## How does a dog walk? Surprisingly, many of us don't really know

Despite the fact that most of us see our four-legged friends walking around every day, most of us-including many experts in natural history museums and illustrators for veterinary anatomy text books-apparently still don't know how they do it. A new study published in the January 27th issue of Current Biology, a Cell Press publication, shows that anatomists, taxidermists, and toy designers get the walking gait of horses and other quadruped animals wrong about half the time. That's despite the fact that their correct walking behavior was described and published more than 120 years ago.

"Our key finding is that the chance to find erroneous depictions of quadruped walking in our surrounding environment is about 50 percent, which corresponds to nothing else than pure accident," said Gábor Horváth of Eötvös University. "This was quite unexpected because the experts of animal locomotion have known well the characteristics of quadruped walking ever since the famous and pioneering work of Eadweard Muybridge, published in the 1880s."

So, then, how do they walk? It turns out that all four-legged animals step with their left hind leg followed by their left foreleg. Then they step with their right hind leg followed by the right foreleg, and so on. Animals differ from one another only in the timing of that stepping.

The reason that manner of walking is so universal, Horváth said, is that it provides the maximum static stability. In other words, when walking slowly, a horse's or dog's body is supported at all times by three feet on the ground, which form a triangle. The closer their center of mass is to the center of those three points, the more stable they will be.

Horváth and his colleagues suspect this is so often depicted incorrectly in part due to carelessness. Others probably don't know how the four-legged creatures among us walk, and some likely copy previous illustrations or models, which themselves are wrong.

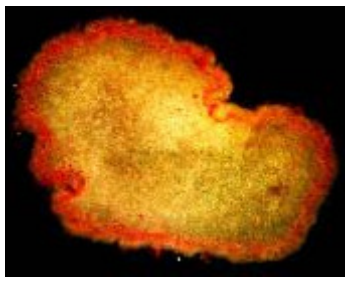
In the case of children's toys, such an error might not be such a big deal, he added. However, model horses-often depicted mid-step-would fall over less if they were presented according to the correct footfall formula. In natural history museums and anatomy textbooks, though, scientific correctness should be a requirement. Horváth did note one major exception that he says proves the rule: Hollywood movies such as Jurassic Park and The Lord of the Rings generally do get the walking of dinosaurs, elephants, and other fantastic, four-legged creatures just right. That's because they often rely behind the scenes on experts in biomechanics and animal locomotion.

*The authors include Gábor Horváth, Eötvös University, Physical Institute, Budapest, Hungary; Adelinda Csapó, Eötvös University, Physical Institute, Budapest, Hungary; Annamária Nyeste, Eötvös University, Physical Institute, Budapest, Hungary; Balázs Gerics, Szent István University, Budapest, Hungary; Gábor Csorba, Hungarian Natural History Museum, Budapest, Hungary; and György Kriska, Eötvös University, Physical Institute, Budapest, Hungary.*

## Move over, sponges

### *New evidence confirms Placozoans are the closest living surrogate to the ancestor of all animals*

A new and comprehensive analysis confirms that the evolutionary relationships among animals are not as simple as previously thought. The traditional idea that animal evolution has followed a trajectory from simple to complex - from sponge to chordate - meets a dramatic exception in the metazoan tree of life. New work suggests that the so-called "lower" metazoans (including Placozoa, corals, and jellyfish) evolved in parallel to "higher" animals (all other metazoans, from flatworms to chordates). It also appears that Placozoans - large amoeba-shaped, multi-cellular animals - have passed over sponges and other organisms as an animal that most closely mirrors the root of this tree of life.



***This is a Trichoplax*. W. Jakob**

"To make inferences about the origin of Bilaterians - animals with a bilateral symmetry, like humans - earlier studies suggested sponges, ctenophores (comb jellies), or a small, interesting group called Placozoa as the most basal or primitive animal," says senior author Rob DeSalle, Curator at the Sackler Institute for Comparative Genomics at the American Museum of Natural History. "But our new analysis implies that the first major event in animal evolution split bilateral animals from all others, and our work firmly places Placozoa as the most primitive of the nonbilaterian animals."

Placozoans were discovered just over 100 years ago, gliding along the glass in laboratory aquariums. Placozoans are simple animals that lack a nervous system and have only four kinds of somatic cells. Because they have never been studied in their oceanic home, however, further characterization of this group has been problematic. The genome of the placozoan species Trichoplax adharens was sequenced in the middle of 2008 by the Trichoplax Genome Consortium team, which was initiated by first author Bernd Schierwater, Director of

ITZ, Ecology and Evolution, Tierärztliche Hochschule Hannover in Germany and a research associate at the Museum.

While several previous studies placed Placozoans at the base of the animal tree of life, these results attracted little attention. The current research may provide the final word, since the number of traits considered was very large and the resulting phylogeny was supported very strongly. Researchers lumped data from many different sources, including mitochondrial and nuclear DNA sequences and information about the morphological structure of RNA molecules, to find over 9,400 variable characters that contain parsimony information - the shared, derived traits that help biologists infer the tree of life, or phylogeny.

The phylogeny drawn from the new analysis places Placozoans as basal within the Diptoblasta, a group of animals that includes sponges, comb jellies, jellyfish, corals, and anemones. This means that sponges and comb jellies, both previously considered candidates for the most basal animal, fall within the clade as more derived than Placozoans and as sister taxa to each other. Study results also identify a very deep division between the Diptoblasta and the Bilateria/Triploblasta: when looking at all animals, scientists now see that Placozoans and their relatives are in a separate lineage from all other metazoans (starfish, bivalves, anthropoids, crustaceans and chordates). This means that the nervous system, once thought to have arisen once, must have evolved twice from the DNA that coded for these complex systems (keeping in mind that while Placozoans and sponges do not have nervous systems, many of the taxa related to them do.)


***This is a new metazoan tree of life presented in Schierwater, et al. 2009.*** **AMNH**

"Some people might initially be shocked to see that nerve cells in cnidarians and higher animals (Bilateria), the group of animals that includes humans, evolved independently," says Schierwater. "But with this new phylogeny, we can take a closer look at the anatomy of these organisms - and we can see that their nervous systems are not all that similar at the morphological level after all."

DeSalle agrees. "It is the underlying genetic tool kit that is similar amongst these basal animals. Placozoa have all of the tools in their genome to make a nervous system, but they just don't do it."

*The new research paper is published in PLoS Biology. Schierwater and several other authors from Tierärztliche Hochschule Hannover in Germany (Michael Eitel, Wolfgang Jakob, Hans-Jürgen Osigus, and Heike Hadrys) and Yale University (Stephen Dellaporta) collected data for the analysis. DeSalle and Sergios-Orestis Kolokotronis, also of the Sackler Institute at the Museum, performed the phylogenetic analyses. Research was funded by many sources, including the Deutsch Forschungsgemeinschaft, Lower Saxony Graduate Program, the Human Frontier Science Program, the Lewis B. and Dorothy Cullman Program in Molecular Systematics at the Sackler Institute at AMNH, and the Alfred P. Sloan Foundation.*

## Aspirin can prevent liver damage that afflicts millions, Yale study finds

Simple aspirin may prevent liver damage in millions of people suffering from side effects of common drugs, alcohol abuse, and obesity-related liver disease, a new Yale University study suggests.

The study in the January 26 edition of Journal of Clinical Investigation documents that in mice, aspirin reduced mortality caused by an overdose of acetaminophen, best known by the brand name Tylenol. It further showed that a class of molecules known as TLR antagonists, which block receptors known to activate inflammation, have a similar effect as aspirin. Since these agents seem to work by reducing injury-induced inflammation, the results suggest aspirin may help prevent and treat liver damage from a host of non-infectious causes, said Wajahat Mehal, M.D., of the Section of Digestive Diseases and Department of Immunobiology at Yale School of Medicine.

"Many agents such as drugs and alcohol cause liver damage, and we have found two ways to block a central pathway responsible for such liver injury," Mehal said. "Our strategy is to use aspirin on a daily basis to prevent liver injury, but if it occurs, to use TLR antagonists to treat it."

Promising drugs that have failed clinical trials because of liver toxicity might be resurrected if combined with aspirin, Mehal said. "This offers the exciting possibility of reducing a lot of pain and suffering in patients with liver diseases, using a new and very practical approach," Mehal said.

*Other researchers from Yale who contributed to this study are Avlin Imaeda, Azuma Watanabe, Adnan Sohail, Shamail Mahmood, Mehdi Mohamadnejad, Fayyaz Sutterwala, and Richard Flavell.*

*The National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health, the Ellison Foundation, and the Howard Hughes Medical Institute funded the study.*
*Citation: Journal of Clinical Investigation, Jan. 26, 2009*

## Unmasked and vulnerable

### *World-first clinical trial shows mask-wearing significantly boosts flu protection*

Donning a face mask is an easy way to boost protection from severe respiratory illnesses such as influenza and SARS, new research from the University of New South Wales (UNSW) has found, but convincing a reluctant public and health workers is proving a struggle.

In a world-first clinical trial of the efficacy of masks, researchers found adult mask wearers* in the home were four times more likely than non-wearers to be protected against respiratory viruses, including the common cold.

The findings – published this week in Emerging Infectious Diseases, the journal of the US Centres for Disease Control and Prevention – have global implications and are particularly relevant to efforts to combat the spread of flu pandemics and other emerging respiratory diseases such as SARS.

"In the event of a severe pandemic, demand for protection could become a law and order issue," said lead author of the paper, Raina MacIntyre, who is Professor of Infectious Diseases Epidemiology and head of UNSW's School of Public Health and Community Medicine.

"In a crisis, vaccine development is likely to be delayed and drugs may be in short supply or not available at all," she said. "Limited supplies will be directed first to front line health workers, so masks are an important means of protection for the community, who otherwise may be last in line for vaccines and drugs."

While some governments are already stockpiling masks for use in emergencies, Professor MacIntyre said these guidelines had been implemented without evidence to support them.

"We now have provided that evidence. Masks play an important role in reducing transmission if they are worn properly." At a day-to-day level, the study is also good news for parents of toddlers and young children.

"There is no effective treatment for the 90 or so common cold viruses that make families sick each winter, but masks could provide simple and effective protection," Professor MacIntyre said.

Commissioned and funded by the Australian Department of Health and Ageing in response to an urgent policy need, the study is the first randomised controlled clinical trial of masks to be conducted internationally. Researchers at UNSW, Sydney's Westmead Hospital, Imperial College (London) and the National Centre for Immunisation Research studied more than 280 adults in 143 families in Sydney during the winter seasons of 2006 and 2007. The adults were randomly allocated masks when exposed to a sick child in the household.

Professor MacIntyre said a drawback was participants' low compliance, with less than half reporting having worn the masks often or always. However, adherence to preventative measures is known to vary depending on perception of risk and would be expected to increase during a pandemic.

The next pressing research question is the value of the use of masks among health care workers. Preliminary work in Australia in 2007 showed very low acceptance of and compliance with mask use by hospital doctors and nurses.

Professor MacIntyre and her team, along with the Beijing Centers for Disease Control and Prevention, are now running a large trial of masks in close to 2,000 health care workers in more than 20 hospitals in China, where compliance with masks is much greater. "Results from this trial could have wide implications for not only pandemic influenza, but a range of communicable diseases spread within hospitals,' Professor MacIntyre said.

***both surgical and non-fit-tested P2 masks.***

## 'Great speciators' explained: It's intrinsic

### *White eyes diversify across a hemispheric range faster than any other bird*

New molecular research shows that birds within the family Zosteropidae - named white eyes for the feathers that frame their eyes - form new species at a faster rate than any other known bird. Remarkably, unlike other rapid diversifications, which are generally confined in their geography, white eyes have managed to diversify across multiple continents and far-flung islands spanning much of the eastern hemisphere. The research was published this week in Proceedings of the National Academy of Sciences.

White eyes have long been dubbed "Great Speciators" for their apparent ability to rapidly form new species across geographies where other birds show little or no diversification. The idea has been gestating for nearly 80 years, since Ernst Mayr and Jared Diamond coined the term after encountering white eyes in the Solomon Islands. Each island they visited had distinct white eye species, whereas most other birds varied little from island to island. Thirty years ago, Mayr and Diamond could only guess at an answer, but both thought that some intrinsic trait was driving the extreme patterns observed among the white eyes.

"Their idea was spot on," says Christopher Filardi, Biodiversity Scientist for the Pacific Programs at the Center for Biodiversity and Conservation at the American Museum of Natural History. "There's something

special about these birds. White eyes quickly diverge into new species across water gaps as narrow as a couple of kilometers - gaps that other birds easily bridge to maintain gene flow."
The new research paper demonstrates just how quickly white eyes can diversify. For a glimpse into key aspects of the white eye's evolutionary history, Filardi collaborated with Rob Moyle (University of Kansas), Catherine Smith (Missoula, Montana), and hypothesis originator Jared Diamond (currently at the University of California at Los Angeles). Looking at both nuclear and mitochondrial DNA, the team found that most of the 100-plus species in the Zosteropidae evolved very recently, even though the group is spread from Asia to Africa and into Oceania. The family emerged as a group between 4.46 and 5.57 million years ago, and the Zosterops genus (with about 80 species) exploded into a large number of species within the last 2 million years. The team calculated a rate of diversification in Zosterops and found that this genus has the fastest known rate among birds: between 2.24 and 3.16 species per million years.

***The Splendid White-eye (Zosterops splendidus) is found only on the tiny island of Ranongga is one of seven species endemic to islands of the New Georgia Group, Solomon Islands. This species was among the original 'great speciators' described by Mayr and Diamond in PNAS over 30 years ago.*** **C. Filardi/CBC-AMNH**

"As we started to compile the data, we were shocked," says Moyle, Assistant Professor and Assistant Curator at the University of Kansas. "White eye species from across the family's range had strikingly similar genetics, indicating a recent origin and incredibly rapid diversification."

To put these results in perspective, only a few vertebrates in the world, such as the cichlid fishes found in lakes of the African Rift Valley, exceed this rate of diversification. But while cichlid diversification can be explained by climate shifts and geological changes within their narrow geographic range, rapid speciation among white eyes cannot be linked to environmental factors because of their recent hemispheric spread. In their paper, the team supports the classical "Great

Speciator" hypothesis and suggests that intrinsic traits of white eyes drive the system. These traits include sociability, the ability to survive in a variety of habitats, and a short time between generations relative to other birds. Some species may also have become more sedentary over the course of evolution, similar to historically dispersive human populations that "settled down," minimizing further dispersal and gene flow. The team concludes that the new genetic data sheds light on the paradoxical ability of some organisms to rapidly form new species while simultaneously dispersing over large geographic distances.
"I am delighted to see this molecular evidence supporting ideas that I had only been able to guess at over the last several decades," says Diamond, a professor of the Geography Department at UCLA. "I know that Ernst Mayr, if he had still been alive, would have been delighted at this confirmation 78 years after he visited the Solomons."

Filardi adds, "This leaves the question: are the white eyes really special, or have we simply caught them at a special time in their evolution? That we don't know, but our results indicate that high rates of diversification may have as much to do with a species' 'personality' as they have to do with more classical geographic or geological drivers of speciation."

*The research was funded in part by the National Geographic Society's Committee for Research and Exploration, the F.M. Chapman Memorial Fund and the L.C. and L.J. Stanford Funds of the American Museum of Natural History, the University of Kansas Research Fund, and the University of Washington Burke Museum of Natural History.*

## Statewide study confirms 'paperless' hospitals are better for patients

Results from a large-scale Johns Hopkins study of more than 40 hospitals and 160,000 patients show that when health information technologies replace paper forms and handwritten notes, both hospitals and patients benefit strongly.

"Patients appear safer and hospital bottom lines may improve when health care information is gathered and stored on computers rather than on paper," says senior author Neil R. Powe, M.D., M.P.H. M.B.A, of the Department of Medicine at Johns Hopkins University School of Medicine and director of the Welch Center for Prevention, Epidemiology and Clinical Research.

In the study, published Jan. 26 in the Archives of Internal Medicine. Powe, lead author Ruben Amarasingham, M.D., M.B.A. and colleagues rated clinical information technologies at 41 hospitals in Texas and compared those results with discharge information for 167,233 patients. Amarasingham was a Robert Wood Johnson Clinical Scholar in the Department of Medicine at Johns Hopkins the time the study began.

"Previous studies only told us how well one particular electronic system used by one particular hospital worked," says Amarasingham. "This study gives us a better sense about the general success of paperless systems in a diverse set of community, academic and safety-net hospitals. We were also able to examine the many components contained in a hospital information system."

Results showed that with computerized automation of notes and records, hospitals whose technologies ranked in the top third were associated with a 15 percent decrease in the odds that a patient would die while hospitalized.

"If these results were to hold for all hospitals in the United States, computerizing notes and records might have the potential to save 100,000 lives annually," says Powe.

Similarly, the highest scores for electronic "order entry" systems were linked to a 9 percent and 55 percent decrease in the odds of death from heart attacks and coronary artery bypass procedures respectively.

The highest scores in so-called decision-support systems - computerized clinical information that guides a physician's treatment choices - were associated with a 21 percent decrease in the odds that a patient would develop complications. The researchers also found that hospitals with the highest technology scores in the rating system showed significantly lower patient costs.

The paperless systems ranked by the Hopkins team included electronic notes, previous treatment records, test results, orders for drugs, procedures and blood tests, and decision-support systems that offer up-to-date information on treatment options and drug interactions. To rate the effectiveness of the clinical information technologies, the Hopkins researchers developed a questionnaire for physicians that asked whether an electronic system was in place in their hospitals, whether they knew how to use it and whether they used it consistently. The questionnaire produced numbered scores that allowed the researchers to place hospitals in three groups, highest third, middle third and lowest third.

"Most prior studies did not focus on the success of the interface between technology and health care professionals," says Powe. "Our assessment tool examines that important interface." Prior to its use in Texas, the tool was successfully tested in several pilot studies among hospitals around the country.

Powe says he hopes the results will not only encourage more hospitals to go paperless, but also encourage broad use of this assessment tool to guide hospitals in building better information systems that improve health outcomes.

*Amarasingham is an associate chief of medicine at Parkland Health and Hospital System and assistant professor of medicine at University of Texas Southwestern Medical Center in Dallas. Other researchers who contributed to this study include Marie Diener-West, Ph.D., Darrell Gaskin, Ph.D., and Laura Plantinga, Sc.M., of the Johns Hopkins Bloomberg School of Public Health.*

*On the Web: http://www.hopkinsmedicine.org/welchcenter http://archinte.ama-assn.org*

## Frequent sex and masturbation in 20s and 30s linked to higher prostate cancer risk

### *But study also shows that risks diminish with age, particularly in a man's 50s*

Men who are very sexually active in their twenties and thirties are more likely to develop prostate cancer, especially if they masturbate frequently, according to a study of more than 800 men published in the January issue of BJU International.

However the UK research team also found that frequent sexual activity in a man's forties appears to have little effect and even small levels of activity in a man's fifties could offer protection from the disease. Most of the differences were attributed to masturbation rather than sexual intercourse.

The study, led by the University of Nottingham, looked at the sexual practices of more than 431 men who had been diagnosed with prostate cancer before the age of 60, together with 409 controls.

Men who took part in the study were asked about all aspects of their sex life from their twenties onwards, including how old they were when they became sexually active, how often they masturbated and had intercourse, how many sexual partners they had had and whether they had had any sexually transmitted diseases.

"We were keen to look at the links between sexual activity and younger men as a lot of prostate cancer studies focus on older men as the disease is more prevalent in men over 50" says lead author Dr Polyxeni Dimitropoulou, who is now at the University of Cambridge.

"Hormones appear to play a key role in prostate cancer and it is very common to treat men with therapy to reduce the hormones thought to stimulate the cancer cells. A man's sex drive is also regulated by his hormone levels, so this study examined the theory that having a high sex drive affects the risk of prostate cancer."

The study participants, who were recruited by their family doctors, were asked to fill in a questionnaire about their sexual habits in each decade of their life since their twenties.

All the men with prostate cancer had been diagnosed in their fifties. Most of the men who took part in the study (97%) were white and the majority were currently married (84%) or widowed, separated or divorced (12%).

A number of interesting points came out of the study:

* 59% of the men in both groups said that they had engaged in sexual activity (intercourse or masturbation) 12 times a month or more in their twenties. This fell steadily as they got older, to 48% in their thirties, 28% in their forties and 13% in their fifties.

* 39% of the cancer group had had six female partners or more, compared with 31% of the control group.

* Men with prostate cancer were more likely to have had a sexually transmitted disease than those without prostate cancer.

* More men with prostate cancer fell into the highest frequency groups in each decade when it came to sexual activity (intercourse and masturbation) than men in the control group. 40% of men in the cancer group fell into the highest frequency category in their twenties (20 or more times a month) compared to 32% in the control group. Similar patterns were observed in the men's thirties and forties. By the fifties it had evened out, with 31% in each group falling into the most frequent category (ten or more times a month).

* Men with prostate cancer were also more likely to masturbate frequently than men in the control group, with the greatest difference in the twenties (34% versus 24%) and thirties (41% versus 31%). The differences were less pronounced in their forties (34% versus 28%) and by the fifties the cancer group was slightly lower (25% versus 26%).

"What makes our study stand out from previous research is that we focused on a younger age group than normal and included both intercourse and masturbation at various stages in the participants' lives" says Dr Dimitropoulou.

"Overall we found a significant association between prostate cancer and sexual activity in a man's twenties and between masturbation and prostate cancer in the twenties and thirties. However there was no significant association between sexual activity and prostate cancer in a man's forties.

"A possible explanation for the protective effect that men in their fifties appear to receive from overall sexual activity, and particularly masturbation, is that the release of accumulated toxins during sexual activity reduces the risk of developing cancer in the prostate area. This theory has, however, not been firmly established and further research is necessary."

***Notes to editors***

*Sexual activity and prostate cancer risk in men diagnosed at a younger age. Dimitropoulou et al. BJU International. 103, pp 178-185. (January 2009).*

*Established in 1929, BJU International is published 23 times a year by Wiley-Blackwell and edited by Professor John Fitzpatrick from Mater Misericordiae University Hospital and University College Dublin, Ireland. It provides its international readership with invaluable practical information on all aspects of urology, including original and investigative articles and illustrated surgery. www.bjui.org*

## Scientists Identify Bacteria That Increase Plant Growth

### *Findings have implications for increasing biomass for the production of biofuels*

UPTON, NY - Through work originally designed to remove contaminants from soil, scientists at the U.S. Department of Energy's (DOE) Brookhaven National Laboratory and their Belgium colleagues at Hasselt University have identified plant-associated microbes that can improve plant growth on marginal land. The findings, published in the February 1, 2009 issue of Applied and Environmental Microbiology, may help scientists design strategies for sustainable biofuel production that do not use food crops or agricultural land.

"Biofuels are receiving increased attention as one strategy for addressing the dwindling supplies, high costs, and environmental consequences of fossil fuels," said Brookhaven biologist and lead author Daniel (Niels) van der Lelie, who leads the Lab's biofuels research program. "But competition with agricultural resources is an important socioeconomic concern."

Ethanol produced by fermenting corn, for example, diverts an important food source - and the land it's grown on - for fuel production. A better approach would be to use non-food plants, ideally ones grown on non-agricultural land, for biofuel production.

Van der Lelie's team has experience with plants growing on extremely marginal soil - soil contaminated with heavy metals and other industrial chemicals. In prior research, his group has incorporated the molecular "machinery" used by bacteria that degrade such contaminants into microbes that normally colonize poplar trees, and used the trees to clean up the soil. An added benefit, the scientists observed, was that the microbe-supplemented trees grew faster - even when no contaminants were present.

**Poplar Plants**

"This work led to our current search for bacteria and the metabolic pathways within them that increase biomass and carbon sequestration in poplar trees growing on marginal soils, with the goal of further improving poplar for biofuel production on non-agricultural lands," said co-author Safiyh Taghavi. In the current study, the

scientists isolated bacteria normally resident in poplar and willow roots, which are known as endophytic bacteria, and tested selected strains' abilities to increase poplar growth in a controlled greenhouse environment. They also sequenced the genes from four selected bacterial species and screened them for the production of plant-growth promoting enzymes, hormones, and other metabolic factors that might help explain how the bacteria improve plant growth. "Understanding such microbial-plant interactions may yield ways to further increase biomass," van der Lelie said.

The plants were first washed and surface-sterilized to eliminate the presence of soil bacteria so the scientists could study only the bacteria that lived within the plant tissues – true endophytic bacteria. The plant material was then ground up so the bacterial species could be isolated. Individual strains were then supplemented with a gene for a protein that "glows" under ultraviolet light, and inoculated into the roots of fresh poplar cuttings that had been developing new roots in water. The presence of the endophytic bacteria was confirmed by searching for the glowing protein. Some bacterial species were also tested for their ability to increase the production of roots in the poplar cuttings by being introduced during the rooting process rather than afterward.

**The results**

The scientists identified 78 bacterial endophytes from poplar and willow. Some species had beneficial effects on plant growth, others had no effect, and some resulted in decreased growth. In particular, poplar cuttings inoculated with Enterobacter sp. 638 and Burkholderia cepacia BU72 repeatedly showed the highest increase in biomass production - up to 50 percent - as compared with non-inoculated control plants. Though no other endophyte species showed such dramatic effects, some were effective in promoting growth in particular cultivars of poplar.

In the studies specifically looking at root formation, non-inoculated plants formed roots very slowly. In contrast, plant cuttings that were allowed to root in the presence of selected endophytes grew roots and shoots more quickly.

The analysis of genes and metabolically important gene products from endophytes resulted in the identification of many possible mechanisms that could help these microbes thrive within a plant environment, and potentially affect the growth and development of their plant host. These include the production of plant-growth-promoting hormones by the endophytic bacteria that stimulate the growth of poplar on marginal soils. endophytic bacteria on the surface of a poplar root

The scientists plan to conduct additional studies to further elucidate these mechanisms. "These mechanisms are of prime importance for the use of plants as feedstocks for biofuels and for carbon sequestration through biomass production," van der Lelie said.

*This study was funded by the Office of Biological and Environmental Research within DOE's Office of Science, by Brookhaven's Laboratory Directed Research and Development Fund, and by the Flanders Science Foundation and the Institute for the Promotion of Innovation by Science and Technology in Flanders, both in Belgium.*

## Astronauts on International Space Station lose alarming amounts of hipbone strength

### *UCI study reveals greater rate of bone deterioration than previously thought*

Irvine, Calif., January 26, 2009

Astronauts spending months in space lose significant bone strength, making them increasingly at risk for fractures later in life.

UC Irvine and UC San Francisco led a study evaluating 13 astronauts who spent four to six months on the International Space Station and found that, on average, astronauts' hipbone strength decreased 14 percent. Three astronauts experienced losses of 20 percent to 30 percent, rates comparable to those seen in older women with osteoporosis.

These results alarmed researchers because they revealed a greater rate of bone deterioration than previously measured using less powerful technologies.

"If preventive measures are not taken, some of our astronauts may be at increased risk for age-related fractures decades after their missions," said study leader Joyce Keyak, UCI orthopedic surgery and biomedical engineering professor.

For as long as there have been astronauts, researchers have studied why the microgravitational environment of space makes bones more fragile. While previous studies looked at bone mineral density, this study is the first to specifically evaluate bone strength.

Keyak and her colleagues used a novel computer program she developed over the past 20 years to identify hipbone fracture risk in people with osteoporosis. The study team used this program to analyze structurally the hipbone CT scans of one female and 12 male International Space Center crewmembers.

The decrease in bone strength measured between 0.6 percent and 5.0 percent for each month of service on the station, Keyak said, which was noticeably greater than monthly reductions in bone mineral density of 0.4 percent to 1.8 percent observed in previous studies on the same subjects.

Orthopedic researchers looking into the effects of long-duration spaceflight usually study the hipbone or spine. The hip experiences the greatest rate of bone loss in space, and a hip fracture almost always requires hospitalization and major surgery. It can impair a person's ability to walk unassisted and may cause prolonged or permanent disability or even death. Fractures of the vertebra also have serious consequences, including loss of height, severe back pain and deformity.

*Along with Keyak, Alain K. Koyama, Ying Lu and Thomas F. Lang of UC San Francisco, and Adrian Leblanc of the Universities Space Research Association in Houston participated in the NASA-funded study. Study results appear in the online version of Bone.*

## Common Medication Associated With Cognitive Decline in Elderly

New Haven, Conn. - A study published in Journal of the American Geriatrics Society suggested that the use of certain medications in elderly populations may be associated with cognitive decline. The study examined the effects of exposure to anticholinergic medications, a type of drug used to treat a variety of disorders that include respiratory and gastrointestinal problems, on over 500 relatively healthy men aged 65 years or older with high blood pressure.

Older people often take several drugs to treat multiple health conditions. As some of these drugs also have properties that affect neurotransmitters in the brain that are important to overall brain function, the researchers examined the total effects of all medications taken by the patients, both prescription and over-the-counter, that were believed to affect the function of a particular neurotransmitter, acetylcholine.

The findings show that chronic use of medications with anticholinergic properties may have detrimental effects on memory and the ability to perform daily living tasks, such as shopping and managing finances. Participants showed deficits in both memory and daily function when they took these medications over the course of a year. The degree of memory difficulty and impairment in daily living tasks also increased proportionally to the total amount of drug exposure, based on a rating scale the authors developed to assess anticholinergicity of the drugs.

According to study co-author Dr. Ling Han of the Yale University Department of Internal Medicine, elderly patients may be more vulnerable to these types of medications due to neurological and pharmacokinetical changes related to aging..

"This study extends our previous findings on acute cognitive impairment following recent anticholinergic exposure in older medical inpatients," says Han. "Prescribing for older adults who take multiple prescription and over-the-counter medications requires careful attention to minimize the risk of potential harms of the drugs while maximizing their health benefits."

*This study is published in Journal of the American Geriatrics Society. Media wishing to receive a PDF of this article may contact medicalnews@bos.blackwellpublishing.net*

*To view the abstract for this article, please click here.*

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## Cutting Salt Isn't The Only Way To Reduce Blood Pressure

### *Study Suggests Boosting Potassium is also Effective*

MAYWOOD, Ill. -- Most people know that too much sodium from foods can increase blood pressure.

A new study suggests that people trying to lower their blood pressure should also boost their intake of potassium, which has the opposite effect to sodium.

Researchers found that the ratio of sodium-to-potassium in subjects' urine was a much stronger predictor of cardiovascular disease than sodium or potassium alone.

"There isn't as much focus on potassium, but potassium seems to be effective in lowering blood pressure and the combination of a higher intake of potassium and lower consumption of sodium seems to be more effective than either on its own in reducing the risk of cardiovascular disease," said Dr. Paul Whelton, senior author of the study in the January 2009 issue of the Archives of Internal Medicine. Whelton is an epidemiologist and president and CEO of Loyola University Health System.

Researchers determined average sodium and potassium intake during two phases of a study known as the Trials of Hypertension Prevention. They collected 24-hour urine samples intermittently during an 18-month period in one trial and during a 36-month period in a second trial. The 2,974 study participants initially aged 30-to-54 and with blood pressure readings just under levels considered high, were followed for 10-15 years to see if they would develop cardiovascular disease. Whelton was national chair of the Trials of Hypertension Prevention.

Those with the highest sodium levels in their urine were 20 percent more likely to suffer strokes, heart attacks or other forms of cardiovascular disease compared with their counterparts with the lowest sodium levels. However this link was not strong enough to be considered statistically significant.

By contrast, participants with the highest sodium-to-potassium ratio in urine were 50 percent more likely to experience cardiovascular disease than those with the lowest sodium-to-potassium ratios. This link was statistically significant.

Most previous studies of the relationship between sodium or potassium and cardiovascular disease have had to rely on people's recall or record of what foods they eat to estimate their level of sodium consumption. This is a less precise measure of sodium intake than urine samples. In addition, many have been cross-sectional rather than follow-up studies. The new study "is a quantum leap in the quality of the data compared to what we have had before," Whelton said.

Whelton was a member of a recent Institute of Medicine panel that set dietary recommendations for salt and potassium. The panel said healthy 19-to-50 year-old adults should consume no more than 2,300 milligrams of sodium per day -- equivalent to one teaspoon of table salt. More than 95 percent of American men and 75 percent of American women in this age range exceed this amount.

To lower blood pressure and blunt the effects of salt, adults should consume 4.7 grams of potassium per day unless they have a clinical condition or medication need that is a contraindication to increased potassium intake. Most American adults aged 31-to-50 consume only about half as much as recommended in the Institute of Medicine report. Changes in diet and physical activity should be under the supervision of a health care professional.

Good potassium sources include fruits, vegetables, dairy foods and fish. Foods that are especially rich in potassium include potatoes and sweet potatoes, fat-free milk and yogurt, tuna, lima beans, bananas, tomato sauce and orange juice. Potassium also is available in supplements.

Whelton is among the nation's top experts on high blood pressure. He has published more than 400 papers on the subject, and has been the principal investigator on more than $100 million of studies funded by the National Institutes of Health.

*Co-authors of the Archives study include Nancy Cook (first author), Julie Buring and Dr. Kathryn Rexrode of Brigham and Women's Hospital; Eva Obarzanek and Dr. Jeffrey Cutler of the National Heart, Lung and Blood Institute; Dr. Lawrence Appel of Johns Hopkins University and Shiriki Kumanyika of the University of Pennsylvania.*

## Male bonding is rife in chimp society too

* 11:10 26 January 2009 **by Ewen Callaway**

Everyone needs a best friend, even chimpanzees. A decade-long study shows that nearly all adult male chimps form enduring social bonds with other males, exchanging back scratches, sharing meat, and generally chumming around.

On average these bonds lasted seven years, says John Mitani, a primatologist at the University of Michigan, who observed chimpanzees in Uganda several months a year for 10 years.

The colony, in the jungles of Kibale National Park, is about three times the size of other chimpanzee populations in Africa, but is no more social than others, he says.

For the study, Mitani spent a block of time recording the interactions of a specific adult male chimp, including every individual he interacted with, while noting grooming behaviour. Females tend to leave their colony once they reach maturity and therefore forge fewer social bonds, Mitani says.

***Adult male chimps form enduring friendships, maintaining them by grooming each other*** **(Image: John Mitani)**

As with human friendship, the strongest bonds seemed to be based on mutual respect. Chimpanzees that groomed each other for roughly equal amounts of times tended to stay friends longer

### Brotherly love

Fraternity also played an important role in chimpanzee friendships, Mitani found. Animals that shared a mother were more likely to form lasting bonds than other pairs. However, chimpanzees with a common father weren't any more likely to become buddies.

Nearly every chimpanzee that Mitani tracked formed at least one long-term social bond, and some had multiple "best friends". Out of 35 males, two never formed close friendships with other adults during the study period. However, both found friendship in a younger, still adolescent brother, Mitani notes.

Exactly why chimpanzees form these stable bonds is unknown, Mitani says. It could be that having a best friend boosts reproductive success or survival somehow. But this will require "staying out there to see who does what with whom, and how often, and counting up the babies," he says.

Joan Silk, a primatologist at the University of California in Los Angeles, notes that chimp friendships aren't so different from the baboon she studies.

Equitable grooming and sisterhood seemed to determine friendships among female baboons in Botswana, she says. "These similarities suggest that there are common principles for building strong bonds which extend across species." *Journal reference: Animal Behaviour (DOI: 10.1016/j.anbehav.2008.11.021)*

## Alcohol stops men being a flop in bed

* 17:45 26 January 2009 **by Ewen Callaway**

Men might want to remember a new rhyme: a drink a day keeps erectile dysfunction away.

Despite traditional views about the effects of booze on male performance, new research suggests that moderate drinking actually protects against impotence in the long term – perhaps for the same reason a glass or two of wine a day cuts the odds of suffering from heart disease.

There is good evidence that excessive drinking can hinder sexual performance after a night out – a phenomenon sometimes called "brewer's droop". The effect has been noted for many years: "[Drink] provokes the desire, but it takes away the performance," Shakespeare reminds us in Macbeth.

But over longer periods, moderate drinking doesn't seem to be linked to erectile dysfunction, says Kew-Kim Chew, an epidemiologist at the University of West Australia in Nedlands, whose team conducted an anonymous postal survey of 1770 West Australian men.

After accounting for differences due to age, smoking and heart disease – all risk factors for ED – Chew and colleagues found that drinkers experienced rates of impotence 25% to 30% below those of teetotallers.

**Heart link**

The study did not examine how alcohol seems to protect against ED, but he thinks antioxidants in some kinds of alcohol play a role. Other studies suggest that both red and white wine protect against heart disease via a similar mechanism.

One theory holds that ED and heart disease are both manifestations of the same disease. Indeed, Chew found that men who suffer from ED are more likely to go onto develop heart disease.

Chew calls for further research on the connection between alcohol, impotence and heart disease. And he says his team's study should not give men a new reason to hit the bottle. "It would be socially irresponsible to say that even a binge drinker can get some benefits."

*Journal reference: Journal of Sexual Medicine (DOI: 10.1111/j.1743-6109.2008.01115.x)*

## Apollo 17 sample helps date Moon

* 17:59 26 January 2009 **by Eugenie Samuel Reich**

A SPECK of the mineral zircon that's older than any yet found on Earth has been recovered from a rock sample brought back by Apollo 17 astronauts. The grain has helped pinpoint the age at which the molten moon solidified.

Lunar zircons were not studied at the time of the Apollo missions because the technology to date them did not exist, says geologist Clive Neal of the University of Notre Dame, Indiana. "It's serendipitous to find this, and really emphasises the [value] of sample returns," he says.

Until now, the zircon found in lunar rocks was between 3.90 and 4.35 billion years old, the same as the oldest zircon found on Earth. But many of these lunar grains came from low-lying areas on the moon, where the crust had been resurfaced after being melted by meteorite impacts.

The new sample, found by Alexander Nemchin at Curtin University of Technology in Perth, Australia, and colleagues, is 4.42 billion years old, and came from the lunar highlands. That means it crystallised after the crust first solidified, within 100 million years of the moon's formation (Nature Geoscience, DOI: 10.1038/NGEO417).

The grain sets limits on the moon's age, says Dianne Taylor of the University of California, Los Angeles, who has studied similar samples. The moon is thought to have formed from debris ejected by a giant impact between Earth and a smaller body between 10 and 100 million years after the formation of the solar system, 4.57 billion years ago. Taylor reckons the lunar crust formed within 90 million years of the impact, which tallies well with the age of the zircon.

Zircons from Earth tell the story of a fast-cooling planet that developed a solid crust within 200 million years of formation from the solar nebula, says John Valley at the University of Wisconsin-Madison, whose group dated the oldest terrestrial samples. "It's reasonable that there would be something older from the moon than on Earth," he says, because the smaller moon cooled more quickly after the colossal impact.

## Billion-year revision of plant evolution timeline may stem from discovery of lignin in seaweed

Land plants' ability to sprout upward through the air, unsupported except by their own woody tissues, has long been considered one of the characteristics separating them from aquatic plants, which rely on water to support them.

Now lignin, one of the chemical underpinnings vital to the self-supporting nature of land plants – and thought unique to them – has been found in marine algae by a team of researchers including scientists at UBC and Stanford University.

Lignin, a principal component of wood, is a glue-like substance that helps fortify cell walls and is instrumental in the transport of water in many plants.

In a study published in today's issue of the journal Current Biology, lead author Patrick Martone and colleagues describe using powerful chemical and microscopic anatomy techniques to identify and localize lignin within cell walls of a red alga that thrives along the wave-swept California coast. Martone conducted the work described in the paper while a graduate student and postdoctoral researcher in the laboratory of co-author Mark Denny, Professor of Biology at Stanford's Hopkins Marine Station.

"All land plants evolved from aquatic green algae and scientists have long believed that lignin evolved after plants took to land as a mechanical adaptation for stabilizing upright growth and transporting water from the root," says Martone, an assistant professor in the UBC Dept. of Botany, where he is continuing his work on lignin. “Because red and green algae likely diverged more than a billion years ago, the discovery of lignin in red algae suggests that the basic machinery for producing lignin may have existed long before algae moved to land."

Alternatively, algae and land plants may have evolved the identical compound independently, after they diverged. "The pathways, enzymes and genes that go into making this stuff are pretty complicated, so to come up with all those separately would be really, really amazing," says Denny. "Anything is possible, but that would be one hell of a coincidence."

The team's finding provides a new perspective on the early evolution of lignified support tissues – such as wood - on land, since the seaweed tissues that are most stressed by waves crashing on shore appear to contain the most lignin, possibly contributing to mechanical support, says Martone.

The new discovery may affect one of the ways land plants are distinguished from aquatic algae in textbooks - by the presence of lignin. It is also of interest to biofuel researchers since lignin binds cell walls and prevents the extraction of cellulose, a key component in biofuel production.

Funded primarily by the U.S. National Science Foundation and the U.S. Department of Energy, Martone says the research team has started looking for billion-year-old lignin genes that might be shared among land plants and red algae, and has started exploring whether lignin exists in other aquatic algae and what role it plays in the evolution and function of aquatic plants.

*NB: Photos of the red seaweed are available at www.publicaffairs.ubc.ca/download.*
*The full study is available online at http://www.cell.com/current-biology/abstract/S0960-9822(08)01687-4.*

## New twist on old medical technology may prevent amputations

### *Infection now widespread among soldiers wounded in Iraq and Afghanistan*

Old technologies, bone cement and a well known antibiotic, may effectively fight an emerging infection in soldiers with compound bone fractures, according to a study published online today in the Journal of Orthopedic Research. An urgent search for solutions is underway as 20,000 additional American soldiers head for Afghanistan, and as evidence emerges that the infection studied may set the stage for more dangerous infections that can lead to amputation.

Osteomyelitis is (OM) a bone infection caused by various bacteria, and usually occurs in severe fractures when bone is exposed to open air. Although Acinetobacter baumannii rarely causes OM in the United States, it is very prevalent in the Middle East, and is now present in more than 30 percent of soldiers recovering from open fractures in field hospitals in Iraq and Afghanistan. Past studies have established that one in four severe war wounds in Iraq is a fracture, more than 80 percent of which are open, where the bone is exposed to airborne bacteria.

Not common in the United States and not potentially fatal, A. baumannii OM had been largely ignored until recently by physicians and the pharmaceutical industry, which focuses on life-threatening infections that affect millions, not hundreds. Then military outbreaks of the infection started among American soldiers returning from Iraq in 2003, with the number of A. baumannii OM infections seen in field hospitals, and in stateside facilities receiving injured soldiers, growing. At the same time, data began to emerge from hospitals treating soldiers suggesting that easily contracted A. baumannii may be arriving first at the fracture site and "priming" it

so that it becomes more vulnerable to methicillin-resistant Staphylococcus aureus (MRSA), which recently surpassed HIV as the most deadly pathogen in the United States despite nearly universal use of the best available antibiotics.

"If you apply the findings from two small studies to the entire U.S. military, which is a leap, perhaps 2,000 soldiers come into field hospitals with compound fractures each year that become infected with A. baumannii," said Edward Schwarz, Ph.D., professor of Orthopaedics within the Center for Musculoskeletal Research at the University of Rochester Medical Center. "About a third of them go on to get a staph infection after they reach the hospital, with about a third of those, perhaps 200 soldiers, suffering infectious complications that could cost them a limb. Studies already underway in our lab seek to clarify how the initial infections could gradually be replaced by catastrophic MRSA, and to prove that we can save limbs by putting an established antibiotic into bone cement for the first time."

Current antibiotics often kill a strain of bacteria responsible for a disease, only to create a vacuum quickly filled by related strains. The widespread overprescribing of antibiotics and the speed of bacterial evolution have greatly increased the likelihood that the strains most able to resist antibiotics will thrive. Multi-drug resistant (MDR) bacterial strains are now widespread in all hospitals.

MDR strains tend to cluster in hospitals, where patients may pass the infection to each other no matter how sterile the environment, although the exact cause is not known. Multi-drug resistant Acinetobacter baumannii (MDRAB) infections is oftentimes treated with an older class of drugs known as polymyxins, including colistin, one of the last-resort antibiotics for multidrug resistant A. baumannii. Approaches commonly used to overcome MDR infections after orthopaedic injuries include applying a large dose of antibiotic locally to the site of infection via bone cement. Bone cements composed of Plexiglas (polymethyl methacrylate or PMMA) have been used for decades for plastic surgery, to anchor in bone prostheses and to fill in holes in bone caused by trauma. Such materials became even more useful when researchers realized decades ago that they could load them with antibiotics to deliver large doses of drug directly to the injury site without subjecting the whole body to toxic levels of antibiotic. While bone cements laced antibiotics against staph and strep infections are common (e.g. vancomycin), no group had ever developed a bone cement treatment using colistin against A. baumannii.

To begin the process of providing such a treatment for soldiers, a team of orthopaedic, military and pharmaceutical researchers came together to conduct the current study, the results of which argue for a human clinical trial with colistin-laced bone cement, researchers said. Such a trial would likely proceed within the military medical system, where treatments for maladies suffered specifically by the troops are pursued under military research contracts, which use with the same standard required by the U.S. Food and Drug Administration when approving medications and devices for civilian use.

Schwarz and colleagues developed a group of mice infected with drug resistant A. baumannii strains isolated directly from soldiers wounded in Iran and Afghanistan. The mice were then treated with either colistin by injection, local colistin via PMMA bead bone cement or a bone cement control with no drug. Researchers measured the amount of bacteria in the mice as they responded to treatment with a new test of parC gene activity, a gene known to be present only in A. baumannii. Experiments confirmed that all study mice were infected with the bacteria, and that 75 percent of the strains were resistant to multiple antibiotics. Importantly, the bone cement containing colistin significantly reduced the infection rate such that only 29.2 percent of mice had detectable levels of parC after 19 days ($p < 0.05$ vs. i.m. colistin and placebo). Colistin via injection failed to control the infection and was no better than placebo.

*Along with Schwarz, Daniel Crane, Kirill Gromov, Dan Li, Matthew Hilton and Regis O'Keefe led the study effort within the Center for Musculoskeletal Research in Rochester, along with Kjeld Søballe from the Department of Orthopedics at Aarhus University Hospital in Denmark. Christian Wahnes and Hubert Büchner led the effort within Research & Development with Heraeus Medical GmbH, which donated the colistin for testing. Clinton Murray of the Infectious Disease Service at Brooke Army Medical Center in San Antonio made available to researchers the strains of A. baumannii taken from soldiers. The work was supported by research grants from the U.S. Army Medical Research Acquisition Activity (USAMRAA) Orthopaedic Trauma Research Program, and the National Institutes of Health Public Health Service Awards.*

The team also took the first close look at the effect of A. baumannii and S. aureus osteomyletis on bone biochemistry. When bacteria infect bone, they uncouple delicately balanced biochemical signaling responsible for the recycling of bone to preserve its strength, typically resulting in bone loss (osteolysis) that can be seen as a hole on X-rays. In the current study, researchers found that staph infection did indeed encourage bone breakdown, but were surprised to find that A. baumannii infection did the opposite, encouraging bone formation.

"These findings have implications for clinical care, as imaging technologies that capture unusual bone cell growth may be used to diagnose A. baumannii earlier," Schwarz said.

## Dog owners more likely to share germs with pets by not washing hands than by sleeping with dog

Manhattan, Kan. - Dog owners who sleep with their pet or permit licks on the face are in good company. Surveys show that more than half of owners bond with their pets in these ways.

Research done by a veterinarian at Kansas State University found that these dog owners are no more likely to share the same strains of E coli bacteria with their pets than are other dog owners.

Dr. Kate Stenske, a clinical assistant professor at K-State's College of Veterinary Medicine, studied this association as part of her doctoral research at the University of Tennessee. The research is scheduled to appear in an upcoming issue of the American Journal of Veterinary Research.

***Dog owners are more likely to share germs with pets by not washing hands than by sleeping with their dog, or getting licks on the face*. Kansas State University**

Stenske said the finding that these human-animal bonding behaviors aren't more likely to spread germs is good news because there are physical and psychological benefits of pet ownership.

"I became interested in the topic because there is such a strong bond between dogs and their owners," Stenske said. "If you look at one study, 84 percent of people say their dog is like a child to them."

Stenske said surveys also show that nearly half of all dog owners share food with their dogs, and more than half allow the dog to sleep in the bed and lick them on the face.

"We also know diseases can be shared between dogs and people," Stenske said. "About 75 percent of emerging diseases are zoonotic, meaning they are transferrable between humans and other animals. With these two pieces of knowledge, I wanted to examine the public health aspects of such activities."

Stenske's study centered on E. coli bacteria, which is common in the gastrointestinal tracts of both dogs and humans.

"People have it, dogs have it, and it normally doesn't cause any problems," she said. "But it can acquire genes to make it antibiotic resistant."

The study examined fecal samples from dogs and their owners and looked at the bacteria's DNA fingerprints. Stenske found that 10 percent of dog-human pairs shared the same E. coli strains. She also found that the E. coli had more resistance to common antibiotics than expected, although the owners had more multiple-drug resistant strains than their pets.

"This makes us think that dogs are not likely to spread multiple drug-resistant E. coli to their owners, but perhaps owners may spread them to their dogs," Stenske said. "What we learn from this is that antibiotics really do affect the bacteria within our gastrointestinal tract, and we should only take them when we really need to -- and always finish the entire prescription as directed."

The research showed that bonding behaviors like sharing the bed or allowing licks on the face had no association to an increase in shared E. coli. However, Stenske said the research did show an association between antibiotic-resistant E. coli and owners who didn't wash their hands after petting their dogs or before cooking meals.

"We should use common sense and practice good general hygiene," she said.

Stenske said future research might focus on the relationship between shared E. coli and the behaviors of cat owners. Not only is cat ownership higher than dog ownership in the United States, but cats also interact with people in different ways than dogs, she said.

"We have a lot to learn," Stenske said. "In the meantime, we should continue to own and love our pets because they provide a source of companionship. We also need to make sure we are washing our hands often."

## Names give cows a lotta bottle

A cow with a name produces more milk than one without, scientists at Newcastle University have found.

Drs Catherine Douglas and Peter Rowlinson have shown that by giving a cow a name and treating her as an individual, farmers can increase their annual milk yield by almost 500 pints.

The study, published online today in the academic journal Anthrozoos, found that on farms where each cow was called by her name the overall milk yield was higher than on farms where the cattle were herded as a group.

"Just as people respond better to the personal touch, cows also feel happier and more relaxed if they are given a bit more one-to-one attention," explains Dr Douglas, who works in the School of Agriculture, Food and Rural Development at Newcastle University.

"What our study shows is what many good, caring farmers have long since believed.

"By placing more importance on the individual, such as calling a cow by her name or interacting with the animal more as it grows up, we can not only improve the animal's welfare and her perception of humans, but also increase milk production."

Dairy farmer Dennis Gibb, who co-owns Eachwick Red House Farm outside Newcastle, Northern England, with his brother Richard, says he believes treating every cow as an individual is "vitally important".

"They aren't just our livelihood - they're part of the family," says Dennis. "We love our cows here at Eachwick and every one of them has a name. Collectively we refer to them as 'our ladies' but we know every one of them and each one has her own personality."

*The personal touch - an example of human-animal interaction*

**What the study found**

The Newcastle University study looked at how farmers' attitudes to their cows influences milk production.

Dr Douglas and Dr Rowlinson questioned 516 UK dairy farmers about how they believed humans could affect the productivity, behaviour and welfare of dairy cattle.

Almost half – 46 per cent – said the cows on their farm were called by name. Those that called their cows by name had a 258 litre higher milk yield than those who did not.

Sixty six per cent of farmers said they "knew all the cows in the herd" and 48 per cent agreed that positive human contact was more likely to produce cows with a good milking temperament. Almost 10 per cent said that a fear of humans resulted in a poor milking temperament.

Dr Douglas added: "Our data suggests that on the whole UK dairy farmers regard their cows as intelligent beings capable of experiencing a range of emotions.

"Placing more importance on knowing the individual animals and calling them by name can – at no extra cost to the farmer – also significantly increase milk production."

**Personal Health**

## Babies Know: A Little Dirt Is Good for You

**By JANE E. BRODY**

Ask mothers why babies are constantly picking things up from the floor or ground and putting them in their mouths, and chances are they'll say that it's instinctive - that that's how babies explore the world. But why the mouth, when sight, hearing, touch and even scent are far better at identifying things?

When my young sons were exploring the streets of Brooklyn, I couldn't help but wonder how good crushed rock or dried dog droppings could taste when delicious mashed potatoes were routinely rejected.

Since all instinctive behaviors have an evolutionary advantage or they would not have been retained for millions of years, chances are that this one too has helped us survive as a species. And, indeed, accumulating evidence strongly suggests that eating dirt is good for you.

**Greg Neill**

In studies of what is called the hygiene hypothesis, researchers are concluding that organisms like the millions of bacteria, viruses and especially worms that enter the body along with "dirt" spur the development of a healthy immune system. Several continuing studies suggest that worms may help to redirect an immune system that has gone awry and resulted in autoimmune disorders, allergies and asthma.

These studies, along with epidemiological observations, seem to explain why immune system disorders like multiple sclerosis, Type 1 diabetes, inflammatory bowel disease, asthma and allergies have risen significantly in the United States and other developed countries.

**Training the Immune System**

"What a child is doing when he puts things in his mouth is allowing his immune response to explore his environment," Mary Ruebush, a microbiology and immunology instructor, wrote in her new book, "Why Dirt Is Good" (Kaplan). "Not only does this allow for 'practice' of immune responses, which will be necessary for protection, but it also plays a critical role in teaching the immature immune response what is best ignored."

One leading researcher, Dr. Joel V. Weinstock, the director of gastroenterology and hepatology at Tufts Medical Center in Boston, said in an interview that the immune system at birth "is like an unprogrammed computer. It needs instruction."

He said that public health measures like cleaning up contaminated water and food have saved the lives of countless children, but they "also eliminated exposure to many organisms that are probably good for us."

"Children raised in an ultraclean environment," he added, "are not being exposed to organisms that help them develop appropriate immune regulatory circuits."

Studies he has conducted with Dr. David Elliott, a gastroenterologist and immunologist at the University of Iowa, indicate that intestinal worms, which have been all but eliminated in developed countries, are "likely to be the biggest player" in regulating the immune system to respond appropriately, Dr. Elliott said in an interview. He added that bacterial and viral infections seem to influence the immune system in the same way, but not as forcefully.

Most worms are harmless, especially in well-nourished people, Dr. Weinstock said.

"There are very few diseases that people get from worms," he said. "Humans have adapted to the presence of most of them."

**Worms for Health**

In studies in mice, Dr. Weinstock and Dr. Elliott have used worms to both prevent and reverse autoimmune disease. Dr. Elliott said that in Argentina, researchers found that patients with multiple sclerosis who were infected with the human whipworm had milder cases and fewer flare-ups of their disease over a period of four and a half years. At the University of Wisconsin, Madison, Dr. John Fleming, a neurologist, is testing whether the pig whipworm can temper the effects of multiple sclerosis.

In Gambia, the eradication of worms in some villages led to children's having increased skin reactions to allergens, Dr. Elliott said. And pig whipworms, which reside only briefly in the human intestinal tract, have had "good effects" in treating the inflammatory bowel diseases, Crohn's disease and ulcerative colitis, he said.

How may worms affect the immune system? Dr. Elliott explained that immune regulation is now known to be more complex than scientists thought when the hygiene hypothesis was first introduced by a British epidemiologist, David P. Strachan, in 1989. Dr. Strachan noted an association between large family size and reduced rates of asthma and allergies. Immunologists now recognize a four-point response system of helper T cells: Th 1, Th 2, Th 17 and regulatory T cells. Th 1 inhibits Th 2 and Th 17; Th 2 inhibits Th 1 and Th 17; and regulatory T cells inhibit all three, Dr. Elliott said.

"A lot of inflammatory diseases - multiple sclerosis, Crohn's disease, ulcerative colitis and asthma - are due to the activity of Th 17," he explained. "If you infect mice with worms, Th 17 drops dramatically, and the activity of regulatory T cells is augmented."

In answer to the question, "Are we too clean?" Dr. Elliott said: "Dirtiness comes with a price. But cleanliness comes with a price, too. We're not proposing a return to the germ-filled environment of the 1850s. But if we properly understand how organisms in the environment protect us, maybe we can give a vaccine or mimic their effects with some innocuous stimulus."

**Wash in Moderation**

Dr. Ruebush, the "Why Dirt Is Good" author, does not suggest a return to filth, either. But she correctly points out that bacteria are everywhere: on us, in us and all around us. Most of these micro-organisms cause no problem, and many, like the ones that normally live in the digestive tract and produce life-sustaining nutrients, are essential to good health.

"The typical human probably harbors some 90 trillion microbes," she wrote. "The very fact that you have so many microbes of so many different kinds is what keeps you healthy most of the time."

Dr. Ruebush deplores the current fetish for the hundreds of antibacterial products that convey a false sense of security and may actually foster the development of antibiotic-resistant, disease-causing bacteria. Plain soap and water are all that are needed to become clean, she noted.

"I certainly recommend washing your hands after using the bathroom, before eating, after changing a diaper, before and after handling food," and whenever they're visibly soiled, she wrote. When no running water is available and cleaning hands is essential, she suggests an alcohol-based hand sanitizer.

Dr. Weinstock goes even further. "Children should be allowed to go barefoot in the dirt, play in the dirt, and not have to wash their hands when they come in to eat," he said. He and Dr. Elliott pointed out that children who grow up on farms and are frequently exposed to worms and other organisms from farm animals are much less likely to develop allergies and autoimmune diseases.

Also helpful, he said, is to "let kids have two dogs and a cat," which will expose them to intestinal worms that can promote a healthy immune system.

# Spread of Malaria Feared as Drug Loses Potency

**By THOMAS FULLER**

TASANH, Cambodia - The afflictions of this impoverished nation are on full display in its western corner: the girls for hire outside restaurants, the badly rutted dirt roads and the ubiquitous signs that warn “Danger Mines!”

But what eludes the naked eye is a potentially graver problem, especially for the outside world. The parasite that causes the deadliest form of malaria is showing the first signs of resistance to the best new drug against it.

Combination treatments using artemisinin, an antimalaria drug extracted from a plant used in traditional Chinese medicine, have been hailed in recent years as the biggest hope for eradicating malaria from Africa, where more than 2,000 children die from the disease each day.

Now a series of studies, including one recently published in The New England Journal of Medicine and one due out soon, have cemented a consensus among researchers that artemisinin is losing its potency here and that increased efforts are needed to prevent the drug-resistant malaria from leaving here and spreading across the globe.

“This is something we can’t just slide under the carpet,” said R. Timothy Ziemer, a retired admiral in the United States Navy who heads the President’s Malaria Initiative, the $1.2 billion program started by the Bush administration three years ago to cut malaria deaths in half in the countries affected worst.

Admiral Ziemer met with Thai and Cambodian officials last month to assess the resistance problem, which affects the same drugs used by the malaria initiative in Africa. “We feel that we not only have to beat the drum but shake the cage: guys, this is significant,” he said.

Though the studies show relatively early signs of resistance to artemisinin, the drugs were judged to have failed in only two patients in the recently published study. Even they were eventually cured.

But malaria experts note that several times in the past, this same area around the Thai-Cambodian border appears to have been a starting point for drug-resistant strains of malaria, starting in the 1950s with the drug chloroquine.

Introduced immediately after World War II, chloroquine was considered a miracle cure against falciparum malaria, the deadliest type. But the parasite evolved, the resistant strains spread, and chloroquine is now considered virtually useless against falciparum malaria in many parts of the world, including sub-Saharan Africa. It took decades for this resistance to spread across the world, so by the same token artemisinin-based drugs are almost sure to be useful for many years to come.

To protect against artemisinin resistance, the global health authorities are trying to assure that it is sold only as a combination pill with other antimalaria medicines that linger longer in the blood, mopping up any artemisinin-resistant parasites.

The two most recent tests showing artemisinin resistance were done with pills that had no combination drug. But if resistance spreads, there are no new drugs to take the place of artemisinin-based combinations and no immediate prospects under development. This could spread in any direction; we have to make sure it doesn’t,” said Pascal Ringwald, malaria coordinator at the World Health Organization, who three years ago led a study of drug resistance in Cambodia and is co-author of a coming study on the subject. “We know it’s not yet in Bangladesh,” he said. “It’s not yet in India.”

Scientists have documented how malarial parasites that were resistant to chloroquine in the 1950s spread across Thailand, Burma, India and over to Africa, where a vast majority of the nearly one million annual malaria-related deaths occur.

To prevent a recurrence with artemisinin therapies, the United States has put aside political considerations and approved a malaria monitoring center in military-run Myanmar, formerly Burma. The Bill and Melinda Gates Foundation, one of the largest donors to malaria research, is giving $14 million to the Thai and Cambodian governments to help pay for a containment program.

That program includes efforts to supply the area with mosquito nets, a screening program for everyone living in affected areas and follow-up visits by health workers to assess the effectiveness of the drugs, said Dr. Duong Socheat, director of Cambodia’s National Malaria Center. On the Thai side of the border, the government has “motorcycle microscopists” who take blood samples from villagers and migrant workers, analyze them on the spot and distribute antimalaria drugs. But some experts would like to see an even more aggressive approach.

“Many of us think this should be treated on the same order as SARS,” said Col. Alan J. Magill, a researcher at the Walter Reed Army Institute of Research in Maryland. “This should be a global emergency that is addressed in a global fashion.” SARS, the respiratory disease that spread rapidly through Asia and beyond in 2003, killed more than 700 people.

The falciparum parasite is one of four types of malaria and by far the most virulent. It enters the bloodstream through a mosquito bite, and after incubating about two weeks, it multiplies and takes over red blood cells.

There it causes fever, chills, headaches and nausea, among other symptoms. If untreated, the infected cells can block blood vessels and fatally cut off blood supply to vital organs.

The recent studies show that artemisinin-based drugs are becoming less effective in removing the parasite from the bloodstream. While a few years ago it took the drugs 48 hours to clear the bloodstream of parasites, it now can take 120 hours.

"What our study demonstrates is that therapy for some patients fails - the malaria goes away and comes back," said Lt. Col. Mark M. Fukuda, a United States Army doctor whose study was published in The New England Journal of Medicine in December.

Different regions rely on different artemisinin combinations. The Cambodian government recommends that artemisinin be combined with mefloquine, which was developed by the American military and is known commercially as Lariam. Artemether, a derivative of artemisinin, is often combined with another antimalarial drug, lumefantrine. This was recently judged to be the most effective combination in a study of children in Papua New Guinea. The same combination is also expected to be approved for sale in the United States soon, marketed by Novartis and mainly intended for people traveling overseas or for those who arrive in the United States with malaria.

The mosquito responsible for transmission of malaria is still endemic in the United States. But modern housing, better access to health care and the use of insecticides have virtually eradicated the disease in wealthier countries.

Here in Tasanh, a village 20 miles east of the Thai border, Dr. Fukuda and a team of researchers work in what is euphemistically called a more challenging environment. Tasanh is served by a dirt road and has no running water and no public supply of electricity.

In a small, spartan clinic, Chet Chen, an 18-year-old malaria patient, lies listlessly on an old metal-framed bed next to a sample of his urine in a used water bottle. The male nurse who examines blood samples is out helping to fix the weed whacker, which has broken.

In a small but newer annex to the clinic, Dr. Fukuda and his researchers work in a trilingual environment - Khmer (Cambodian), Thai and English - that sometimes sows confusion.

Americans in the clinic recently chuckled when a Thai researcher described a patient as having a "hot body" - a literal translation of "fever" in Thai, but one that evoked nightclub images.

Dr. Fukuda calls this region of Cambodia the "canary in the coal mine" for drug resistance.

In the past, migrant workers in plantations and gem mines are believed to have helped spread drug-resistant strains westward. A history of civil unrest, counterfeit drugs and a weak and underfinanced government has made it difficult to control malaria. In the case of chloroquine, preventive use of the drug - including putting it in table salt to protect a wide swath of the population - might have actually encouraged resistance to the drug, Dr. Fukuda and others say. It was not until the 1990s that mefloquine, the American army drug, was combined with artemisinin, made from a Chinese herb.

Artemisinin-based combinations turned out to be fast-acting and seemed to slow transmission of the disease, said Dr. John MacArthur, an infectious disease expert with the United States Agency for International Development in Bangkok. Dr. MacArthur and others say resistance to malaria drugs is a natural consequence of widespread use of the drug. "In the case of malaria, it's the Darwinism of the parasite," he said. "It likes to survive."

Still, some researchers remain concerned about sending the wrong message to the public about the efficacy of artemisinin-based drugs.

"This is not the death knell of artemisinin," said Dr. Nicholas White, a malaria expert who is chairman of a joint research program between Oxford University and Mahidol University in Thailand. "The drug still works in Cambodia, maybe not as well as before." But given the history of drug failures here, there appears to be a consensus on the solution. "Get rid of all malaria from Cambodia," Dr. White said. "Eradicate it. Eliminate it."

## The Epidemic That Wasn't

**By SUSAN OKIE**

BALTIMORE - One sister is 14; the other is 9. They are a vibrant pair: the older girl is high-spirited but responsible, a solid student and a devoted helper at home; her sister loves to read and watch cooking shows, and she recently scored well above average on citywide standardized tests.

There would be nothing remarkable about these two happy, normal girls if it were not for their mother's history. Yvette H., now 38, admits that she used cocaine (along with heroin and alcohol) while she was pregnant with each girl. "A drug addict," she now says ruefully, "isn't really concerned about the baby she's carrying."

When the use of crack cocaine became a nationwide epidemic in the 1980s and ’90s, there were widespread fears that prenatal exposure to the drug would produce a generation of severely damaged children. Newspapers carried headlines like “Cocaine: A Vicious Assault on a Child,” “Crack’s Toll Among Babies: A Joyless View” and “Studies: Future Bleak for Crack Babies.”

But now researchers are systematically following children who were exposed to cocaine before birth, and their findings suggest that the encouraging stories of Ms. H.’s daughters are anything but unusual. So far, these scientists say, the long-term effects of such exposure on children’s brain development and behavior appear relatively small.

“Are there differences? Yes,” said Barry M. Lester, a professor of psychiatry at Brown University who directs the Maternal Lifestyle Study, a large federally financed study of children exposed to cocaine in the womb. “Are they reliable and persistent? Yes. Are they big? No.”

Cocaine is undoubtedly bad for the fetus. But experts say its effects are less severe than those of alcohol and are comparable to those of tobacco - two legal substances that are used much more often by pregnant women, despite health warnings.

Surveys by the Department of Health and Human Services in 2006 and 2007 found that 5.2 percent of pregnant women reported using any illicit drug, compared with 11.6 percent for alcohol and 16.4 percent for tobacco.

“The argument is not that it’s O.K. to use cocaine in pregnancy, any more than it’s O.K. to smoke cigarettes in pregnancy,” said Dr. Deborah A. Frank, a pediatrician at Boston University. “Neither drug is good for anybody.”

But cocaine use in pregnancy has been treated as a moral issue rather than a health problem, Dr. Frank said. Pregnant women who use illegal drugs commonly lose custody of their children, and during the 1990s many were prosecuted and jailed.

Cocaine slows fetal growth, and exposed infants tend to be born smaller than unexposed ones, with smaller heads. But as these children grow, brain and body size catch up.

At a scientific conference in November, Dr. Lester presented an analysis of a pool of studies of 14 groups of cocaine-exposed children - 4,419 in all, ranging in age from 4 to 13. The analysis failed to show a statistically significant effect on I.Q. or language development. In the largest of the studies, I.Q. scores of exposed children averaged about 4 points lower at age 7 than those of unexposed children.

In tests that measure specific brain functions, there is evidence that cocaine-exposed children are more likely than others to have difficulty with tasks that require visual attention and “executive function” — the brain’s ability to set priorities and pay selective attention, enabling the child to focus on the task at hand.

Cocaine exposure may also increase the frequency of defiant behavior and poor conduct, according to Dr. Lester’s analysis. There is also some evidence that boys may be more vulnerable than girls to behavior problems.

But experts say these findings are quite subtle and hard to generalize. “Just because it is statistically significant doesn’t mean that it is a huge public health impact,” said Dr. Harolyn M. Belcher, a neurodevelopmental pediatrician who is director of research at the Kennedy Krieger Institute’s Family Center in Baltimore.

And Michael Lewis, a professor of pediatrics and psychiatry at the Robert Wood Johnson Medical School in New Brunswick, N.J., said that in a doctor’s office or a classroom, “you cannot tell” which children were exposed to cocaine before birth.

He added that factors like poor parenting, poverty and stresses like exposure to violence were far more likely to damage a child’s intellectual and emotional development — and by the same token, growing up in a stable household, with parents who do not abuse alcohol or drugs, can do much to ease any harmful effects of prenatal drug exposure.

Possession of crack cocaine, the form of the drug that was widely sold in inner-city, predominantly black neighborhoods, has long been punished with tougher sentences than possession of powdered cocaine, although both forms are identically metabolized by the body and have the same pharmacological effects.

Dr. Frank, the pediatrician in Boston, says cocaine-exposed children are often teased or stigmatized if others are aware of their exposure. If they develop physical symptoms or behavioral problems, doctors or teachers are sometimes too quick to blame the drug exposure and miss the real cause, like illness or abuse.

“Society’s expectations of the children,” she said, “and reaction to the mothers are completely guided not by the toxicity, but by the social meaning” of the drug.

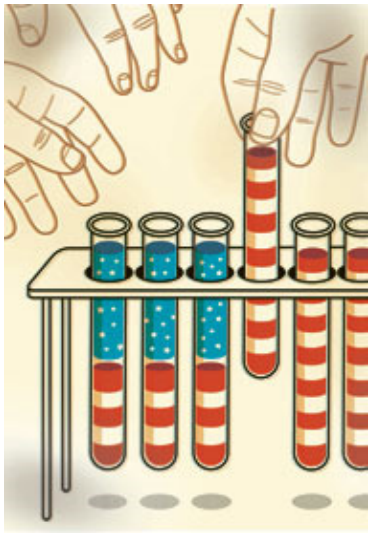
Research on the health effects of illegal drugs, especially on unborn children, is politically loaded. Researchers studying children exposed to cocaine say they struggle to interpret their findings for the public without exaggerating their significance — or minimizing it, either.

Dr. Lester, the leader of the Maternal Lifestyle Study, noted that the evidence for behavioral problems strengthened as the children in his study and others approached adolescence. Researchers in the study are collecting data on 14-year-olds, he said, adding: "Absolutely, we need to continue to follow these kids. For the M.L.S., the main thing we're interested in is whether or not prenatal cocaine exposure predisposes you to early-onset drug use in adolescence" or other mental health problems.

Researchers have long theorized that prenatal exposure to a drug may make it more likely that the child will go on to use it. But so far, such a link has been scientifically reported only in the case of tobacco exposure.

Teasing out the effects of cocaine exposure is complicated by the fact that like Yvette H., almost all of the women in the studies who used cocaine while pregnant were also using other substances.
Moreover, most of the children in the studies are poor, and many have other risk factors known to affect cognitive development and behavior - inadequate health care, substandard schools, unstable family situations and exposure to high levels of lead. Dr. Lester said his group's study was large enough to take such factors into account.

Ms. H., who agreed to be interviewed only on the condition that her last name and her children's first names not be used, said she entered a drug and alcohol treatment program about six years ago, after losing custody of her children.



Another daughter, born after Ms. H. recovered from drug and alcohol abuse, is thriving now at 3. Her oldest, a 17-year-old boy, is the only one with developmental problems: he is autistic. But Ms. H. said she did not use cocaine, alcohol or other substances while pregnant with him.

After 15 months without using drugs or alcohol, Ms. H. regained custody and moved into Dayspring House, a residential program in Baltimore for women recovering from drug abuse, and their children.

There she received psychological counseling, parenting classes, job training and coaching on how to manage her finances. Her youngest attended Head Start, the older children went to local schools and were assigned household chores, and the family learned how to talk about their problems.

Now Ms. H. works at a local grocery, has paid off her debts, has her own house and is actively involved in her children's schooling and health care. She said regaining her children's trust took a long time. "It's something you have to constantly keep working on," she said.

Dr. Belcher, who is president of Dayspring's board of directors, said such programs offered evidence-based interventions for the children of drug abusers that can help minimize the chances of harm from past exposure to cocaine or other drugs.

"I think we can say this is an at-risk group," Dr. Belcher said. "But they have great potential to do well if we can mobilize resources around the family."

**Essay**

## Elevating Science, Elevating Democracy

**By DENNIS OVERBYE**

All right, I was weeping too.

To be honest, the restoration of science was the least of it, but when Barack Obama proclaimed during his Inaugural Address that he would "restore science to its rightful place," you could feel a dark cloud lifting like a sigh from the shoulders of the scientific community in this country.

When the new president went on vowing to harness the sun, the wind and the soil, and to "wield technology's wonders," I felt the glow of a spring sunrise washing my cheeks, and I could almost imagine I heard the music of swords being hammered into plowshares.

Wow. My first reaction was to worry that scientists were now in the awkward position of being expected to save the world. As they say, be careful what you wish for.

My second reaction was to wonder what the "rightful place" of science in our society really is.

The answer, I would argue, is On a Pedestal — but not for the reasons you might think.

Forget about penicillin, digital computers and even the Big Bang, passing fads all of them.

The knock on science from its cultural and religious critics is that it is arrogant and materialistic. It tells us wondrous things about nature and how to manipulate it, but not what we should do with this knowledge and power. The Big Bang doesn't tell us how to live, or whether God loves us, or whether there is any God at all. It

provides scant counsel on same-sex marriage or eating meat. It is silent on the desirability of mutual assured destruction as a strategy for deterring nuclear war.

Einstein seemed to echo this thought when he said, “I have never obtained any ethical values from my scientific work.” Science teaches facts, not values, the story goes.

Worse, not only does it not provide any values of its own, say its detractors, it also undermines the ones we already have, devaluing anything it can’t measure, reducing sunsets to wavelengths and romance to jiggly hormones. It destroys myths and robs the universe of its magic and mystery.

So the story goes.

But this is balderdash. Science is not a monument of received Truth but something that people do to look for truth.

That endeavor, which has transformed the world in the last few centuries, does indeed teach values. Those values, among others, are honesty, doubt, respect for evidence, openness, accountability and tolerance and indeed hunger for opposing points of view. These are the unabashedly pragmatic working principles that guide the buzzing, testing, poking, probing, argumentative, gossiping, gadgety, joking, dreaming and tendentious cloud of activity — the writer and biologist Lewis Thomas once likened it to an anthill — that is slowly and thoroughly penetrating every nook and cranny of the world.

Nobody appeared in a cloud of smoke and taught scientists these virtues. This behavior simply evolved because it worked.

It requires no metaphysical commitment to a God or any conception of human origin or nature to join in this game, just the hypothesis that nature can be interrogated and that nature is the final arbiter. Jews, Catholics, Muslims, atheists, Buddhists and Hindus have all been working side by side building the Large Hadron Collider and its detectors these last few years.

And indeed there is no leader, no grand plan, for this hive. It is in many ways utopian anarchy, a virtual community that lives as much on the Internet and in airport coffee shops as in any one place or time. Or at least it is as utopian as any community largely dependent on government and corporate financing can be.

Arguably science is the most successful human activity of all time. Which is not to say that life within it is always utopian, as several of my colleagues have pointed out in articles about pharmaceutical industry payments to medical researchers.

But nobody was ever sent to prison for espousing the wrong value for the Hubble constant. There is always room for more data to argue over.

So if you’re going to get gooey about something, that’s not so bad.

It is no coincidence that these are the same qualities that make for democracy and that they arose as a collective behavior about the same time that parliamentary democracies were appearing. If there is anything democracy requires and thrives on, it is the willingness to embrace debate and respect one another and the freedom to shun received wisdom. Science and democracy have always been twins.

Today that dynamic is most clearly and perhaps crucially tested in China. As I pondered Mr. Obama’s words, I thought of Xu Liangying, an elderly Chinese physicist and Einstein scholar I met a couple of years ago, who has spent most of his life under house arrest for upholding Einstein’s maxim that there is no science without freedom of speech.

The converse might also be true. The habit of questioning that you learn in physics is invaluable in the rest of society. As Fang Lizhi, Dr. Xu’s fellow dissident whose writings helped spark the 1989 Tiananmen Square demonstrations and who now teaches at the University of Arizona, said in 1985, “Physics is more than a basis for technology; it is a cornerstone of modern thought.”

If we are not practicing good science, we probably aren’t practicing good democracy. And vice versa.

Science and democracy have been the watchwords of Chinese political aspirations for more than a century. When the Communist Party took power it sought to appropriate at least the scientific side of the equation. Here, for example, is what Hu Yaobang, the party’s general secretary, said in 1980. “Science is what it is simply because it can break down fetishes and superstitions and is bold in explorations and because it opposes following the beaten path and dares to destroy outmoded conventions and bad customs.”

Brave words that have yet to be allowed to come true in China. Mr. Hu was purged, and in fact it was to mourn his death that students first began assembling in Tiananmen Square in 1989.

Dr. Fang got in trouble initially because he favored the Big Bang, but that was against Marxist orthodoxy that the universe was infinitely unfolding. Marxism, it might be remembered, was once promoted as a scientific theory, but some subjects were off-limits.

But once you can't talk about one subject, the origin of the universe, for example, sooner or later other subjects are going to be off-limits, like global warming, birth control and abortion, or evolution, the subject of yet another dustup in Texas last week.

There is no democracy in China, and some would argue that despite that nation's vast resources and potential, there will not be vigorous science there either until the Chinese leaders take seriously what Mao proclaimed back in 1955 and then cynically withdrew: Let a hundred flowers bloom, let a hundred schools of thought contend.

In the meantime I look forward to Mr. Obama's cultivation of our own wild and beautiful garden.

## Truck-mounted laser shoots down spy drone

* 11:46 27 January 2009 **by Paul Marks**

Uncrewed aerial vehicles are "revolutionary" technology that America must invest more in. Not the military's view, but that of President Obama in a statement on his defence priorities. But a technology designed to make UAVs history is already showing promise – aerospace firm Boeing reports that their prototype truck-mounted laser has shot down a UAV at a missile range in New Mexico.

Uncrewed aircraft are powerful tools because they remove pilots from harm's way and because they can be built smaller than conventional spy or combat planes, making them harder to knock out of the sky.

UAVs come in all shapes and sizes: from the hand-launched Aerovironment Raven surveillance plane to the small airliner-sized Global Hawk.

***Uncrewed drones have become popular with armed forces around the world and they are tricky to defend against, but a truck-mounted laser that can shoot them down could dilute their usefulness*** **(Image: Boeing)**

**Track and destroy**

The Laser Avenger is an infrared laser with power levels somewhere in the tens of kilowatts range mounted on a Humvee off-road vehicle. It is designed to take down the smaller variety of UAV, which are hardest for conventional air-defence weapons to target.

The power of its laser has been doubled since 2007, when it was shown off destroying a stationary improvised bomb. Now it has tracked three small UAVs – the exact model has not been given - and shot one of them down. The laser tracks an object and holds fire until the target is close enough for it to cause burning with a single blast. Late last year, an airborne laser carried by a modified 747 destroyed its first target, albeit from the ground, using an IR laser in the megawatt range.

Marc Selinger, a Boeing spokesman based in Crystal City, Virginia, won't say at what distance this was achieved, saying it was "an operationally relevant range". The feat is all the more important, he says, because the tracking was achieved against the complex, cluttered visual background of the New Mexico mountains and desert scenery.

**Defence boost**

The Laser Avenger is a modified version of an existing US Army air defence system that uses two Stinger missile launchers and a heavy machine gun, with one missile pod swapped for the laser and its target tracker. "If funded by the Pentagon, the Laser Avenger could be available within a year," says Selinger. Boeing has so far funded the project itself.

Surface to air missiles designed to target normal-sized aircraft struggle to lock onto small, light, UAVs sometimes made from plastics rather than metal, Nick Brown, editor-in-chief of the journal International Defence Review told New Scientist. "Lasers are a natural extension of their capability." Firing a laser multiple times would also be cheaper than firing many missiles, and could continue as long as power can be supplied.

However, Brown's colleague Peter Felstead, editor of Jane's Defence Weekly, says the first battlefield lasers will not have UAVs in their sights. "Laser weapons are more likely to be fielded first to counter rockets and mortars, and that capability is not that far away," he says.

## How the 'Mouse Man' changed medical research

* 28 January 2009 **by Sharon Oosthoek**

*One hundred years ago in a lab at Harvard University, a young zoology student was busily overseeing the breeding of pair after pair of brother and sister mice. The "Mouse Man", as he was known on campus, was trying to create the first inbred lab animal - a strain of mouse whose genes would be stable and identical. Such a mouse would allow biologists to reliably replicate their experiments for the first time. His professor said it couldn't be done, but the Mouse Man proved him wrong. We are all indebted to those inbred mice and their descendants, which have helped researchers develop treatments for a wide range of human diseases.*

IT BEGAN with one small mouse and a simple, if tedious, instruction. Clarence Cook Little was a Harvard undergraduate when his zoology professor thrust a live mouse across the lab bench and told him to learn everything he could about it. Little went one better. In the third year of his degree, in 1909, he created the first inbred strain of mouse, providing researchers with a homogeneous genetic background on which to experiment. Before that, they could never be certain whether the results of their research were genuinely the result of an experiment or stemmed from genetic inconsistencies in their test animals.

Little, the great-grandson of America's most famous patriot, the Revolutionary Paul Revere, would remain a champion of the laboratory mouse all his life. He was particularly interested in cancer and was convinced that the key to understanding the disease lay in the study of genetics and that the best way to study genetics was by using inbred mice.

In 1929, the student who had once sketched mice in the margins of his zoology notes founded the Jackson Laboratory, a centre for research into mouse genetics, in Bar Harbor, Maine. But even he could not have foreseen the enormous power of inbred strains, says Steve Brown, director of the Mammalian Genetics Unit at MRC Harwell in Oxfordshire, UK. "The concept of creating inbred strains is fundamental to genetic studies," says Brown.

***Clarence Cook shows off his creations at the Jackson Lab*** **(Image: The Jackson Laboratory)**

Today, Little's original lab mouse has been joined by thousands of strains. About 25 million mice are used in labs around the world each year, making it the most common animal research model. Tiny Mus musculus has helped clarify the nature of a raft of human illnesses, from cancer and diabetes to Alzheimer's disease and obesity. Crucially, the lab mouse has been a stand-in for humans, testing treatments which have led to the development of drugs for rheumatoid arthritis, leukaemia and osteoporosis to name but a few.

While Little is indisputably the man behind modern lab mice, he was not the first to experiment with them. Researchers of yore recognised that mice share many physiological systems with humans. They are also easy to feed and house, have a three-week gestation, produce large litters and reach maturity in just 10 weeks. They have one other big advantage, says Karen Rader, a historian at Virginia Commonwealth University in Richmond, who has written the definitive book on lab mice, Making Mice. "The mouse is enough like us that results can apply to us, but not so much like us that people get upset about conducting experiments on them."

In fact, the lab mouse might have got off to a much earlier start if Gregor Mendel - the father of genetics - hadn't been thwarted by his bishop. In the 1850s, Mendel began his investigation of inheritance by studying coat-colour traits in mice. But he was a monk and his bishop decreed that a monastery was no place to experiment with copulating mice. Mendel switched to a study of peas.

Nor were biologists the only people to experiment with mice. Breeders of fancy mice had tinkered with mouse genes for centuries. Seventeenth-century illustrations show how people in Japan bred and collected unique strains, creating albinos and mice with spotted coats. They also bred "waltzing mice" that seemed to dance, a peculiarity later discovered to be the result of an inner-ear defect.

By the 20th century, such breeders had established clubs and exhibited their prize specimens at mouse shows. As a student, Little often judged these shows at the behest of his professor William Castle, who saw it as way to scout for genetic mutants of interest to science. It was this link to mouse fanciers that ultimately led to Little's lab mouse.

More specifically, it led to one mouse fancier, retired schoolteacher Abbie Lathrop. After a failed attempt at raising poultry, Lathrop hoped to make a living from the fancy mouse craze and began to breed popular strains on her farm in Granby, Massachusetts. She soon attracted scientific customers. "I know it sounds bizarre, in terms of genetics, that people would seek out this mouse breeder on a farm in Granby," says Rader. "But she always had the best mice. She was a local celebrity."

Lathrop was also a scientist in her own right. When she noticed some of her mice suffered from skin lesions, she sent samples to her scientific clients, including Leo Loeb, a pathologist at the University of Pennsylvania. He confirmed Lathrop's suspicions that the lesions were cancerous and the pair spent the next five years publishing joint research on tumour transmission in mice.

Little, meanwhile, had recognised the potential in Lathrop's stock. Lathrop had bred many generations of brother and sister mice to create unique strains, and such relative genetic similarity would make an excellent starting point for his work. Little began his project largely because he needed to do some independent research to qualify for Harvard's doctoral programme, but he was also eager to prove one of Castle's hypotheses wrong,

says Rader. Castle believed interbreeding could never create a stable and pure genetic strain. He also doubted that the mice would remain fertile after generations of inbreeding.

Indeed, Little soon found he had taken on something of a challenge. As fancy mouse breeders had already discovered, few progeny of brother-sister matings survive. Litters are small and the young sometimes sterile. But Little eventually found a strain that flourished. He named it dilute brown non-agouti (DBA) - dilute because it had less pigment than its wild cousins, brown as opposed to the more common black, and non-agouti because it didn't have the grizzled-looking fur of other mice.

By 1947, scientists understood the value of inbred mice. That year, the Jackson Laboratory was destroyed in a fire that consumed the town of Bar Harbor, killing 14 people and 90,000 mice. The following day, research institutes and individual geneticists who had acquired mice from the lab began sending back breeding pairs so that Little could re-establish his colonies, says Rader.

Little claimed to have received just one angry letter from an anti-vivisectionist women's club, which suggested it might have been better if he and his scientists had burned instead of the mice. Anti-vivisectionists of the time were largely concerned with cats and dogs. The public's sympathy rarely extended to rodents, which were regarded as vermin and carriers of disease.

The return of the mice paved the way for two important discoveries. George Snell's studies of tumour transplantation and rejection in mice in the late 1940s laid the foundation for modern immunology. Without it, human organ transplants would be impossible. Another of the rebuilt lab's scientists, Leroy Stevens, also made great strides with his own studies of tumour transplantation, which eventually led to the discovery of embryonic stem cells.

The decoding of the mouse genome in 2002 opened up still greater possibilities. We now know that 99 per cent of human genes have a comparable version in mice and many of them are located in the same place on the chromosome. That means scientists can work out the role of any human gene by creating mice lacking the equivalent gene. When the mice exhibit a defect, scientists can pinpoint the gene's function and test treatments.

"Little wouldn't have dreamed about this, but he would have been thrilled," says Rader. Indeed, on his 80th birthday in 1968, Little drew a cartoon of a lab mouse on a pedestal. The drawing shows him looking up at the mouse which says: "You're not so damn smart. You've had 80 years. Look what my family has done in 39 years."

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## Ötzi's Last Days – Glacier man may have been attacked twice

München, 28.01.2009

Another chapter in a murder case over 5000 years old. New investigations by an LMU research team working together with a Bolzano colleague reconstructed the chronology of the injuries that Ötzi, the glacier man preserved as a frozen mummy, received in his last days. It turns out, for example, that he did in fact only survive the arrow wound in his back for a very short time – a few minutes to a number of hours, but no more – and also definitely received a blow to the back with a blunt object only shortly before his death. In contrast, the cut wound on his hand is some days older. "We are now able to make the first assertions as to the age and chronology of the injuries," reports Professor Andreas Nerlich, who led the study. "It is now clear that Ötzi endured at least two injuring events in his last days, which may imply two separate attacks. Although the ice mummy has already been studied at great length, there are still new results to be gleaned. The crime surrounding Ötzi is as thrilling as ever!"

It is the oldest ice mummy ever found. Ötzi, the man from the Neolithic Age, is giving science critical information about life more than 5000 years ago, not least from his equipment. His copper axe, for example, reveals that metalworking was already much more advanced in that era than was previously assumed. Yet Ötzi's body, too, gives us many details as to his diet, state of health – and not least to his murder.

"Some time ago, we detected a deep cut wound on Ötzi's hand that he must have survived for at least a couple of days," says Nerlich, head of the Institute of Pathology at Municipal Hospital Munich-Bogenhausen and member of the Medical Faculty of LMU. "Another team at about the same time found an arrow tip in Ötzi's left armpit. The shaft of the arrow was missing, but there is an entry wound on the back." It is probable, in that case, that the man died of internal bleeding because the arrow hit a main artery. What was unclear, however, was the age and exact chronology of the injuries.

Now, Nerlich has reconstructed the missing chronology while working together with LMU forensic scientist Dr. Oliver Peschel and Dr. Eduard Egarter-Vigl, head of the Institute for Pathology in Bolzano. According to the new information, Ötzi did in fact only survive the arrow wound for a very short period of time, of no more

than a few hours. A few centimeters below the entry wound they detected an additional small discoloration of the skin, which was probably caused by a blow from a blunt object. In both cases, the researchers, using new immunohistochemical detection methods, managed to detect very briefly survived, yet unequivocally fatal bleeding.

Above the spine are more discolorations that are not associated with bleeding. They probably occurred after the man's death, due to his interment, for example. "Ötzi had only shortly survived the arrow wound and the blow on the back," Nerlich summarizes. "At least a couple of days before his death, however, he sustained a severe cut wound on his right hand. Over several days, then, Ötzi suffered at least two injuring events – which could point towards two separate attacks." (suwe)

***Publication:***

*"New evidence for Ötzi's final trauma", Andreas G. Nerlich, Oliver Peschel, Eduard Egarter-Vigl Intensive Care Medicine, online, January 2009*

## Weizmann Institute Scientists Create Working Artificial Nerve Networks

Scientists have already hooked brains directly to computers by means of metal electrodes, in the hope of both measuring what goes on inside the brain and eventually healing conditions such as blindness or epilepsy. In the future, the interface between brain and artificial system might be based on nerve cells grown for that purpose. In research that was recently featured on the cover of Nature Physics, Prof. Elisha Moses of the Physics of Complex Systems Department and his former research students Drs. Ofer Feinerman and Assaf Rotem have taken the first step in this direction by creating circuits and logic gates made of live nerves grown in the lab.

When neurons – brain nerve cells – are grown in culture, they don't form complex 'thinking' networks. Moses, Feinerman and Rotem wondered whether the physical structure of the nerve network could be designed to be more brain-like. To simplify things, they grew a model nerve network in one dimension only – by getting the neurons to grow along a groove etched in a glass plate. The scientists found they could stimulate these nerve cells using a magnetic field (as opposed to other systems of lab-grown neurons that only react to electricity). Experimenting further with the linear set-up, the group found that varying the width of the neuron stripe affected how well it would send signals. Nerve cells in the brain are connected to great numbers of other cells through their axons (long, thin extensions), and they must receive a minimum number of incoming signals before they fire one off in response. The researchers identified a threshold thickness, one that allowed the development of around 100 axons. Below this number, the chance of a response was iffy, while just a few over this number greatly raised the chance a signal would be passed on.

The scientists then took two thin stripes of around 100 axons each and created a logic gate similar to one in an electronic computer. Both of these 'wires' were connected to a small number of nerve cells. When the cells received a signal along just one of the 'wires,' the outcome was uncertain; but a signal sent along both 'wires' simultaneously was assured of a response. This type of structure is known as an AND gate. The next structure the team created was slightly more complex: Triangles fashioned from the neuron stripes were lined up in a row, point to rib, in a way that forced the axons to develop and send signals in one direction only. Several of these segmented shapes were then attached together in a loop to create a closed circuit. The regular relay of nerve signals around the circuit turned it into a sort of biological clock or pacemaker.

Moses: 'We have been able to enforce simplicity on an inherently complicated system. Now we can ask, 'What do nerve cells grown in culture require in order to be able to carry out complex calculations?' As we find answers, we get closer to understanding the conditions needed for creating a synthetic, many-neuron 'thinking' apparatus.' *For the scientific paper, please see: http://www.nature.com/nphys/journal/v4/n12/pdf/nphys1099.pdf*

## Study Shows Younger Women With Endometrial Cancer Can Safely Keep Ovaries, Avoid Early Menopause

***In this New Digest:***

** Summary of study being published online January 26, 2009 in the Journal of Clinical Oncology, showing no survival difference between premenopausal women with early-stage endometrial cancer whose ovaries were left intact during cancer surgery compared with those whose ovaries were surgically removed.*

** Quote for attribution from Beth Karlan, MD, American Society of Clinical Oncology gynecologic cancer expert and Director, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology at Cedars-Sinai Medical Center*

** Links to additional information on Cancer.Net, ASCO's patient Web site*

**Study Summary**

In the largest study to date on the safety of ovarian preservation in women aged 45 and younger who were surgically treated for early-stage endometrial cancer, researchers have found that there is no survival benefit associated with surgical removal of the ovaries, compared to women whose ovaries were left intact. Leaving the

ovaries in place could spare many women from the side effects of surgery-induced early menopause, such as hot flashes and vaginal dryness, as well as the long-term increased risk of heart disease, osteoporosis and hip fractures.

“Our research suggests that oncologists may no longer need to remove the ovaries during surgery in younger women with early-stage endometrial cancer, which has been the standard approach for many years. Leaving the ovaries intact appears to be a safe option that offers women a range of important short- and long-term health and quality of life benefits,” said lead author Jason D. Wright, MD, assistant professor of obstetrics and gynecology in the Division of Gynecologic Oncology at Columbia University College of Physicians & Surgeons.

Surgical removal of the uterus (hysterectomy) is the standard of care for endometrial cancer. During the procedure, surgeons usually remove the ovaries as well, a procedure called oophorectomy. Oophorectomy is usually performed to reduce the risk of cancer spreading to the ovaries and also to lower estrogen levels that may fuel the growth of any remaining endometrial cancer cells. However, studies have shown that these risks are small, and the benefits of oophorectomy have not been established by research.

In this study, Dr. Wright and his colleagues compared five-year survival between 402 women aged 45 and younger who were diagnosed with stage I endometrial cancer (cancer confined to the uterus) whose ovaries were preserved, and 3,269 similar women whose ovaries were removed. All patients had a hysterectomy and were diagnosed between 1988 and 2004. Data were derived from the Surveillance, Epidemiology and End Results (SEER) Database, a collection of cancer data on one-quarter of the U.S. population.

Five-year overall survival was similar between the two groups: Among women who had oophorectomy, 98 percent of those with stage IA disease, 96 percent of those with stage IB disease and 89 percent of those with stage IC disease were still alive. The corresponding figures for women whose ovaries were preserved were 98, 100 and 86 percent, respectively.

The investigators also noted that women were more likely to have had ovarian preservation if they were younger (under age 30), were diagnosed later in the study period, lived in the eastern United States and had a low tumor grade and earlier tumor stage.

***About Endometrial Cancer***

*The American Cancer Society estimates that approximately 40,100 women were diagnosed with endometrial cancer in the U.S. in 2008, and that 7,470 died from the disease. According to SEER data, about 8 percent of women diagnosed with endometrial cancer are under age 45.*

***ASCO Perspective***

*Beth Karlan, MD, Director, Division of Gynecologic Oncology at Cedars-Sinai Medical Center and Professor of Obstetrics and Gynecology at Geffen School of Medicine at UCLA*

*“Increasing attention is rightly being paid to improving the quality of life of cancer survivors. These findings are good news for younger women with early-stage endometrial cancer, who may be able to safely keep their ovaries, avoiding adverse health effects and maintaining quality of life.”*

## Charcoal evidence tracks climate changes in Younger Dryas

### *Idea of widespread fires sparked by theorized Clovis-age comet strike is not supported, researchers say*

A new study reports that charcoal particles left by wildfires in sediments of 35 North American lake beds don't readily support the theory that comets exploding over the continent 12,900 years ago sparked a cooling period known as the Younger Dryas.

The study -- appearing online this week ahead of regular publication in the Proceedings of the National Academy of Sciences -- however, did find clear links between abrupt climate changes and fire activity during the transition between the last Ice Age and the warm interglacial period that began 11,700 years ago. These links are also consistent with the impacts of climate-change conditions on wildfires during recent decades in North America, the researchers noted.

Charcoal particles, along with tree pollen, provide snapshots of types of vegetation and frequencies of wildfire activity in a given area, said study co-author Patrick J. Bartlein, a professor of geography at the University of Oregon. His doctoral student Jennifer R. Marlon led the collaborative study of 23 co-authors (including seven current or former UO students) at institutions in the U.S., Canada and Europe.

"The charcoal data don't support the idea of widespread fires at the beginning of the Younger Dryas interval," Bartlein said. "The results don't reject the comet hypothesis, but do suggest that one element of it -- widespread fires -- didn't occur. Instead, the data show that biomass burning tracked general climate changes closely. Biomass burning increased as conditions warmed during deglaciation until the beginning of the Younger Dryas cold interval at 12,900 years ago, leveled off during the cool interval, and then increased again as warming resumed after the end of the cold interval, about 11,700 years ago."

The fires that left the charcoal records reflect the impact of climate changes independent of potential contributions of early Paleoindians who may have been living on the continent. Proponents of the comet theory suggest Clovis culture may have been dramatically disrupted across the continent.

Marlon began the National Science Foundation-sponsored study of charcoal-pollen records soon after the comet theory was proposed in PNAS by an international team of 26 researchers led by Richard B. Firestone. A co-author of that study, UO archaeologist Douglas Kennett, in the Jan. 2 issue of Science, documented the existence of possible comet-triggered nanodiamond-rich soil at six North American sites dating to 12,900 years ago in apparent support of the hypothesis.

"We had the data to look for widespread fires if they had occurred," Marlon said, "but what we saw instead was a general increase in biomass burning whenever the climate warmed."

The lakes containing the charcoal are in Alaska (3 sites), British Columbia (7), U.S. Pacific Northwest (6), the Sierra Nevada (3), northern U.S. Rocky Mountains (6), Southwest (4), Midwest (2), Northeast (3 sites in Quebec), and Southeast (1). Thirty of the samples came from the Global Charcoal Database; another five were drawn from more recent research by co-authors currently studying sediments from the Younger Dryas.

The new study's conclusion that climate is a major control of wildfires matched that of a study published last year in Nature Geosciences by the same researchers on global biomass burning over the last 2,000 years. "Together," Bartlein said, "these studies suggest that episodes of global warming are accompanied by increases in wildfires."

*Co-authors of the study were Marlon, Bartlein and Megan K. Walsh, all currently of the UO; Walsh is a postdoctoral researcher in Kennett's lab. Others were S.P. Harrison of the University of Bristol (UK); K.J. Brown of the Geological Survey of Denmark and Greenland and of the Royal British Columbia Museum in Victoria, B.C.; M.E. Edwards of the University of Southampton (UK) and University of Alaska; P.E. Higuera, C. Briles and C. Whitlock of Montana State University; M.J. Power and A. Brunelle of the University of Utah; R.S. Anderson and M. Daniels of Northern Arizona University; C. Carcaillet of the French National Centre for Scientific Research and University of Montpellier (France); Feng-Sheng Hu of the University of Illinois at Urbana-Champaign; M. Lavoie of Laval University in Quebec City; C. Long of the University of Wisconsin at Oshkosh; T. Minckley of the University of Wyoming; P.J.H. Richard of the University of Montreal; A.C. Scott of the University of London; D.S. Shafer of the Nevada System of Higher Education's Desert Research Institute; W. Tinner of the University of Bern, Switzerland; and C.E. Umbanhowar Jr. of St. Olaf College in Minnesota.*

## Improved method for comparing genomes as well as written text

**By Robert Sanders**, Media Relations | 28 January 2009

BERKELEY — Taking a hint from the text comparison methods used to detect plagiarism in books, college papers and computer programs, University of California, Berkeley, researchers have developed an improved method for comparing whole genome sequences.

With nearly a thousand genomes partly or fully sequenced, scientists are jumping on comparative genomics as a way to construct evolutionary trees, trace disease susceptibility in populations, and even track down people's ancestry.

To date, the most common techniques have relied on comparing a limited number of highly conserved genes - no more than a couple dozen - in organisms that have all these genes in common.

The new method can be used to compare even distantly related organisms or organisms with genomes of vastly different sizes and diversity, and can compare the entire genome, not just a selected small fraction of the gene-containing portion known to code for proteins, which in the human genome is only 1 percent of the DNA.

The technique produces groupings of organisms largely consistent with current groupings, but with some interesting discrepancies, according to Sung-Hou Kim, professor of chemistry at UC Berkeley and faculty researcher at Lawrence Berkeley National Laboratory. However, the relative positions of the groups in the family tree - that is, how recently these groups evolved - are quite different from those based on conventional gene alignment methods.

The computational results have surprised scientists in being able to classify some bacteria and viruses that until now were enigmatic.

The technique, which employs feature frequency profiles (FFP), is described in a paper to appear this week in the early online edition of the journal Proceedings of the National Academy of Sciences.

**Whole-genome vs. gene-centric methods**

Current methods for comparing the genomes of different organisms focus on a small set of genes that the organisms being compared have in common. The genomes are then lined up in order to count the sequence similarities and differences, from which a computer program constructs a family tree, with near relatives assumed to have more similar sequences than distant relatives.

This technique assumes organisms have genes in common, however, or that these "homologous" genes can be identified. When comparing distantly related species - such as bacteria that live in vastly different environments - this gene-centric method may not work, Kim said.

"What do you do when one gene tells you the organisms are closely related, and another gene tells you they're distantly related?" he asked. "It happens."

Kim, who in the past focused on creating three-dimensional demographic maps of all known protein structures, wanted a technique that could be used to compare genomes of all sizes, and even genomes only partially sequenced. He also wanted a method that would compare all regions of the genome, not just the exons - that is, the DNA transcribed into mRNA, the blueprint for proteins. Exons make up only 1 percent of the human genome, with the remainder being non-coding "introns," regulatory DNA, duplicate or redundant DNA and transposons - genes that have jumped from other places in the genome.

Kim thought that traditional text comparison - used, for example, to assess the authorship of a work of literature or to identify plagiarized text - might provide a model for whole genome comparison and a way to test comparison methods. But while text comparison involves looking at word frequency; genomes cannot be broken down into words.

"I can compare two books in two different ways. I can pick a few sentences, say a hundred that I subjectively decided are important, and compare them, but some are very similar and some very different in the two books," he explained. "So, how can I decide? I need a second method to compare some features representing one whole book to those of the other whole book."


***Text comparison of English books with the FFP method yields a relationship tree that groups similar books together, by genre, period or author.*** **(Sung-Hou Kim lab/UC Berkeley)**

**A different vocabulary**

Teaming up with biophysicist Gregory E. Sims, statistical mathematician Se-Ran Jun and theoretical physicist Guohong A. Wu, Kim decided to try a simple variant of the word frequency technique. They eliminated all punctuation and spaces from a text, created a dictionary of all the two-letter, three-letter, and other word combinations in the books, and counted the variety of each fixed-length "word" or feature. The features were not consecutive letter combinations, but overlapping sequences obtained by sliding a two-, three- or more-letter window along the text, advancing one letter at a time.

In a test of free online books obtained through Project Gutenberg, they found that this method, which they called the feature frequency profile (FFP) method, was more successful at identifying related books - books by the same author, books of the same genre, books from the same historical era - than word frequency profile analysis. In fact, a good tree can be constructed by looking at a single "optimal" feature length, such as nine letters, where the "vocabulary" is very large, instead of looking at all possible lengths.

"I was just stunned when I saw this," Kim said. One of the reasons this method works better, he said, may be that, while word frequency analysis treats each word independently, feature frequency analysis picks up syntax.

"Here, if I take a 9-letter window and slide it along the text," he said, "I am actually picking up the relationship between the first and second words - the local syntax - which was impossible to pick up from the word frequency method. Apparently, that is very important."

**Mammalian and bacterial genomes**

Buoyed by this success, the researchers applied the technique to whole genomes of mammals, where there is the least controversy in evolutionary relationship. "We treat the genome like a book without spaces," Kim said.

Since these genomes are very large, the researchers translated the genome sequences using a reduced, two-letter alphabet - R for the purine nucleic acids, adenine and guanine, and Y for the pyrimidine nucleic acids, thymine and cytosine - to reduce the complexity of calculation. Using an optimal feature length of 18 base pairs, this test created a family tree identical to the phylogenetic trees constructed by scientists using genetic, morphological, anatomical, fossil and behavioral information. This was surprising, especially since the overwhelming majority of the mammalian genomes do not code for genes, Kim said.

Next, they tried the FFP method on 518 genomes, the bulk of them bacteria and Archaea, but also six eukaryotes of varying complexity and two random sequences. The eurkaryotic genomes used were as much as

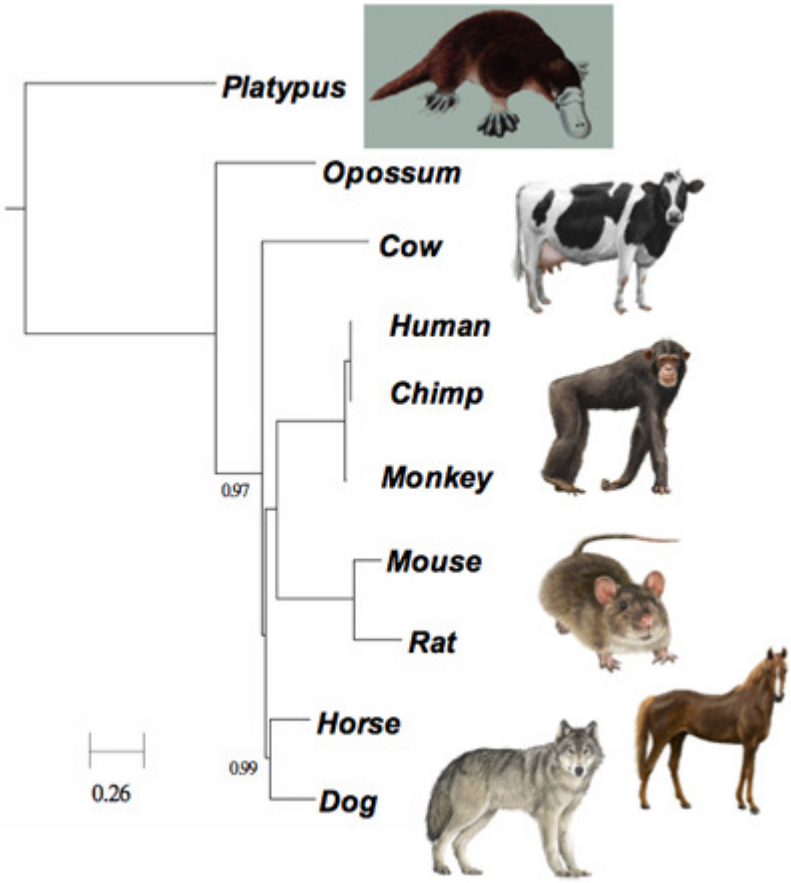
1,000 times longer than the bacterial and Archaeal genomes. Because most of the bacterial and Archaeal genomes code for genes, as opposed to very little of the genomes of higher eukaryotes, the researchers used a different alphabet and vocabulary for the FFP method: short strings of amino acids, the building blocks of proteins, with a 20-word alphabet representing the 20 possible amino acids.

"The question is: Can we then group all living organisms based on the whole proteome, that is, the assembly of all proteins, instead of using just a selection of a small set of proteins, which is equivalent to using a small set of genes?" said Kim.

The researchers found that the FFP method clearly segregates whole proteomes of all bacteria, archaea, eukaryotes and random sequences into separate groups or domains. Most of the phylum groups within each domain and class groups in each phylum also were well segregated, with some interesting discrepancies compared to the currently accepted groupings.

In most of the cases where the FFP grouping disagreed with an accepted phylogenetic grouping, the problem organism had been the subject of debate among biologists because of conflicting conclusions from genetics, behavior and morphology, Kim said. The new method did classify several so-far unclassified bacteria, however.

The major differences are found not in how the organisms are grouped, but in the relative position of these groups in the organism trees, he said.




***FFP comparison of mammalian genomes produces the same phylogenetic tree whether using whole genomes or just introns, which supposedly carry no genetic information.*** **(Sung-Hou Kim lab/UC Berkeley)**

**Viral genomes**

Finally, Kim and his colleagues analyzed the genomes of several hundred viruses, including several that could not be classified.

"Some viruses have no or few highly conserved common genes to other viruses, thus, the gene alignment-based method cannot find relationship among such groups, but we think we can," he said.

Because of the vast amount of whole genome sequence data, all of Kim's analyses monopolized a computer cluster of 320 CPUs (central processing units) for over a year.

Kim stressed the major difference between FFP and gene-centric comparisons of genomes: FFP takes into account all or most of the DNA or protein sequences in the genome, while gene alignment analysis chooses a small set of genes out of large number of genes in each organisms, and uses that to represent the organism.

"The fallacy of the view that organisms can be represented by a small set of their genes is really due to our prejudice that genes are us," Kim said. "We know now, more and more, that this is oversimplification.

"It is likely that some of the observations we come up with will turn out to be wrong, but the method will evolve and get better and better as experts come in and tell us where we have gone wrong. The math is there, now we have to remove the human bias as much as possible."

In addition to applying the method to comparative genomics, Kim expects it will help in grouping and finding relationships among sets of other information, such as electronic information encoding text, sounds and images. It may also help in tracing human ancestry and disease demography using whole genome sequences, and in grouping of metagenomic data - the sequences of genome fragments from many organisms, most of which are unknown species, found in a given environmental niche or body organ.

Kim hopes someday to return to Shakespearean texts and sort out their provenance as well.

*The work was funded by the National Institutes of Health and by a grant from the Korean Ministry of Education, Science and Technology.*

## Plums poised to give blueberries run for the money

**Writer(s): Kathleen Phillips**, 979-845-2872,ka-phillips@tamu.edu

College Station – There's an emerging star in the super-food world. Plums are rolling down the food fashion runway sporting newly discovered high levels of healthy nutrients, say scientists at Texas AgriLife Research.

Plainly, "blueberries have some stiff competition," said Dr. Luis Cisneros, AgriLife Research food scientist. "Stone fruits are super fruits with plums as emerging stars."

Far from fruit snobbery, the plum is being ushered in after Cisneros and Dr. David Byrne, AgriLife Research plant breeder, judged more than 100 varieties of plums, peaches and nectarines and found them to match or exceed the much-touted blueberries in antioxidants and phytonutrients associated with disease prevention.

***Plums in study at Texas AgriLife Research.*** **(Texas AgriLife Research photo by Dr. David Byrne).**

The duo acknowledge that blueberries remain a good nutritional choice. But Byrne said their findings are plum good news, especially in tight economic times, because one relatively inexpensive plum contains about the same amount of antioxidants as a handful of more expensive blueberries.

"People tend to eat just a few blueberries at a time – a few on the cereal or as an ingredient mixed with lots of sugar," Cisneros said. "But people will eat a whole plum at once and get the full benefit."

Discovery of the plum's benefits – along with that of fellow stone fruits, the peach and the nectarine – came after the researchers measured at least five brands of blueberries on the market. Against those numbers, the team measured the content of more than 100 different types of plums, nectarines and peaches.

The first comparison was for antioxidants, molecules that sweep through a body looking for free radicals to knock out. Free radicals are atoms or molecules that lurk where diseases like cancer and heart disease are found.

"If the radicals aren't taken care of," Cisneros said, "they will cause the problems that lead to disease."

But the scientists didn't stop at knowing that plums and peaches were flexing their antioxidant muscles.

"Knowing that we had all these varieties with high levels of antioxidants, then the possibility of preventing these diseases would also be high with their consumption, so we went to the next step – how these compounds could actually inhibit chronic diseases," Cisneros said.

The team examined the full content of plums and peaches, then tested the effect of the compounds they found on breast cancer cells and cholesterol in the lab.

"We screened the varieties again with the biological assays," Cisneros said. "And that had never been done before, because it is expensive and a lot of work. But that investment is small in terms of the information we got, and how it can be used now for breeding efforts to produce even better fruit."

Byrne noted, for example, that one benefit the team found was that the phytonutrients in plums inhibited in vitro breast cancer growth without adversely affecting normal cell growth.

He said this type of research needs further study but is an indication that breeders ultimately will be able to produce new crop varieties with the best ratio of various phytochemicals to have an impact on disease prevention and inhibition. And these fruits will be available as fresh produce as well as in extracts for dietary supplements.

"Future work with stone fruits will focus on cardiovascular and cancer using animal models and identification of specific compounds that exert the properties," Cisneros added.

Bottom line from the researchers: "We suggest that consumers take seriously the recommendation to eat at least five servings of fruits and vegetables – or even more – every day and to make sure that plums are part of that," Byrne said.

*Funding comes from the Vegetable and Fruit Improvement Center at Texas A&M University and the California Tree Fruit Agreement. Web Page Address: http://agnews.tamu.edu/showstory.php?id=950*

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## Marching to the Beat of the Same Drum Improves Teamwork

Armies train by marching in step. Religions around the world incorporate many forms of singing and chanting into their rituals. Citizens sing the National Anthem before sporting events. Why do we participate in these various synchronized activities? A new study, published in the January issue of Psychological Science, a journal of the Association for Psychological Science, suggests that when people engage in synchronous activity together, they become more likely to cooperate with other group members.

Stanford University psychologists Scott S. Wiltermuth and Chip Heath conducted a series of experiments to see how synchronous movement affects group interactions. In the first experiment, two groups of volunteers walked around campus - one group was told to walk normally and the other group was told to walk in-step. Following the walks, the volunteers participated in an economics game that measures expectations of cooperation- the more the volunteers cooperate, the larger the payoff they would receive at the end of the experiment.

. In the second experiment, volunteers listened to music via headphones and had to move cups back and forth in time to the music. The volunteers were divided into different groups, so that some of the groups listened to the same music and thus moved their cups in a synchronous manner. In the other groups, the volunteers listened to music at different tempos, so their movements were not synchronized. This was again followed by an economics game where more cooperation would result in larger payoff. This final game was designed so that players could put tokens in a public account, or keep the tokens for themselves. The general economic strategy in this game is to behave selfishly keeping one's tokens in a private account while at the same time taking advantage of others' contributions to the public account.

The results showed that synchrony fosters cooperation- even when all of the volunteers had financial incentives to cooperate, the volunteers from the synchronized groups tended to be more cooperative during the games (and ended up earning more money) than volunteers from groups who had moved asynchronously. And even more interesting, in the last economics game, participants from the synchronized groups were more willing to contribute tokens to the public account, sacrificing their own money to help their group. In addition, volunteers from the synchronous groups reported greater feelings of being on the same team. Thus, the synchronous participants cooperated during the games in part because they felt as though they were part of a team.

Societies rely on cooperation among their members to thrive and be successful. These findings suggest that cultural practices which involve synchrony (such as dancing, singing or marching) may enable groups to produce members who are cooperative and willing to make personal sacrifices, for the benefit of the group. The authors conclude that "synchrony rituals may have therefore endowed some cultural groups with an advantage in societal evolution, leading some groups to survive where others have failed."

*For more information about this study, please contact: Scott S. Wiltermuth (scwilter@stanford.edu)*

## Some of Earth's climate troubles should face burial at sea, scientists say

Making bales with 30 percent of global crop residues – the stalks and such left after harvesting – and then sinking the bales into the deep ocean could reduce the build up of global carbon dioxide in the atmosphere by up to 15 percent a year, according to just published calculations.

That is a significant amount of carbon, the process can be accomplished with existing technology and it can be done year after year, according to Stuart Strand, a University of Washington research professor. Further the technique would sequester – or lock up – the carbon in seafloor sediments and deep ocean waters for thousands of years, he says.

All these things cannot be said for other proposed solutions for taking carbon dioxide out of the atmosphere, methods such as ocean fertilization, growing new forests or using crop residues in other ways, says Strand, who is lead author of a paper on the subject in the journal Environmental Science & Technology, published by the American Chemical Society.

Strand has devised a formula to measure the carbon-sequestration efficiency of this process and others using crop residues, something no one has done before.


***Just past the continental shelf in the Gulf of Mexico – the shelf is marked with the blue line – a fan of sediment has formed on the seafloor made up of silt and debris that settles out of Mississippi River waters flowing into the gulf. These alluvial, or submarine, fans are found wherever rivers run into the ocean. Crop residues sunk in such fans would become covered with silt, further ensuring that carbon would be locked away for long periods.*** **Credit: S. Strand/UW/U.S. Geological Survey**

Carefully tallying how much carbon would be released during the harvest, transportation and sinking of 30 percent of U.S. crop residues and comparing that to how much carbon could be sequestered, Strand says the process would be 92 percent efficient. That's more efficient than any other use of crop residue he considered, including simply leaving crop residue in the field, which is 14 percent efficient at sequestering carbon, or using crop residue to produce ethanol, which avoids the use fossil fuels, but is only 32 percent efficient.

Worldwide, farming is mankind's largest-scale activity. Thirty percent of the world's crop residue represents 600 megatons of carbon that, if sequestered in the deep ocean with 92 percent efficiency, would mean the amount of carbon dioxide in the atmosphere would be reduced from 4,000 megatons of carbon to 3,400 megatons annually, Strand says. That's about a 15 percent decrease.

The proposed process would remove only above-ground residue. Strand bases his calculations on using 30 percent of crop residue because that's what agricultural scientists say could sustainably be removed, the rest being needed to maintain carbon in the soil. Crop residue would be baled with existing equipment and transported by trucks, barges or trains to ports, just as crops are. The bales would be barged to where the ocean is 1,500 meters, or nearly a mile, deep and then the bales would be weighted with rock and sunk.

"The ocean waters below 1,500 meters do not mix significantly with the upper waters," Strand says. "In the deep ocean it is cold, oxygen is limited and there are few marine organisms that can break down crop residue. That means what is put there will stay there for thousands of years."

The article calls for research on the environmental effects of sinking crop residues in the ocean, effects that most likely will be borne by organisms living in the ocean sediments where the bales fall.

Strand says one way to minimize environmental effects would be to drop the residue onto alluvial fans found off the continental shelf wherever rivers pour into the ocean. Alluvial fans, sometimes call submarine fans when underwater, form as silt and debris from river water settles to the seafloor. Runoff from current agricultural fields means alluvial fans in the ocean are already partly made up of crop residue. Any bales dumped there would quickly be covered with silt, further ensuring the carbon would be sequestered for long periods.

Effects might also be minimized by concentrating the residue in a compact area. At the Mississippi alluvial fan in the Gulf of Mexico, spreading 30 percent of U.S. crop residue in an annual layer 4 meters, or 13 feet, deep would cover 260 square kilometers, or 100 square miles. That's about 0.02 percent of the area of the Gulf of Mexico, Strand says.

"Whatever the environmental impacts of sinking crop residue in the oceans turn out to be, they will need to be viewed in light of the damage to oceans because of acidification and global warming if we don't remove carbon dioxide from the atmosphere," Strand says.

Co-author of the paper is Gregory Benford, a professor of physics at the University of California, Irvine.

Strand, a faculty member with the UW's College of Forest Resources, is an environmental engineer known for his work on using plants to remediate contaminated groundwater, soil and sediment. He said he's been interested in ways to remove carbon dioxide from the atmosphere for nearly a decade and first read about sequestering crop residue in the deep ocean in Climatic Science in 2001. Benford was a co-author on that paper.

Strand says he thinks any method for removing excess carbon dioxide must do seven things: move hundreds of megatons of carbon, sequester that carbon for thousands of years, be repeatable for centuries, be something that can be implemented immediately using methods already at hand, not cause unacceptable environmental damage and be economical. He says sequestering crop residue in the deep ocean fits the criteria better than any other proposed solution.

"To help save the upper ocean and continental ecosystems from severe disruption by climate change, we must not only stop our dependence on fossil fuels, but also go carbon negative," Strand says. "Fossil fuels that are removed from sediments and burned are producing the increased atmospheric carbon that is driving climate warming. Sequestering crop residue biomass in the deep ocean is essentially recycling atmospheric carbon back into deep sediments."

*For more information: Strand, 206-543-5350, 206-605-2221, sstrand@u.washington.edu*

*"Ocean Sequestration of Crop Residue Carbon: Recycling Fossil Fuel Carbon Back to Deep Sediments" is available online to subscribers of Environmental Science & Technology (see Jan. 12) and is expected to appear in the print edition next month.*

## Study finds 'rescue course' of antenatal steroids improves outcome in premature babies

San Diego — In a study to be presented today at the Society for Maternal-Fetal Medicine's (SMFM) annual meeting, researchers will unveil findings that show that premature babies born before 34 weeks have a 31 percent reduction in serious complications when given a "rescue course" of Antenatal Corticosteroids (ACS) steroids with no adverse side effects noted.

"Premature babies are very susceptible to respiratory problems which may lead to additional severe complications," said Dr. James Kurtzman, M.D. (Associate Professor, UC Irvine Medical Center). "Antenatal steroids clearly reduce the risk of these respiratory complications."

Years ago doctors gave multiple courses of antenatal steroids to mothers who were at risk for delivering prematurely. However, certain studies found that there were possible adverse affects to multiple ACS courses because babies were found to have slightly smaller head circumferences and lower birth weights. As a result the National Institutes of Health (NIH) recommended further study.

"The effect (of the NIH recommendation) was that doctors were only giving one ACS course, and they were nervous about when to give it for the best effect. They often waited until the last minute, and some women didn't get a complete treatment or didn't get it at all," said Dr. Kurtzman. "What this study has found is that we can give women who threaten to deliver prematurely an initial ACS course, and if they remain pregnant, we can give one 'rescue course' closer to delivery. By doing so, the babies' complications are reduced by about a third with no adverse side effects found."

In this study, which took place over five years in 18 different medical centers and was supported by the Pediatrix Medical Group, 437 patients were randomized (233 in the study group, and 214 in the placebo group). The results showed a significant reduction in composite neonatal morbidity for babies born prior to 34 weeks in the "rescue steroid" group vs. placebo (43.9% vs. 63.6%) as well as significant decrease in respiratory distress syndrome, ventilator support, and surfactant use. When all neonates were included in the analysis (regardless of the gestational age at delivery), a significant reduction in composite morbidity in the "rescue steroid" group was still demonstrated (32.1% vs. 42.6%).

*The study was authored by James Kurtzman, M.D., University of California Irvine and Saddleback Women's Hospital; Thomas Garite, M.D., University of California Irvine; Reese Clark, M.D., and Kimberly Maurel, R.N., M.S.N., Pediatrix Medical Group on behalf of the Pediatrix Collaborative Research Network..*

*The study will be published in the March 2009 issue of the American Journal of Obstetrics and Gynecology.*

*For interviews or a copy of the abstract please contact Vicki Bendure, Vicki@bendurepr.com, 202-374-9259*

## New study explores the relationship between preterm birth and autism spectrum disorder

Cincinnati, OH, January 29, 2009 -- Recent studies have suggested that autism spectrum disorder (ASD) may be more prevalent among children born very prematurely. The early symptoms of ASD are also associated with other conditions related to preterm births, such as cerebral palsy, which can make it difficult to correctly screen children for ASD. Because of this, researchers have begun to explore the relationship between preterm birth, cognitive and developmental impairments, and ASD. Two articles soon to be published in The Journal of Pediatrics explore this possible correlation between preterm birth and ASD.

Dr. Karl Kuban and colleagues from Boston University, Wake Forest University, and Harvard University studied 988 children born between 2002 and 2004 who participated in the ELGAN (Extremely Low Gestational Age Newborn) study, a large, multi-center study that enrolled more than 1500 infants born at least three months prematurely. They wanted to explore whether children born preterm are more likely to screen positive on the Modified Checklist for Autism in Toddlers (M-CHAT), a survey administered to a caregiver regarding a child's behavior. Pediatricians typically wait to formally diagnose ASD until after a child's third birthday. In this study, however, the caregivers of the infants completed the M-CHAT when the children were 24 months of age. The researchers found that 21% of the preterm children screened positive for ASD.

Dr. Kuban and his colleagues were also interested in learning whether a child born prematurely who had motor, visual, hearing, or cognitive impairments was more likely to screen positive on the M-CHAT. Of the 988 children, 26% had cognitive impairments, 11% had cerebral palsy, 3% had visual impairments, and 2% had hearing impairments. They also observed that nearly half of the children with cerebral palsy and more than two-thirds of the children with visual or hearing impairments screened positive. According to Dr. Kuban, "Children who are born more than three months premature appear to be twice as likely to screen positive on the M-CHAT." He notes, however, that the percentage of children who screened positive for ASD dropped to 10% when the variables of cognitive, visual, hearing, and motor impairments were removed.

In a related editorial, Dr. Neil Marlow and Dr. Samantha Johnson of University College London stress that because early identification leads to early treatment of children with ASD, screening tests are designed to over-identify children at risk. They suggest that useful knowledge may be gained by following the children as they mature to determine how many of those who initially screened positive actually develop ASD. Dr. Marlow notes that the study is valuable because "it raises our awareness of the difficulties in interpreting screening results." He cautions that further research is needed before conclusions can be drawn about the direct correlation between preterm birth and ASD.

*The study is reported in "Positive Screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in Extremely Low Gestational Age Newborns" by Karl C. K. Kuban, MD, SM, Epi, T. Michael O'Shea, MD, MPH, Elizabeth N. Alfred, MS, Helen Tager-Flusberg, PhD, Donald J. Goldstein, PhD, Alan Leviton, M, DOI: 10.1016/j.jpeds.2008.10.011. The accompanying editorial is "Positive Screening Results on the Modified Checklist for Autism in Toddlers: Implications for Very Preterm Populations" by Neil Marlow, MD, and Samantha Johnson, PhD, DOI: 10.1016/j.jpeds.2008.11.028. The articles appear in The Journal of Pediatrics, published by Elsevier.*

## Tobacco companies target girls

Tobacco marketing in South Korea has been deliberately aimed at girls and young women. Research published in the open access journal Globalization and Health has shown that transnational tobacco companies (TTCs) are using tactics long used with devastating effect in Western countries to snare new female smokers in Asia.

Kelley Lee from the London School of Hygiene & Tropical Medicine led a team of researchers who studied internal documents from the tobacco industry that reveal the scheme to seduce a generation of girls. She said, "Since the opening of the South Korean tobacco market in the late 1980s, females have been targeted by TTCs as an important source of future market growth and profitability. The rise in smoking rates among females within certain age groups since the late 1980s suggests that these efforts have been successful".

The tactics used recall advertising campaigns carried out in the United States and Europe since the 1920s that link smoking with feminism and the liberation of women. According to Lee, "Product design associating smoking with body image and female emancipation, familiarly deployed elsewhere, have been extensively used in South Korea to appeal to female smokers. So-called "ultra light", "low tar" and "superslim" cigarettes have been particularly effective, falsely suggesting certain brands offer a healthier or safer option, as well as appealing to female concerns about weight gain. Tighter restrictions on the use of such descriptors, alongside public education on the fallacy of such claims, are badly needed in South Korea".

South Korea's cigarette market was opened to the world in 1988 under the threat of US trade sanctions. In 1989, the country passed laws banning tobacco advertising, marketing and sponsorship directly targeted at women and children. During the authors' literature search, they found evidence of the companies' efforts to circumvent this law by, for example, using images of couples in their adverts – something not covered by the country's guidelines, but known to appeal to the female market. One TTC wrote "Although obviously targeted to women, the campaign extension would also not be as overt in markets sensitive to female targeting".

Lee concludes, "The implementation of comprehensive tobacco control measures in South Korea, as set out under the Framework Convention on Tobacco Control, is urgently needed to protect and promote the health of Korean women and girls".

*Notes to Editors*

*1. The strategic targeting of females by transnational tobacco companies in South Korea following trade liberalisation*
*Kelley Lee, Carrie Carpenter, Chaitanya Challa, Sungkyu Lee, Gregory N Connolly and Howard K Koh*
*Globalization and Health (in press)*
*During the embargo, article available here:*
*http://www.globalizationandhealth.com/imedia/1817383034214690_article.pdf?random=683222*
*After the embargo, article available at journal website: http://www.globalizationandhealth.com/*

## Sudden cardiac death without recognizable cause

In about 10% of cases, sudden cardiac death (SCD) in young people is due to a cardiac gene defect. This was the conclusion drawn by Silke Kauferstein of the Department of Forensic Medicine of the Johann Wolfgang Goethe University, Frankfurt, and her coauthors in the current Deutsches Ärzteblatt International (Dtsch Arztebl Int 2009; 106(4): 41-7).

Sudden cardiac death is defined as unexpected death occurring rapidly - usually within 1 h of the onset of symptoms—in persons who had previously seemed to be healthy. It is one of the most frequent causes of death in Europe. Each year, about 100 000 people die of sudden cardiac death in Germany alone. Although SCD mostly affects older people, 5% to 15% of cases are in young people who had previously been asymptomatic.

Most cases of sudden cardiac death can be explained by cardiovascular changes. However, in 10% to 30% of cases, no cause of death can be established, even after a postmortem. Genetically linked diseases of cardiac ion channels are responsible for at least a third of these deaths. As the ion channels are involved in stimulation and conduction in the heart, malfunction can cause cardiac arrythmias, which may lead to ventricular fibrillation.

These primary electrical heart disorders are mostly subject to autosomal dominant inheritance. This means that family members have a 50% risk of being carriers of the modified gene causing the disorder. A genetic study of the affected family is therefore essential if further cases of sudden cardiac death are to be prevented.
*http://www.aerzteblatt.de/v4/archiv/pdf.asp?id=63144*

## Researchers identify protein that may explain 'healthy' obesity

DALLAS - Mice whose fat cells were allowed to grow larger than fat cells in normal mice developed “healthy” obesity when fed a high-fat diet, researchers at UT Southwestern Medical Center found in a new study.

The fat but healthy mice lacked a protein called collagen VI, which normally surrounds fat cells and limits how large they can grow, like a cage around a water balloon. The findings appear online and in a future edition of Molecular and Cellular Biology.

"The mice lacking collagen VI fared much better metabolically than their counterparts that retained this particular collagen," said Dr. Philipp Scherer, director of the Touchstone Center for Diabetes Research at UT Southwestern and the study's senior author. "The mice without collagen VI don't develop inflammation or insulin resistance. They still get obese, but it's a 'healthy' obesity."

When people take in more calories than needed, excess calories are stored in adipose or fatty tissue. The fat cells are embedded in and secrete substances into an extracellular matrix, a type of connective tissue that provides support to fat tissue, like scaffolding. Collagen VI is one component of the extracellular matrix. Too much of this connective tissue prevents individual cells from expanding and can lead to fibrosis and eventually inflammation.

Inflammation is thought to be an underlying cause of metabolic disorders in humans, said Dr. Scherer. Large fat cells are often considered a bad omen, he said, because they typically lead to increased cell death and systemic insulin resistance. Under normal circumstances, fat cells continue to grow until they reach a point where the extracellular matrix they've built around themselves is so strong that it's no longer flexible.

"In this particular case, however, the large fat cells are not as inflamed as they would normally be," Dr. Scherer said. "Fat cells that lack collagen VI can grow to a huge size without becoming inflamed, suggesting that collagen VI directly affects the ability of fat cells to expand."

Dr. Scherer said the current finding is clinically relevant and probably will translate well from the mice to humans. "Our study highlights the fact that collagen VI, and possibly other extracellular matrix constituents, are extremely important in modulating fat-cell physiology," he said.

The next step is to determine precisely how collagen VI functions in the body.

"We need to get a better grip on targets that may allow us to interfere in this process. Unfortunately collagen VI can't be knocked out in humans, but we may be able to manipulate it," Dr. Scherer said.

Other UT Southwestern researchers involved in the study were Dr. Zhao Wang, postdoctoral researcher in internal medicine, as well as volunteer faculty members Drs. Nicola Abate and Manisha Chandalia, who are now on staff at the UT Medical Branch at Galveston. Scientists from the Albert Einstein College of Medicine, Merck Research Laboratories and the University of Padua in Italy also participated.

*The work was supported by the National Institutes of Health.*

## Stem cell transplant reverses early stage multiple sclerosis

Chicago - Researchers from Northwestern University's Feinberg School of Medicine appear to have reversed the neurological dysfunction of early-stage multiple sclerosis patients by transplanting their own immune stem cells into their bodies and thereby "resetting" their immune systems.

"This is the first time we have turned the tide on this disease," said principal investigator Richard Burt, M.D. chief of immunotherapy for autoimmune diseases at the Feinberg School. The clinical trial was performed at Northwestern Memorial Hospital where Burt holds the same title.

The patients in the small phase I/II trial continued to improve for up to 24 months after the transplantation procedure and then stabilized. They experienced improvements in areas in which they had been affected by multiple sclerosis including walking, ataxia, limb strength, vision and incontinence. The study will be published online January 30 and in the March issue of The Lancet Neurology.

Multiple sclerosis (MS) is an autoimmune disease in which the immune system attacks the central nervous system. In its early stages, the disease is characterized by intermittent neurological symptoms, called relapsing-remitting MS. During this time, the person will either fully or partially recover from the symptoms experienced during the attacks. Common symptoms are visual problems, fatigue, sensory changes, weakness or paralysis of limbs, tremors, lack of coordination, poor balance, bladder or bowel changes and psychological changes.

Within 10 to 15 years after onset of the disease, most patients with this relapsing-remitting MS progress to a later stage called secondary progressive multiple sclerosis. In this stage, they experience a steady worsening of irreversible neurological damage.

The 21 patients in the trial, ages 20 to 53, had relapsing-remitting multiple sclerosis that had not responded to at least six months of treatment with interferon beta. The patients had had MS for an average of five years. After an average follow-up of three years after transplantation, 17 patients (81 percent) improved by at least one point on a disability scale. The disease also stabilized in all patients.

In the procedure, Burt and colleagues treated patients with chemotherapy to destroy their immune system. They then injected the patients with their own immune stem cells, obtained from the patients' blood before the chemotherapy, to create a new immune system. The procedure is called autologous non-myeloablative haematopoietic stem-cell transplantation.

"We focus on destroying only the immune component of the bone marrow and then regenerate the immune component, which makes the procedure much safer and less toxic than traditional chemotherapy for cancer," Burt said. After the transplantation, the patient's new lymphocytes or immune cells are self-tolerant and do not attack the immune system. "In MS the immune system is attacking your brain," Burt said. "After the procedure, it doesn't do that anymore."

In previous studies, Burt had transplanted immune stem cells into late-stage MS patients. "It didn't help in the late stages, but when we treat them in the early stage, they get better and continue to get better," he said.

"What we did is promising and exiting, but we need to prove it in a randomized trial," Burt noted. He has launched a randomized national trial. *For more information visit : http://clinicaltrials.gov/ct2/show/NCT0027336*

## Discovery of ionic elemental crystal against chemical intuition

### *New phase of elemental boron discovered*

Zurich/New York . An ETH Zurich researcher has developed a computational method for predicting the structure of materials. He used it to solve the structure of a newly synthesized form of pure boron that displays some unusual physical properties and brings a surprise: it is partially ionic.

The new structure can be viewed as a NaCl-type structure, with anionic and cationic positions occupied by two different clusters of boron atoms (B12 and B2). The difference of the electronic properties of these clusters brings about charge transfer, making this material a partially ionic boron boride $(B2)^{\delta+}(B12)^{\delta-}$. Results have been published in today's "Nature" online magazine.

Boron is the chemical element most sensitive to impurities. This enhanced sensitivity makes experimental studies of this element very difficult. However, with the discovery of a new, superhard phase of the element, the theorists and experimentalists involved in the research have now come a big step closer to understanding boron. A separate publication by the authors in the "Journal of Superhard Materials" demonstrated that the new phase is superhard.

**Independently synthesized**

The new superhard material was independently synthesized by two researchers who eventually joined forces with crystallographer Artem Oganov's theoretical team. Initially, Jiuhua Chen, a material scientist at Florida International University, and Vladimir Solozhenko, a physical chemist at the Centre National de la Recherche Scientifique (CNRS) in France, conducted experiments on extremely pure boron material, containing at most one foreign atom to one million boron atoms. They exposed this material to temperatures of over 1,500 degrees Celsius and to pressures in the range 12-30 GPa, similar to those found several hundreds of kilometers inside the Earth. Under these conditions both teams of experimentalists found a new polymorph of boron, but could not solve its structure.

**New method leads to breakthrough**

Artem Oganov, working at ETH Zurich's Department of Material Science, has now developed a computational method for predicting the stable crystal structures of materials. His calculations reveal that in the new phase, boron atoms form two different kinds of nanoclusters: an icosahedron B12 consisting of twelve atoms and dumbbell B2 consisting of just two boron atoms.

These nanoclusters are arranged in the new phase of boron just as are sodium and chlorine ions in the rock salt (table salt) structure (see diagram). The new phase is predicted to remain stable to 89 GPa. The new knowledge obtained in this study allowed the researchers to propose a phase diagram for boron – the only light element whose phase diagram remained unknown until now.

**Unusual properties identified**

The unexpected structure of the new phase, which the authors called γ-B, contains atoms which are ionized, meaning that the electrons are distributed between the atoms unevenly. According to classical textbooks, ionic bonds are possible only between two different elements, such as sodium and chlorine in table salt. But in the new structure ionic bonds occur between atoms of the same element, though belonging to two kinds of nanoclusters. This ionicity leads to unusual for an element phenomena in dielectric properties, lattice dynamics, and anomalous electronic properties. Additional experiments carried out by the researchers also show that the new phase is superhard.

Oganov and his colleagues expect that forms of other elements, such as carbon heterofullerites, might display charge transfer and partial ionicity. Now a professor at State University of New York at Stony Brook (USA), Oganov anticipates that sooner or later applications will be developed which are based on ionic elements. These applications could be based on switching on or off the anomalous properties (for example, strong infrared absorption) possessed by ionic elements – such properties will display dramatic changes as a result of pres-sure- or temperature-induced phase transitions. In addition, interesting effects related to superconductivity may appear as well.

## Blue light destroys antibiotic-resistant staph infection

***Results reported in Photomedicine and Laser Surgery Journal***

New Rochelle, NY, - common strains of methicillin-resistant Staphylococcus aureus, commonly known as MRSA, were virtually eradicated in the laboratory by exposing them to a wavelength of blue light, in a process called photo-irradiation that is described in a paper published online ahead of print in Photomedicine and Laser Surgery. The article will appear in the April 2009 issue (Volume 27, Number 2) of the peer-reviewed journal published by Mary Ann Liebert, Inc. The paper is available free online at www.liebertpub.com/pho

Antibiotic-resistant bacterial infections represent an important and increasing public health threat. At present, fewer than 5% of staphylococcal strains are susceptible to penicillin, while approximately 40%-50% of Staph aureus isolated have developed resistance to newer semisynthetic antibiotics such as methicillin as well.

Chukuka S. Enwemeka, Deborah Williams, Sombiri K. Enwemeka, Steve Hollosi, and David Yens from the New York Institute of Technology (Old Westbury, NY) had previously demonstrated that photo-irradiation using 405-nm light destroys MRSA strains grown in culture. In the current study, "Blue 470-nm Light Kills Methicillin-Resistant Staphylococcus aureus (MRSA) in Vitro," the authors exposed bacterial colonies of MRSA to various doses of 470-nm light, which emits no UV radiation.

The two MRSA populations studied—the US-300 strain of CA-MRSA and the IS-853 strain of HA-MRSA—represent prominent community-acquired and hospital-acquired strains, respectively.

The authors report that the higher the dose of 470-nm blue light, the more bacteria were killed. High-dose photo-irradiation was able to destroy 90.4% of the US-300 colonies and the IS-853 colonies. The effectiveness of blue light in vitro suggests that it should also be effective in human cases of MRSA infection, and particularly in cutaneous and subcutaneous infections.

"It is inspiring that an inexpensive naturally visible wavelength of light can eradicate two common strains of MRSA. Developing strategies that are capable of destroying MRSA, using mechanisms that would not lead to further antibiotic resistance, is timely and important for us and our patients," says Chukuka S. Enwemeka, PhD, FACSM, Co-Editor-in-Chief of the Journal and first author of the study.

## Stress May Hasten The Growth Of Melanoma Tumors But Common Beta-Blocker Medications Might Slow That Progress

Columbus, Ohio – For patients with a particularly aggressive form of skin cancer – malignant melanoma – stress, including that which comes from simply hearing that diagnosis, might amplify the progression of their disease.

But the same new research that infers this also suggests that the use of commonly prescribed blood pressure medicines might slow the development of those tumors and therefore improve these patients' quality of life.

The study, the third by Ohio State University scientists in the last two years that looked for links between stress hormones and diseases like cancer, is published in the journal Brain, Behavior and Immunity.

Eric V. Yang, a research scientist at the Institute for Behavioral Medicine Research (IBMR), exposed samples of three melanoma cell lines to the compound norepinephrine, a naturally occurring catecholamine that functions as a stress hormone. In times of increased stress, levels of norepinephrine increase in the bloodstream.

Yang and colleague Ronald Glaser were looking for changes in the levels of three proteins released by the cells. Glaser is a professor of molecular virology, immunology and medical genetics, member of the university's Comprehensive Cancer Center and director of the IBMR.

One of the proteins – vascular endothelial growth factor, or VEGF – plays a key role in stimulating the growth of new blood vessels needed to feed a growing tumor, a process called angiogenesis. The other two proteins, Interleukin-6 and Interleukin-8, are both involved in fostering tumor growth.

All three of the cell lines were grown from tissues taken from secondary tumors that had metastasized from a primary site and they signify aggressive forms of cancer. But one of them – C8161 – represented the most aggressive and advanced form of melanoma. "We noticed that all three of these proteins increased in response to the norepinephrine," Yang explained, adding that in the C8161 cells, "we got a 2,000 percent increase in IL-6. In untreated samples from this cell line, you normally can't detect any IL-6 at all.

The research is showing not only that different forms of cancer react differently to stress hormones but also that those reactions can vary within a specific form of the disease, with the possibility of a more aggressive form of the disease reacting more strongly to the stressors. "What this tells us is that stress might have a worse effect on melanoma that is in a very aggressive or advanced stage, and that one marker for that might be increased levels of IL-6," he said.

The researchers ruled out cell proliferation – an increase in the number of cells present – as a reason for the increase in all three proteins. That meant that the only other answer was that the cells were increasing their expression of the genes responsible for producing these compounds.

The researchers showed that the norepinephrine molecule binds to receptors on the surface of cancer cells and once this linkage occurs, it stimulates the release of the proteins that support angiogenesis and tumor growth.

Yang and Glaser first confirmed that the receptors were present on cells in all three cell lines and then tested what would happen when the receptors were blocked by common blood pressure medicine – the so-called "beta-blockers." When the beta-blockers did bind to the receptors, the production of the three proteins reduced significantly, suggesting that in patients with melanoma, using these types of medications might be used to slow the progression of the disease in patients.

While the study was restricted to tumor cell lines, rather than using animal models or human patients, the findings are still exciting. The researchers found strong evidence that the same receptors are expressed on the surface of tumor cells from biopsies that were taken from melanoma patients. That supports the clinical importance of the results.

Two earlier studies on different tumor cell lines – one prepared from a multiple myeloma and the other from a nasopharyngeal carcinoma – also showed that exposure to norepinephrine increased the levels of proteins responsible for accelerating tumor growth.

The research is showing not only that different forms of cancer react differently to stress hormones but also that those reactions can vary within a specific form of the disease, with the possibility of a more aggressive form of the disease reacting more strongly to the stressors.

For melanoma patients, that can be very important since these tumors are able to metastasize, or spread, when they are much smaller than most other solid cancers. The American Cancer Society estimates that nearly 48,000 cases of melanoma are diagnosed each year and nearly 8,000 people are killed each year by the disease.

*This research was supported in part by the National Cancer Institute. Other collaborators in the study included Sanford Barsky, professor and chair of pathology; and IBMR members Elise Donovan, Min Chen, Amy Gross, Jeanette Webster Marketon and Seung-jae Kim.*

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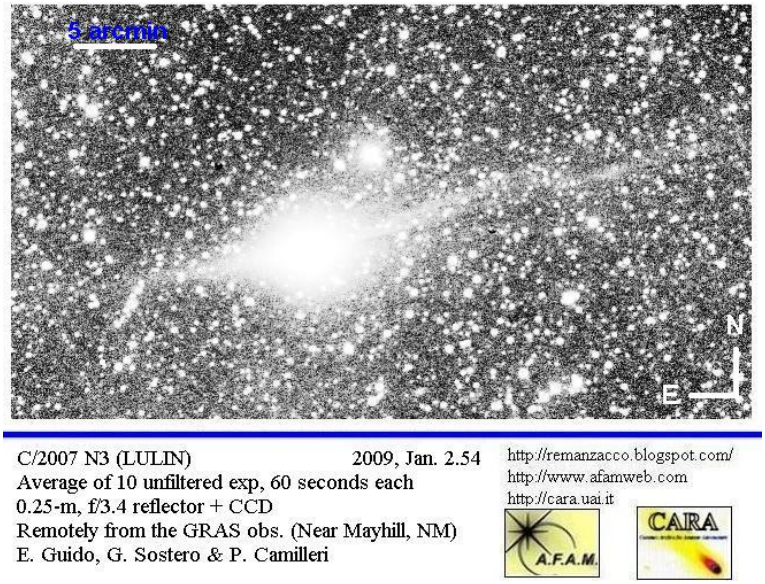
## New comet may be visible with the naked eye

* 11:16 30 January 2009 **by Jessica Griggs**

Late next month Earth will receive a new celestial visitor named Lulin - or Comet C/2007 N3 - which astronomers say may have never visited this corner of the solar system before and should be visible to the naked eye.

Comets are icy clumps of dust and small rocks left over from the beginnings of the solar system. As they near the Sun some of the outer layer of ice is vaporised, releasing gas and solid debris that fans out into a tail pointing directly away from the Sun.

Astronomer and author Gary Kronk, based in St Jacob, Illinois, estimates that by 24 February, Lulin's gas tail should appear as long as around eight times the diameter of a full Moon. At that time it will be a mere 38 million miles from Earth, almost as close as Mars reaches to our planet.




***Comet Lulin as seen on 2 January 2009. The image shows both the tail and the anti-tail (left)*** **(Image: Giovanni Sostero and Ernesto Guido, Remanzacco Observatory)**

### First time visitor?

By tracking Lulin since its discovery in the summer of 2007, astronomers have calculated that it had already been on the move for 10 million years before it arrived in the solar system. They say that either Lulin was once here 10 million years ago, or it was somehow knocked out of the Oort cloud of billions of comets that surrounds the solar system and has never entered the inner solar system before.

"If this is its first approach towards the Sun, we don't know how it will respond. Some comets become brighter than expected and some don't," explains Kronk. Lulin's brightness depends on how much the Sun can melt the comet's hard icy coat to release a visible tail of debris.

A comet on its first approach to the Sun can resist its heat, preventing a bright tail from appearing. But Kronk thinks Lulin will get close enough to our star to make that unlikely. He is confident that the comet will be visible with the naked eye, registering magnitude 5 on the standard brightness scale, where 6 is the faintest.

"This is what makes comets so amazing," he told New Scientist. "Every comet has its own personality. No-one knows exactly what the comet is going to do." Lulin will be moving fast enough to appear to be creeping across the background of more distant stars, he adds.

**Twin-tailed comet**

Lulin could also be one of only a few comets that appears to have two rather than one tail. The extra "antitail" becomes visible because Earth happens to be orbiting the Sun on the same plane as Lulin.

When solar wind blows gas and dust particles away from a comet, larger debris moves more slowly and lags behind the moving comet. The fanned tail appears to extend from both sides of the comet's body when viewed from the edge on.

The last comet with a visible antitail was Arend-Roland in 1957, says Kronk. "Lulin could give the best chance in my lifetime to see something like that," he adds.

Professional astronomers are also looking forward to Lulin's visit. Michael Mumma, director of the Goddard Center for Astrobiology, Maryland, and colleagues have scheduled three months of observations, starting next week, at the Keck telescopes on the summit of the Mauna Kea volcano in Hawaii.

By analysing the light from Lulin they hope to detect the hydrogen isotope deuterium, to strengthen their hypothesis that icy comets delivered some of the Earth's water during the first billion years after its formation.

## Men smell of cheese and women of onions

* 30 January 2009 **by Andy Coghlan**

LITTLE girls may be made of sugar and spice and all things nice, but their armpits smell of onions. And while free of slug or snail odours, men's armpits pack a powerful cheesy whiff.

That's the conclusion of research in Switzerland that involved taking armpit sweat samples from 24 men and 25 women after they had spent time in a sauna or ridden an exercise bike for 15 minutes.

The researchers found marked differences in the sweat from men and women. "Men smell of cheese, and women of grapefruit or onion," says Christian Starkenmann of Firmenich, a company in Geneva that researches flavours and perfumes for food and cosmetics companies.

The team found that the women's armpit sweat contained relatively high levels of an odourless sulphur-containing compound - 5 milligrams per millilitre of sweat versus 0.5 milligrams in men. When the researchers mixed this compound in the lab with bacteria commonly found in the armpit, the bugs turned it into a thiol - a previously discovered odour from armpits that is akin to onion.

"The more sulphur precursor we added, the more intense was the malodour," says Starkenmann, whose team's results appear in Chemical Senses (DOI: 10.1093/chemse/bjn076). Bacterial enzymes turn the otherwise odourless precursor into the malodour.

The men, meanwhile, had relatively high levels of an odourless fatty acid which turned into a cheesy odour when exposed to the same types of bacteria.

The balance of oniony to cheesy precursors in women's sweat made it smell worse than men's as rated by independent smell assessors.

Next, the team hope to develop new ingredients for deodorants that fight the smells. "We could make inhibitors that neutralise the precursors, or block the bacterial enzymes that do the conversion," says Starkenmann.

Some researchers are sceptical that gender is the main deciding factor, arguing that the patterns found in Swiss volunteers might not apply to other populations with different diets and genetic backgrounds. "Other factors include what you eat, what you wash with, what you wear and what genes you inherit," says Tim Jacob of Cardiff University in the UK.

## Teaching an old drug new tricks

### *Leprosy medicine holds promise as therapy for autoimmune diseases*

A century-old drug that failed in its original intent to treat tuberculosis but has worked well as an antileprosy medicine now holds new promise as a potential therapy for multiple sclerosis and other autoimmune diseases.

"We never expected that an old antibiotic would hit this target that has been implicated in multiple sclerosis, psoriasis and type 1 diabetes," says Johns Hopkins pharmacologist Jun O. Liu "People have been working for years and spending tens of millions of dollars on developing a drug to inhibit a specific molecular target involved in these diseases, and here, we have a safe, known drug that hits that target," known as the Kv1.3 potassium channel.

The finding about clofazimine, a synthetic compound made in the 1890s, is reported in Public Library of Science (PLoS One) by Johns Hopkins researchers, who uncovered the drug's latest potential during an ongoing and exhaustive screening of FDA-approved drugs designed to identify new uses for them. The Hopkins team was specifically hunting for immune system control agents within the Johns Hopkins Drug Library, a collection

assembled over the past seven years by Liu and colleagues of more than 3,000 drugs in pharmacies or being tested in phase II clinical trials.

The Johns Hopkins scientists say they were surprised to discover that clofazimine interferes with a molecular pathway important in orchestrating the human body's immune response.

"Until now, clofazimine's presumed target was not human cells, but bacteria," says Liu, professor of pharmacology and molecular science, Johns Hopkins University School of Medicine. "But we discovered the drug has a tremendous effect on human immune cells that are heavily involved in both the initiation and execution of an effective immune response."

More specifically, Liu's team sought drugs that stop the molecular signaling pathway that leads from the surface of an immune system cell to the cell's interior, where the signal turns on genes important in activating the immune response, Liu says. In autoimmune diseases, a person's own white blood cells, meant to fight infection or disease, are misguided to target and attack the body's own cells, damaging or destroying them.

To search for such compounds, the team first engineered cells to mimic an immune cell's natural signaling pathway, a complex and circuitous route from the cell surface to the genetic switch inside. They then subjected these specialized cells to the Drug Library, one at a time, and identified more than 200 hits — drugs that inhibited the signaling system significantly, by more than 50 percent.

When they compared the potency of the 200 with each other, "clofazimine was the hit with the highest inhibitory activity," Liu says.

Next, by systematically studying the multistep signaling process, the researchers pinpointed clofazimine's molecular target, a protein "pore" called ion channel Kv1.3, which plays an essential role in the complicated signaling process.

One of the key steps involved in turning on the immune response is the prolonged accumulation of calcium inside of immune cells, Liu explains. When the researchers stimulated an immune cell, setting the signaling event in motion, they noticed that lots of calcium flushed into the cell and lingered there. However, when they pretreated the immune cells with clofazimine, the calcium rush was much less and it didn't hang around as long.

"This let us conclude that clofazimine was blocking the calcium influx into the immune cells," Liu says. "Without enough calcium getting inside a cell, the signaling pathway that turns on the immune response was short-circuited." The Johns Hopkins group also showed that clofazimine tamps down the presence of free calcium in immune cells by disrupting a potassium channel. The combined effect is to shut down a signaling pathway involved in autoimmune disease.

*In addition to Jun O. Liu, authors of this paper are Yunzhao R. Ren, Fan Pan, Curtis R. Chong, Jing Xu, Yongjun Dang, and Jin Zhang, all of Johns Hopkins; Reinhold Penner, Suhel Parvez, and Andrea Fleig, all of the University of Hawaii; and Hongsi Jiang of Northwestern University.*

*On the Web:*

*http://www.hopkinsmedicine.org/pharmacology/research/liu.html*

*http://www.plosone.org/home.action*

## Study suggests that inflammation may be the link between extreme sleep durations and poor health

### *The activation of pro-inflammatory cytokines may be a mechanism by which short and long sleep durations affect health*

Westchester, Ill. — A study in the Feb. 1 issue of the journal SLEEP shows that sleep duration is associated with changes in the levels of specific cytokines that are important in regulating inflammation. The results suggest that inflammation may be the pathway linking extreme sleep durations to an increased risk for disease.

Each additional hour of self-reported sleep duration was associated with an eight-percent increase in C-reactive protein (CRP) levels and a seven-percent increase in interleukin-6 (IL-6), which are two inflammatory mediators. In contrast, each hour of reduction in sleep measured objectively by polysomnography was associated with an eight-percent increase in tumor necrosis factor alpha, another pro-inflammatory cytokine.

"The most surprising finding was that we found different relationships based on how sleep was measured," said lead author Dr. Sanjay R. Patel, assistant professor of medicine at Case Western Reserve University in Cleveland, Ohio.

According to the authors, research has linked both short and long sleep durations with an increased risk for mortality, coronary heart disease, diabetes and obesity. Chronic elevations in cytokines such as CRP and IL-6 also are associated with an increased risk of problems such as diabetes and heart disease.

The study involved 614 individuals from the Cleveland Family Study, a longitudinal family-based epidemiological cohort designed to study the genetics of obstructive sleep apnea (OSA). Participants completed

questionnaires about sleep habits and underwent one night of polysomnography. In the morning a fasting blood sample was collected, and it was analyzed for five inflammatory cytokines.

Mean self-reported habitual sleep duration was 7.6 hours; mean sleep duration measured by polysomnography on the night prior to blood sampling was 6.2 hours. Those with long sleep durations, assessed by either measure, were significantly younger. Short sleep duration measured by polysomnography was associated with an increased prevalence of diabetes, hypertension and obstructive sleep apnea.

According to the authors the differing patterns of association with cytokine levels suggest that self-reported habitual sleep duration may measure chronic sleep exposure, while polysomnography may measure an acute exposure. They also note that the two methods of measuring sleep duration may be influenced differently by an underlying predictor of sleep habits such as stress or mood, which may have a direct effect on cytokine levels.

## Ancient Turtle Migrated from Asia to America Over a Tropical Arctic

### *Fossil Find Suggests CO2 a Possible Culprit in Warm, Freshwater Arctic*

In Arctic Canada, a team of geologists from the University of Rochester has discovered a surprise fossil: a tropical, freshwater, Asian turtle.

The find strongly suggests that animals migrated from Asia to North America not around Alaska, as once thought, but directly across a freshwater sea floating atop the warm, salty Arctic Ocean.

Published today in the journal Geology, the finding also suggests that a rapid influx of carbon dioxide some 90 million years ago was the likely cause of a super-greenhouse effect that created extraordinary polar heat.

"We've known there's been an interchange of animals between Asia and North America in the late Cretaceous period, but this is the first example we have of a fossil in the High Arctic region showing how this migration may have taken place," says John Tarduno, professor of geophysics at the University of Rochester and leader of the Arctic expedition. "We're talking about extremely warm, ice-free conditions in the Arctic region, allowing migrations across the pole."

In 2006, Tarduno led an expedition to the Arctic to study paleomagnetism—the Earth's magnetic field in the distant past. Knowing from previous expeditions to the area that the rocks were rich with fossils, Tarduno kept an eye out for them and was rewarded when one of his undergraduate students uncovered the amazingly well preserved shell of a turtle. Together with collaborator Donald Brinkman of the Royal Tyrrell Museum of Canada, they later named the fossil Aurorachelys, or aurora turtle. The turtle strongly resembles a freshwater Mongolian species, which raised obvious questions about how it came to be in the marine waters of the North American Arctic.

Tarduno's paleomagnetic expertise, which allows him to ascertain when points on Earth's crust were at specific locations, allows him to rule out the possibility that millions of years of tectonic activity had brought the fossil from southern climes. The turtle was clearly a native of the area.

As to how a freshwater turtle migrated across a salty ocean; Tarduno points to the results of drilling by the Integrated Ocean Drilling Program's ACEX expedition that demonstrated episodes of unusually fresh surface waters in the past Arctic Ocean. Tarduno and his students had been studying massive lava flows that cover some of the High Arctic islands, and believes the same volcanic events that produced those igneous rocks also could have produced a series of islands along a low underwater mountain range in the Arctic Ocean called Alpha Ridge. If the ridge did indeed poke above the surface of the water at one time, it would have given the turtles—and countless other species—the ability to island-hop all the way from ancient Russia to Canada.

At the time the aurora turtle lived, the Arctic Ocean was probably even more separated from the global oceanic circulation system than it is today. Numerous rivers from the adjacent continents would have poured fresh water into the ancient Arctic sea. Since fresh water is lighter than marine water, Tarduno thinks it may have rested on top of the salty ocean water, allowing a freshwater animal such as the aurora turtle to migrate with relative ease.

Tarduno also believes it's possible that the same volcanic rock may not have allowed only the turtle's migration, but also would have contributed to creating the climate in which the turtle thrived.

"We found this turtle right on top of the last flood basalts—a large stretch of lava from a series of giant volcanic eruptions," says Tarduno. "That leads us to believe that the warming may have been caused by volcanoes pumping tremendous amounts of carbon dioxide into the Earth's atmosphere. There's evidence that this volcanic activity happened all around the planet—not just the Arctic. If it all happened on a short enough timescale, it could cause a super-greenhouse effect."

He notes that current changes in the recent Arctic climate have affected his field studies. "It is difficult to separate short-term climate trends from a longer-term pattern, but our last few field seasons in the High Arctic have been extraordinarily warm," says Tarduno. "Sometimes students exchange parkas for short-sleeve shirts."

Tarduno plans to return to the Arctic to look for places where other fossils might be located. He says the site he's found is incredibly rich, already yielding fossils he and his team are still analyzing. He says he hopes to paint a more complete picture of the time when the Arctic was warm.

## Particle accelerators could stop isotope shortages

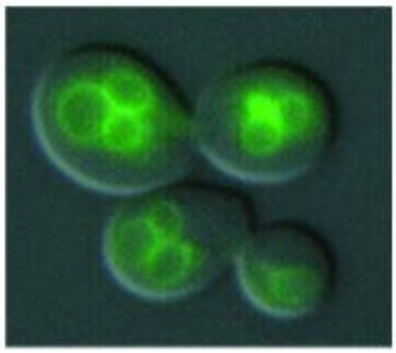
IF MEDICAL isotopes were created using particle accelerators rather than nuclear reactors it might keep the supply going when reactors shut down.

Thomas Ruth at Canada's National Laboratory for Particle and Nuclear Physics in Vancouver says that bombarding uranium with a powerful beam of light, rather than the neutrons used in traditional reactors, could produce the medical isotope molybdenum-99 (Nature, vol 457, p 5). The intense light could be produced by firing a 2-megawatt beam of electrons from a particle accelerator at a tungsten target.

The technique requires uranium-238, a less fissile uranium isotope than that used by reactors, making the fuel less dangerous if it fell into the wrong hands as it could not be used to create nuclear weapons. "It largely removes any security issues," says Ruth. The method, which is cheaper than building reactors, will allow more countries to make their own medical isotopes, he adds.

## Penn study finds link between Parkinson's disease genes and manganese poisoning

PHILADELPHIA – A connection between genetic and environmental causes of Parkinson's disease has been discovered by a research team led by Aaron D. Gitler, PhD, Assistant Professor in the Department of Cell and Developmental Biology at the University of Pennsylvania School of Medicine Gitler and colleagues found a genetic interaction between two Parkinson's disease genes (alpha-synuclein and PARK9) and determined that the PARK9 protein can protect cells from manganese poisoning, which is an environmental risk factor for a Parkinson's disease-like syndrome. The findings appear online this week in Nature Genetics.



*The Yeast PARK9 protein (Ypk9) is localized to the vacuole membrane. Shown are yeast cells expressing Ypk9 fused to the green fluorescent protein.* Alessandra Chesi, Ph.D., and Aaron Gitler, Ph.D., University of Pennsylvania

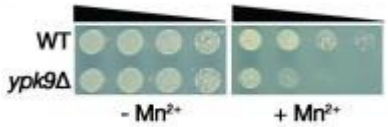
Manganism, or manganese poisoning, is prevalent in such occupations as mining, welding, and steel manufacturing. It is caused by exposure to excessive levels of the metal manganese, which attacks the central nervous system, producing motor and dementia symptoms that resemble Parkinson's disease.

In Parkinson's patients, the alpha-synuclein protein normally found in the brain misfolds, forming clumps. Yeast cells, the model system in which Gitler studies disease proteins, also form clumps and die when this protein is expressed at high levels. These are the same yeast cells that bakers and brewers use to make bread, beer, and wine.

As a postdoctoral fellow at the Whitehead Institute in Cambridge, Massachusetts, Gitler and colleagues started looking for genes that could prevent the cell death caused by mis-folded alpha-synuclein in yeast. Eventually they found a few genes to test in animal models and some were able to protect neurons from the toxic effects of alpha-synuclein. "One of the genes that we found was a previously uncharacterized yeast gene called YOR291W. No one knew what it did back in 2006," he recalls.

In the meantime, researchers in Europe published studies about a family that had an early-onset form of a type of Parkinson's disease caused by mutations in the PARK9 gene. "When I read about this study, I wondered what the closest yeast gene was to the human PARK9 gene and it turned out to be YOR291W," explains Gitler. "It was one of the genes that could rescue alpha-synuclein toxicity from our yeast screen. That was the big Eureka! and completely unexpected. It suggested that Parkinson's disease genes could interact with each other in previously unexpected ways."

Because of its similarity to the human PARK9 gene, Gitler and colleagues renamed the yeast gene to YPK9 (which stands for Yeast PARK9). Researchers at Purdue University and The University of Alabama teamed up with Gitler and his colleagues to show that the PARK9 gene could also protect neurons from alpha-synuclein's toxic effects.




*Yeast PARK9 gene (YPK9) helps protect cells from manganese toxicity. Yeast cells missing the YPK9 gene (ypk9) grow normally under standard conditions (- Mn2+) but are much more sensitive to manganese (+ Mn2+) than wild-type (WT) cells.* Alessandra Chesi, Ph.D., and Aaron Gitler, Ph.D., University of Pennsylvania School of Medicine

Next, the team set out to find the function of YPK9. Study co-first author, postdoctoral fellow Alessandra Chesi, PhD, discovered that YPK9 encodes a metal transporter protein. "Its sequence looks like other proteins that we know transport metals," says Chesi.

She deleted the YPK9 gene from yeast and the cells were fine. Then she exposed YPK9-deficient yeast cells to an excess of different metals -- zinc, copper, manganese, iron, etc. -- to determine which metal it might transport. Of all the metals Chesi tested, she found that in the presence of manganese, the YPK9-deficient yeast did not grow as well. They were hypersensitive to manganese.

"This was astonishing, because it was known for years that welders and miners that inhale manganese get a Parkinson's-like disease called manganese poisoning," says Chesi. "The specific neurons that are lost in the miners are from the globus pallidus, a brain motor center. The European parkinsonism patients with the PARK9 mutation also lose neurons in this region."

Gitler then found that the protein made by YPK9, the yeast gene equivalent of PARK9, is localized to the vacuole membrane in the yeast cell. Vacuoles are inner cell components that wall off toxic substances for later disposal. "Our hypothesis is that the vacuole, a bag in the cell that captures toxins, is sitting there and taking in manganese and sequestering it for detoxification, keeping it away from other cell organelles," explains Gitler. "But, having a mutation in the PARK9 gene causes problems for this process in yeast and possibly in humans".

"It's an interesting story that we've discovered in yeast and it will be important to see if it holds up in people. What's new is the connection between genetic and environmental causes of Parkinson's. How does PARK9 protect against alpha-synuclein toxicity and how does PARK9 help prevent manganese poisoning? This is what we will be investigating next."

*This work was funded in part by a National Institute of Health Director's New Innovator Award.*
*Gitler is an inventor on patents and patent applications that have been licensed to FoldRx Pharmaceuticals, a company that investigates drugs to treat protein-folding diseases.*