a set of genetic defects in a single cell that are different for each person's cancer.

"These were not your average autopsies," says pathologist G. Steven Bova, M.D., assistant professor of pathology at Johns Hopkins. "We dissected every bit of tumor – in the primary and metastatic sites – and recorded exactly where each piece of tissue came from, analyzed it, and databased the findings." In total, Bova estimates that he and his colleagues examined 150,000 slides and 30,000 blocks of tissue.

The study took 14 years to complete, and part of the challenge was in finding men living with prostate cancer who would agree to have their body autopsied immediately after they died. "Many of the men were motivated to join the study in hopes of leaving some legacy that might lead to cures for this cancer," says Bova, who holds secondary appointments in the departments of pathology, genetic medicine, health sciences informatics, oncology, and urology at Johns Hopkins.

"Much is unclear and appears chaotic about how cancer spreads, but analyzing genetic markers allows us to trace its roots backward, somewhat like ancestry," says Bova. Findings from the study were published online April 12 in Nature Medicine.

Clues to finding the genetic culprit for cancer spread are hidden in the changes that occur in a cell's DNA, the alphabetical code made up of chemicals that guide the everyday life of a cell. Cancers are caused by alterations in DNA code that occur in a variety of ways: making errors in the nucleotide alphabet through mutations, changing the balance of chemicals attached to the on/off switches of genes, and altering the number of gene copies in a cell. When the number of gene copies is disrupted in a cell beyond the customary two copies inherited from each parent, a gene's function can be damaged. This process, called copy number variation, can set the stage for unchecked cell growth and spread, a hallmark of cancer.

For this study, the investigators scanned genes spanning the whole genome in the autopsy samples looking for areas of copy number variation. They did this by attaching the DNA to special silicon chips, and then photographed them with a computer program that produces a report with varying colors representing the amount of DNA in the sample.

The scientists compared the patterns of gains and losses in tissue samples from multiple metastatic sites in 29 of the men. Unique copy number changes were identified, as well as ones that were shared between multiple metastatic sites in each man and with other men in the study.

For example, in several men, the investigators found cells in different areas of metastasis that contained missing chunks of DNA in one common region of the genome. The exact location of the DNA loss was different for each man, but all occurred in the same DNA region. "Each person has a different set of defects that contributes to the cancer," explains Bova.

Metastatic sites develop from cancer cells that break off of the primary cancer. If cancer cells at more than one metastatic site carry a common set of nonrandom genetic defects, it is likely that these cells are derived from a single parent cell, says Bova. Tissue samples from 14 of the 33 men were studied at the highest available resolution, and all showed common genetic patterns across metastatic sites, suggesting a single cell source for their cancer.

Bova says that future studies will help determine whether the common set of changes shared by the various metastatic sites arose in a single "big bang" in the prostate or if the changes accumulated more slowly over time.

Bova says that such autopsy studies of metastatic cancer can provide a molecular catalogue of cellular defects specific to individuals and general groups. The findings, he says, could help narrow the focus of research and guide personalized cancer therapy.

The research was funded by the Pirkanmaa Cancer Foundation, Maud Kuistila Foundation, Finnish Medical Foundation, Medical Research Fund of Tampere University Hospital, Academy of Finland, Cancer Society of Finland, Reino Lahtikari Foundation, Sigrid Juselius Foundation, CaPCURE Foundation, John and Kathe Dyson, David Koch, National Cancer Institute, Prostate Cancer Research and Education Foundation, U.S. Department of Defense Congressionally Directed Prostate Cancer Research Program, Grove Foundation and the American Cancer Society.

In addition to Bova, research participants included Wennuan Liu and Jianfeng Xu at Wake Forest University School of Medicine; Sari Laitinen, Sofia Khan, Mauno Vihinen, and Tapio Visakorpi at the University of Tampere and Tampere University Hospital, Tampere, Finland; Guoqiang Yu, Li Chen and Yue Wang at the Virginia Polytechnic Institute and State University; and Jeanne Kowalski, Charles M. Ewing, Mario A. Eisenberger, Michael A. Carducci, William G. Nelson, Srinivasan Yegnasubramanian, Jun Luo, and William B. Isaacs at Johns Hopkins.

Maternal immune response to fetal brain during pregnancy a key factor in some autism

Mouse studies with human antibodies at Hopkins Children's add weight to earlier research

New studies in pregnant mice using antibodies against fetal brains made by the mothers of autistic children show that immune cells can cross the placenta and trigger neurobehavioral changes similar to autism in the mouse pups.

A report on the research from investigators at the Johns Hopkins Children's Center published online in the Journal of Neuroimmunology expands on a 2008 report from the same team showing that mothers of autistic children tested positive for fetal brain antibodies. Antibodies are proteins the body naturally makes to attack foreign tissues, viruses or bacteria. Because a growing fetus is not "rejected" by the mother's immune system even though some of its DNA is "foreign" (from the father), scientists have long suspected that some combination of maternal and fetal biological protection is at work. The new research from Hopkins, however, suggests that the protective system is not perfect and that antibodies are not only made but are re-circulated back to the fetus through the placenta, possibly triggering inflammation in the brain and leading to a cascade of neurological changes resulting in neurodevelopmental disorders, such as autism.

Despite this new evidence, the researchers warn against over-interpreting the results, saying prenatal exposure to maternal antibodies is likely only one of several factors implicated in autism.

"Autism is a complex disorder and it would be naïve to assume there's a single mechanism that can cause it," says Harvey Singer, M.D., director of pediatric neurology at Hopkins Children's. "It's most likely the cumulative result of several factors, including genes, metabolism and environment. We believe we have identified one of these factors."

For the new study, Singer and colleagues injected antibodies from mothers of autistic children into pregnant mice and used several standard neurobehavioral tests to identify neurobehavioral changes in the pups. As control groups, they used offspring of mice injected with antibodies from mothers of nonautistic children and the offspring of mice who received no injections.

"Comparing mice to humans is tricky, and we should be cautious anytime we do so, but our findings strongly suggest that the behaviors we observed in the offspring of mice injected with fetal brain antibodies from human mothers did behave in a manner that mimics some behaviors seen in people with autism," Singer says.

Following the mice throughout adolescence (four to six weeks) and adulthood (four to six months), the Hopkins team measured novelty-seeking (or willingness to explore unfamiliar open spaces), response to loud noise, sociability and anxiety-like behavior.

Overall, mice exposed prenatally to antibodies from mothers of autistic children behaved more anxiously, spent less time in open spaces when placed in an elevated maze, and were overall more hyperactive, fretting back and forth between open and closed spaces in the maze and in an open field environment, both behaviors that in humans would equal abnormal activity.

Again, compared to control mice, the mice exposed to antibodies from mothers of autistic children were also more easily startled by loud noises and were less social, choosing to spend more time visiting an empty cage rather than one with a live mouse in it.

The differences among groups were less pronounced in the adolescent mice, but as the mice aged, researchers observed an increase in autism-like symptoms, a finding consistent with neurodevelopmental disorders in humans, who tend to develop new or more pronounced symptoms over time, investigators point out.

Comparing brain tissues from all groups of mice, researchers observed markedly more activation of microglia -- immune cells in the central nervous system activated during inflammation – in the brain tissues of the group injected prenatally with antibodies from mothers of autistic children.

In further studies, the Hopkins scientists hope to identify which specific brain proteins the antibodies affect and to correlate changes in brain anatomy and function to changes in behavior.

Ultimately, researchers hope to develop ways to detect and analyze culprit antibodies in pregnant women and prevent them from binding to fetal brain proteins.

The causes of autism, a disorder manifesting itself with a range of brain problems, impaired social interactions, communication disorders and repetitive behaviors, remain unknown for an estimated 90 percent of children diagnosed with it. Genetic, metabolic and environmental factors have been implicated in various studies of autism, which affects an estimated 1 in 150 U.S. children, according to the Centers for Disease Control and Prevention.

Co-authors: Mikhail Pletnikov, M.D., Ph.D., Christina Morris, Colin Gause, Matthew Pollard, all of Hopkins; and Andrew W. Zimmerman, M.D., of the Center for Autism and Related Disorders at the Kennedy Krieger Institute.

The study was funded by the Hussman Foundation. On the web: http://www.hopkinschildrens.org

Key role of forests 'may be lost'

By Mark Kinver Science and environment reporter, BBC News

Forests' role as massive carbon sinks is "at risk of being lost entirely", top forestry scientists have warned.

The International Union of Forest Research Organizations (IUFRO) says forests are under increasing degrees of stress as a result of climate change.

Forests could release vast amounts of carbon if temperatures rise 2.5C (4.5F) above pre-industrial levels, it adds.

The findings will be presented at the UN Forum on Forests, which begins on Monday in New York.

Compiled by 35 leading forestry scientists, the report provides what is described as the first global assessment of the ability of forests to adapt to climate change.

"We normally think of forests as putting the brakes on global warming," observed Professor Risto Seppala from the Finnish Forest Research Institute, who chaired the report's expert panel.

"But over the next few decades, damage induced by climate change could cause forests to release huge quantities of carbon and create a situation in which they do more to accelerate warming than to slow it down."

Debate defining

The scientists hope that the report, called Adaption of Forests and People to Climate Change - A Global Assessment, will help inform climate negotiators.

The international climate debate has focused primarily on emissions from deforestation, but the researchers say their analysis shows that attention must also be paid to the impacts of climate change on forests.

While deforestation is responsible for about 20% of greenhouse gas emissions from human activities, forests currently absorb more carbon than they emit.

But the problem is that the balance could shift as the planet warms, the report concludes, and the sequestration service provided by the forest biomes "could be lost entirely if the Earth heats up by 2.5C or more".

The assessment says higher temperatures - along with prolonged droughts, more pest invasions, and other environmental stresses - would trigger considerable forest destruction and degradation.

This could create a dangerous feedback loop, it adds, in which damage to forests from climate change would increase global carbon emissions that then exacerbate global warming.

The report's key findings include:

· Droughts are projected to become more intense and frequent in subtropical and southern temperate forests

· Commercial timber plantations are set to become unviable in some areas, but more productive in others

· Climate change could result in "deepening poverty, deteriorating public health, and social conflict" among African forest-dependent communities

The IUFRO assessment will be considered by delegates at the eighth session of the UN Forum on Forests, which has the objective of promoting the "management, conservation and sustainable development of all types of forest".

Co-author Professor Andreas Fischlin from the Swiss Federal Institute of Technology commented: "Even if adaption measures are fully implemented, unmitigated climate change would - during the course of the current century - exceed the adaptive capacity of many forests.

"The fact remains that the only way to ensure that forests do not suffer unprecedented harm is to achieve large reductions in greenhouse gas emissions."

Risk of vibration-induced vascular injuries linked to vibration frequency differences

Such as loss of dexterity

Speaking on April 19 at the Experimental Biology 2009 meeting in New Orleans, Dr. Kristine Krajnak, a team leader in the Engineering and Control Technologies Branch of the Health Effects Laboratory Division of NIOSH in Morgantown, West Virginia, describes results from the first study to directly link the different

physical responses of tissue that occur with exposure to different vibration frequencies with biological mechanisms underlying the development of vascular dysfunction. Her presentation is part of the scientific program of The American Physiological Society.

The study, along with results of other studies conducted by NIOSH, supports the importance of reducing job-related exposure to vibration. Ongoing research is evaluating the effectiveness of anti-vibration devices, such as anti-vibration gloves and tools.

Higher frequency vibrations produced by an electric sander (greater than 100 Hz) are smoother than the slower vibrations of an electric hand drill (approximately 63 Hz) and therefore are less likely to cause users discomfort.

Don't let that fool you into not using protective devices that can reduce your exposure to vibration, she says. The new research study conducted at the National Institute for Occupational Safety and Health (NIOSH) suggests that exposure to high and low frequencies cause different physiological responses, but both may affect the risk of developing vibration-induced peripheral vascular dysfunction.

Of the 1.1 to 1.5 million U.S. workers exposed to hand transmitted vibration on a fairly regular basis, approximately half eventually develop some disorder such as Vibration White Finger, in which a single finger or sometimes the entire hand turns white and numb when exposed to the cold, due to restricted blood flow.

Workers also may experience reductions in tactile sensitivity, grip strength, and/or manual dexterity. Earlier studies have shown that risk goes up with frequency and duration of exposure, although NIOSH studies are underway to determine why certain people appear more susceptible to shorter exposure durations.

Dr. Krajnak's team looked at two aspects of vibration injury about which very little is known: the mechanisms of injury and the differences in response to frequency of vibration. The researchers used rats, since the tissues, nerves and arteries of rat-tails are similar to those in human fingers and the tails are known to respond to vibration in a way similar to that seen in fingers.

For four hours a day (the longest time a human can be exposed to workplace vibration according to U.S. and international standards) for 10 days, 15 rats (five in each group) were placed in a container where their tails were vibrated at either 63, 125 or 250 Hz. One control group of five rats accompanied them to the experimental area, to make sure any results seen were not related to noise or change of locale. A second control group stayed in their home cages, uninvolved in the activity.

After the last exposure, the scientists examined the tail arteries for changes. Neither control group had changes, suggesting the changes seen were directly related to the effects of vibration. The rats that experienced high frequency (125 and 250 Hz) vibration had higher levels of measures of oxidative stress, while rats that experienced the lower frequency (65 Hz) vibration showed higher levels of pro-inflammatory factors.

The changes seen following higher frequency vibration are associated with more immediate changes in the peripheral vascular system, such as those seen in workers with vibration injury, says Dr. Krajnak, but the changes following lower frequency vibration also can lead to vascular problems.

Co-authors of the Experimental Biology presentation are NIOSH biologists Stacey Waugh, Roger Miller, and Claud Johnson, and NIOSH biostatistician Dr. Michael Kashon, all of Morgantown. The research was funded by National Institute of Occupational Safety and Health.

New drug achieves pancreatic cancer tumor remission and prevents recurrence

DENVER – Pancreatic cancer remains one of the deadliest cancers, but researchers may have found a combination therapy to reduce cancer stem cells and stop pancreatic cancer growth. Results will be presented at the American Association for Cancer Research 100th Annual Meeting 2009.

Rajesh Kumar N.V., Ph.D., a faculty member at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, said a combination therapy using tigatuzumab, a novel humanized death receptor-5 (DR-5) agonist antibody, along with gemcitabine, may result in reducing pancreatic cancer stem cells to achieve tumor remission and prevent tumor recurrence.

"Many advanced cancers, including pancreatic cancer, recur and result in patient death despite the use of chemotherapeutic and radiation modalities that initially lead to therapeutic responses," said Kumar. "A growing body of evidence supports the concept that cancer stem cells are the seeds of the most clinically deadly form of therapy-resistant human cancers. Emerging studies show that cancer stem cells are indeed more resistant to therapy than other cancer cells and might be the reason why conventional chemotherapy, while reducing tumor size, does not result in long-term cures."

Kumar and colleagues analyzed the cancer stem cells in ten patient-derived tumors implanted in laboratory mice and found that DR-5 is enriched in cancer stem cells compared to non-stem cell tumor populations. These mice either received tigatuzumab alone; gemcitabine, the current clinical treatment for pancreatic cancer; or a combination of the two agents.

They found that treatment with gemcitabine alone reduced tumor size, but the tumor cells that remained were rich in pancreatic cancer stem cells. In nearly all cases, the tumors returned.

However, treatment with gemcitabine and tigatuzumab resulted in the reduction of pancreatic cancer stem cells, caused tumor remission, and significantly increased time-to-tumor progression in 50 percent of treated cases from a median of 54 days to 103 days.

From a clinical standpoint, targeting cancer-sustaining pancreatic cancer stem cells will be of paramount significance since there are few effective therapies for pancreatic cancer and most of the patients die within the first year of diagnosis. "Clinically, this discovery could transform the way in which pancreatic cancer is treated and contribute towards making pancreatic cancer a more manageable disease," said Kumar.

Clouds: Lighter than air but laden with lead

Atmospheric lead causes clouds to form more easily, could change pattern of rain and snow

RICHLAND, Wash. -- By sampling clouds -- and making their own -- researchers have shown for the first time a direct relation between lead in the sky and the formation of ice crystals that foster clouds. The results suggest that lead generated by human activities causes clouds to form at warmer temperatures and with less water. This could alter the pattern of both rain and snow in a warmer world.

The lead-laden clouds come with a silver lining, however. Under some conditions, these clouds let more of the earth's heat waft back into space, cooling the world slightly. Atmospheric lead primarily comes from human sources such as coal.

The international team of researchers reported their results in the May issue of Nature Geoscience. The collaboration included researchers from institutions in the United States, Switzerland and Germany.

"We know that the vast majority of lead in the atmosphere comes from man-made sources," said atmospheric chemist Dan Cziczo of the Department of Energy's Pacific Northwest National Laboratory and study author. "And now we show that the lead is changing the properties of clouds and therefore the balance of the sun's energy that affects our atmosphere."

Globe Trotting for Lead

Scientists first attempted to goad rain from the sky with silver and lead iodide in the 1940s. Since then, researchers have known that lead can pump up the ice crystals in clouds. But daily human activities also add lead to the atmosphere. The top sources include coal burning, small airplanes flying at the altitude where clouds form, and construction or wind freeing lead from the ground. Cziczo and colleagues wanted to know how lead from these sources affects clouds.

To find out, the researchers collected air from high atop a mountain peak on the Colorado-Wyoming border. In their high altitude lab, they created artificial clouds from the air in a cloud chamber about the size of a small refrigerator. Half of the ice crystals they plucked from the synthetic clouds, they found, contained lead.

The team then collected a dollop of real cloud atop a mountain in Switzerland. About half of those ice crystals also contained lead. But finding lead in an incriminating position doesn't mean it causes ice crystals.

To determine whether lead causes ice crystals and clouds to form, the team turned to a lab in Germany that houses a cloud chamber three stories tall, as well as a smaller chamber in Switzerland. They created dust particles that were either lead-free or contained one percent lead by weight, which is about what scientists find in the atmosphere. They put these dust particles into the chambers and measured the temperature and humidity at which point ice nucleated around the dust.

They found that lead changed the conditions under which clouds appeared. The air didn't have to be as cold or as heavy with water vapor if lead was present.

"Most of what nucleates clouds are dust particles," said Cziczo. "Half of the ones we looked at had lead supercharging them."

Leaden Clouds, Cooler Climes

To investigate what this might mean for the earth's climate, the researchers simulated the global climate with either lead-free dust particles floating around, or with either 10 percent or all of them containing lead.

The computer simulation showed that the clouds they looked at -- typically high, thin clouds -- formed at lower altitudes and different locations in the northern hemisphere when lead was present in dust particles. This will probably affect precipitation, said Cziczo.

"In our atmosphere, lead affects the distribution and density of the kinds of clouds we looked at," said Cziczo, "which might then affect where and when rain and snow fall."

Clouds at lower altitudes let more of the earth's heat, or so-called longwave radiation, escape out to space. So lead-triggered clouds could partly offset global warming due to greenhouse gases.

But that doesn't mean lead in the atmosphere will simply cool the planet, said Cziczo, since they looked at only one type of cloud. Cloudy skies are far more complicated than their wispy image lets on.

"This work highlights how complex these interactions between lead and water vapor and temperature are," said Cziczo. "They're not as simple as greenhouse gases."

Future work will look at the type of lead and how much is needed to affect clouds and precipitation, as well as the atmospheric distribution of the metal dust.

Reference: D. J. Cziczo, O. Stetzer, A. Worringen, M. Ebert, S. Weinbruch, M. Kamphus, S. J. Gallavardin, J. Curtius, S. Borrmann, K. D. Froyd, S. Mertes, O. Möhler and U. Lohmann, Inadvertent Climate Modification Due to Anthropogenic Lead, Nature Geoscience, May 2009, DOI 10.1038/NGEO499 (http://www.nature.com/ngeo/index.html).

This research was supported by the Atmospheric Composition Change the European Network for Excellence, ETH Zurich, the German Research Foundation, and Pacific Northwest National Laboratory directed research funding.

An herbal extract inhibits the development of pancreatic cancer

PHILADELPHIA An herb recently found to kill pancreatic cancer cells also appears to inhibit development of pancreatic cancer as a result of its anti-inflammatory properties, according to researchers from the Kimmel Cancer Center at Jefferson. The data were presented at the AACR 100th Annual Meeting 2009 in Denver. (Abstract #494)

Thymoquinone, the major constituent of the oil extract from a Middle Eastern herbal seed called Nigella sativa, exhibited anti-inflammatory properties that reduced the release of inflammatory mediators in pancreatic cancer cells, according to Hwyda Arafat, M.D., Ph.D., associate professor of Surgery at the Jefferson Medical College of Thomas Jefferson University and a member of the Jefferson Pancreatic, Biliary & Related Cancers Center.

Nigella sativa seeds and oil are used in traditional medicine by many Middle Eastern and Asian countries. It helps treat a broad array of diseases, including some immune and inflammatory disorders, Dr. Arafat said. Previous studies have also shown it to have anti-cancer effects on prostate and colon cancers.

Based upon their previously published findings that thymoquinone inhibits histone deacetylases (HDACs), Dr. Arafat and her colleagues compared the anti-inflammatory properties of thymoquinone and trichostatin A, an HDAC inhibitor that has previously shown to ameliorate inflammation-associated cancers.

The researchers used pancreatic ductal adenocarcinoma (PDA) cells, some of which were pretreated with the cytokine TNF-alpha to induce inflammation. Thymoquinone almost completely abolished the expression of several inflammatory cytokines, including TNF-alpha, interleukin-1beta, interleukin-8, Cox-2 and MCP-1, an effect that was more superior to the effect of trichostatin A.

The herb also inhibited the activation and synthesis of NF-kappaB, a transcription factor that has been implicated in inflammation-associated cancer. Activation of NF-kappaB has been observed in pancreatic cancer and may be a factor in pancreatic cancer's resistance to chemotherapeutic agents. When animal models of pancreatic cancer were treated with thymoquinone, 67 percent of the tumors were significantly shrunken, and the levels of proinflammatory cytokines in the tumors were significantly reduced.

Inflammation has been implicated in the development of several solid tumor malignancies. Chronic pancreatitis, both hereditary and sporadic, is associated with the risk of developing pancreatic cancer.

"These are very exciting and novel results," Dr. Arafat said. "Not only patients with chronic pancreatitis could benefit from this, but also several other groups with risk of development or recurrence of pancreatic cancer, such as high-risk family members and post-surgical patients. These potent effects show promise for the herb as a potential preventive and therapeutic strategy for pancreatic cancer. More importantly, the herb and oil are safe when used moderately, and have been used for thousands of years without reported toxic effects."

Pancreatic cancer is the fourth leading cause of cancer death in the United States, with approximately 32,000 deaths a year. Only five percent of individuals with pancreatic cancer live for at least one year after diagnosis.

MI5 set to recruit science chief

By Pallab Ghosh Science correspondent, BBC News

MI5 is to appoint a chief scientific adviser, BBC News has learned. The role will involve working with senior intelligence staff to combat terrorism and support counter-intelligence operations.

The advert on MI5's website says candidates will need to have world-class scientific expertise and outstanding communication skills.

MI5 is the more common name for the Security Service, the UK's domestic intelligence agency.

The successful candidate will be "leading and co-ordinating the scientific work of the Security Service", the ad says. The UK government's chief scientific adviser, Professor John Beddington, told BBC News: "There is a really important role in providing scientific and technological advice on addressing problems agents in the field will face.

"[The chief science adviser] has a role to frustrate terrorism to prevent espionage hurting the UK, protect our critical national infrastructure and to frustrate the proliferation of weapons of mass destruction.

"There's an enormous amount of scientific content in this role."

Dr Sally Leivesley, from security consultancy New Risk, told BBC News: "The appointment of a chief scientific adviser is an acknowledgement of the emerging threat of chemical, biological and radiological attack by terrorists and also the security threat to computer systems," she said.

"A chief scientist for MI5 will change Britain's capability to manage terror attacks."

Dr Leivesley believes that the chief scientist would also be an important point of contact for experts in other countries at high risk of terrorist attack, such as the US.

"This means that large science labs around the world can be co-ordinated in the event of an incident," she said.

According to Professor Beddington, the adviser will have to keep up with the latest developments in science and technology - so that British intelligence officers can stay one step ahead of the country's enemies.

"It will involve a sort of future gazing to see where technology will be taking us in a year or so," he explained.

Applications for the job close on April 24.