Tales of the 'Trojan horse drug' and the 'miracle dogs'

SALT LAKE CITY, March 23, 2009 - Diagnosed with an extremely aggressive form of cancer called anal sac adenocarcinoma, Oscar's future seemed bleak. Bedridden and unresponsive to chemotherapy or radiation, he would be lucky to survive three months. But thanks to an innovative new drug treatment, Oscar's cancer receded and he was walking again within two weeks.

Oscar's recovery was extraordinary enough, but his case was unusual for another reason. Oscar is a Bichon Frise, who scientists reporting here today at the 237th National Meeting of the American Chemical Society call "the Miracle Dog." Joseph A. Bauer, Ph.D., and colleagues described promising results with a drug called nitrosylcobalamin (NO-Cbl) in battling cancer in Oscar and three other canines without any negative side effects. While it gives profound hope to dog owners, NO-Cbl also points to a powerful new cancer treatment for humans - one that infiltrates cancer cells like a biological Trojan horse.

"We are one of the few research groups that is offering to treat dogs with cancer that otherwise have no hope," Bauer said. "With no other options available, most people in this situation opt to euthanize so that their pets don't go through the pain of disease and trauma of surgery."

About six million dogs are diagnosed with cancer each year in the United States. According to the National Cancer Institute (NCI), pets with cancer provide a win-win opportunity for cancer researchers. Scientists can study new cancer treatments in animals other than lab mice. And pets get access to new treatments that provide hope and in instances like NO-Cbl, additional time.

Bauer put it this way: "The beauty of using a dog or a cat to test a cancer drug is two-fold. First, the animal can get the benefit of the most up-to-date drug in cancer medicine. Second, the NCI gets data on pets that are exposed to the same environmental factors their owners are. They breathe the same polluted air and drink the same polluted water that you and I do every day. If you can find an agent to treat cancer that occurs in a dog with success, there is a higher likelihood that you can take that to the human population and have a much higher response rate than with mice."

Although NO-Cbl has been used in only a few dogs, daily treatments have led to promising results in each case. "In all four dogs, there has been a significant reduction in tumor size without any toxic side effects or discomfort," says Bauer.

Oscar was the first success story. Since then, Bauer has treated two other dogs. A six-year old golden retriever named Buddy was unable to walk due to a spinal tumor pinching essential nerves leading to his right hind leg. After nine months of daily NO-Cbl treatment, Buddy's tumor shrank by 40 percent and he was going on two mile walks. A 13-year-old female Giant Schnauzer with inoperable thyroid carcinoma also showed tumor reductions of 77 percent in less than 10 weeks.

"Our case studies demonstrate anti-tumor efficacy with limited toxicity to normal tissues," Bauer added. "NO-Cbl sensitizes multidrug-resistant cancer cells to the antitumor effects of several different drugs, so it may be valuable when utilized in combination regimes," he added.

The drug targets cancer cells with "biological Trojan horse technology." Cells have receptors for vitamin B12 on their outer surface. The receptors serve as docking ports where molecules of the vitamin, essential for cells to divide and multiply, attach and then enter the cell. In order to divide at their abnormally rapid pace, cancer cells grow extra B12 receptors - 100 times more than normal cancer cells. Scientists have been trying since the 1950s to exploit that vulnerability and make B12-based drugs that attach to the receptors, sneak into the cell, and deliver a knock-out dose of medication.

Bauer and his colleagues from the Cleveland Clinic attached nitric oxide (NO) molecules to vitamin B12. NO kills cancer cells. The B12 acts as the Trojan horse, easily slipping into cancer cells. The subsequent release of toxic NO kills the cancer cells from within.

The team's goal is to successfully treat 10 dogs with NO-Cbl and slingshot the drug into human use as soon as possible. Because of the genetic similarity between dogs and humans, Bauer says his approach should have a much better chance of getting through the FDA's strict drug approval chain.

But Bauer stresses he wants to get the NO-Cbl dog treatment approved, as well. "I'm committed to the animals, and my goal would be to do a dual clinical trial, Phase One human and Phase One dog," says Bauer.

Oscar is still alive and well. Today, Bauer is treating another Golden Retriever named Haley with a spinal tumor. "This is one of the most rewarding things I've ever done in my life," says Bauer, the owner of a two-year old Beagle. "It gets boring working in the lab, but to see the fruits of your labor in a positive outcome like this and to know you're responsible in some small way, that's pretty cool."

Redefining DNA: Darwin from the atom up

SALT LAKE CITY, March 23, 2009 – In a dramatic rewrite of the recipe for life, scientists from Florida today described the design of a new type of DNA with 12 chemical letters instead of the usual four. Presented here at the 237th National Meeting of the American Chemical Society (ACS), this artificial genetic system already is helping to usher in the era of personalized medicine for millions of patients with HIV, hepatitis and other diseases.

The research may also shed light on how life arose on Earth, by producing a self-sustaining molecule capable of Darwinian evolution and reproduction, much like one that many scientists suggest arose at the dawn of life on Earth nearly four billion years ago.

Led by Steven Benner, Ph.D., this team is rewriting the rulebook that Nobel laureates James Watson and Francis Crick started when they described DNA's structure in 1953. One of the crowning discoveries of 20th century science, Watson and Crick's discovery established how the four chemical "letters" of DNA - A, T, C and G - pair up.

"This is a man on the moon goal," says Steven Benner, Ph.D. "It has dragged us kicking and screaming into uncharted territory. But we've learned all sorts of reasons about how the Watson and Crick rules don't enable technology to do useful things like highly parallel amplification of DNA or highly parallel diagnosis of human diseases. These things are worth a lot of money."

These pairing rules, for instance, make it very difficult for researchers to develop multiplexed diagnostic tests for viral diseases - tests that require identification and tagging of viral DNA. Old methods used regular DNA to bind and tag foreign genetic material. But natural DNA would often bind with non-disease DNA and generate confusing false positive and false negative results.

Benner's artificial genetic system does not operate under Watson-Crick rules, so the tagging gives accurate results. Benner's artificial alphabet already has been applied commercially. It is the basis of a viral load detector, which helps personalize the health care of those 400,000 patients annually infected with hepatitis B, hepatitis C, and HIV, the cause of AIDS,

"This is a hundred million dollar product right now," Benner noted. "It's used to manage cystic fibrosis, as well. We can also use this technology to go into biological samples and extract known genes with cancer-causing mutations. We can do all of this because we have an artificial DNA system.

For patients with HIV and hepatitis, the viral load detector can mean the difference between life and death.

Modern drug cocktails for these diseases are highly effective, reducing the viral load in the bloodstream to nearly zero. But at some point, the virus mutates, enabling it to evade the drugs and repopulate. As the viral tide rises, there are no outward symptoms in the patient, so the mutated strain is often discovered long after the virus has spread again.

The viral load detector, which relies on Benner's 12 letter system to tag DNA, may change that.

"What we want to do with personalized care is to give you a cocktail, and then monitor you and discover when the virus becomes resistant to it," explains Benner. "Now we don't want to do that too soon – that would waste a lifetime of good viral inhibitors - but not too late, of course. The patient would go in once a month to get their viral load measured. At some point the virus mutates and its viral load goes up. Then you know you better change the cocktail."

Benner says that the artificial DNA system is poised to become an essential tool in genomics research. The 12 letter alphabet already underlies new work at the National Human Genome Research Institute to connect large quantities of genomic data with human medicine.

The 12 letter system might also shed light on one of most mysterious times in Earth's history - the dawn of life nearly four billion years ago. Many scientists believe that this might have occurred when DNA's ancient cousin, RNA, began to act like a living organism.

"The idea has been that life originated on earth as RNA molecules assembled randomly and spontaneously in the prebiotic soup," says Benner. "Then, one of them found the ability to make copies of itself. In doing so, it made those copies with imperfections, so that some of its 'kids' were a bit better. Most were worse, so the better ones took over more resources. That started Darwinian processes. The rest is history."

Benner's ultimate goal is to synthesize a similar life form in his lab at the Foundation for Applied Molecular Evolution. His 12 letter genetic system is capable of nearly all of the actions that define a living thing - reproduction, growth and response to its environment - all without the benefit of genes refined over billions of years of evolution.

"But it still isn't self-sustaining," Benner explains. "You need a graduate or post-doc to come in the morning and feed it. It doesn't look for its own food. No one has gotten that first step to work. If you start making estimates of how many molecules you have to look for in order to find one that does this, you're talking about 10,000,000,000,000,000,000,000,000,000,000,000 molecules."

While Benner continues to pursue a chemical system fully capable of Darwinian evolution, he emphasized the lessons already learned from the development of the 12 letter system.

"We haven't just taken things from nature, but we've actually understood something about how chemical structure is related to genetic behavior. With that, we've been able to make new versions of it," says Benner.

Vertigo linked to osteoporosis

ST. PAUL, Minn. – People who have osteoporosis are more likely to also have vertigo, according to a study published in the March 24, 2009, print issue of Neurology®, the medical journal of the American Academy of Neurology.

The study involved 209 people with benign positional vertigo with no known cause such as head trauma or ear surgery. Vertigo is an inner ear disorder that is a common cause of dizziness. The disorder is believed to be caused by loose calcium carbonate crystals that move in the sensing tubes of the inner ear.

The people with vertigo were compared to 202 people with no history of dizziness. People with osteoporosis, or low bone density, were three times more likely to have vertigo, and people with osteopenia, which is the stage before osteoporosis, were twice as likely to have vertigo as people who had normal bone density.

In women, 25 percent of those with vertigo had osteoporosis, compared to nine percent of those who did not have vertigo, and 47 percent of those with vertigo had osteopenia, compared to 33 percent of those without vertigo. For men, 12 percent of those with vertigo had osteoporosis, compared to six percent of those without vertigo, and 40 percent of those with vertigo had osteopenia, compared to 27 percent of those without vertigo.

"These findings suggest a problem with calcium metabolism in people with vertigo," said study author Ji Soo Kim, MD, PhD, of Seoul National University College of Medicine in Korea. "Women most often have their first case of vertigo in their 50s, when they are also having a drop in bone mass due to loss of estrogen. Estrogen is one of the main hormones that influence calcium and bone metabolism."

Kim said researchers haven't determined the role of estrogen in vertigo. Kim noted that the link between osteoporosis and vertigo was also found in men, so other factors must also play a role.

A recent guideline by the American Academy of Neurology found that vertigo can be treated easily and quickly through simple head and body movements. For more information, visit www.aan.com. The study was supported by the Brain Korea 21 Project.

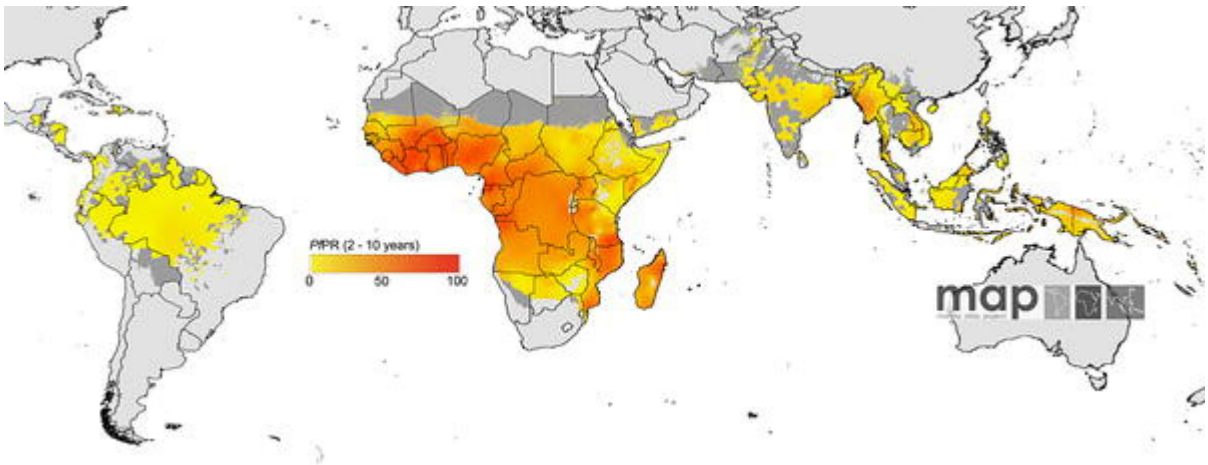
Comprehensive map of global malaria endemicity - a key resource for malaria control and elimination

Press release from PLoS Medicine

Using data from nearly 8000 local surveys of malaria parasite infection rates, an international team of researchers has built a global map showing the proportion of the population infected with the parasite Plasmodium falciparum at locations throughout the globe. Published in this week's PLoS Medicine, the map shows that areas where a high proportion of residents are infected are common – but by no means uniform – in Africa, while lower prevalence levels are found in the Americas and Central and Southeast Asia, although pockets of intermediate and high transmission remain in some parts of Asia.

Malaria is one of the most common infectious diseases in the world; the P. falciparum parasite causes about 500 million cases each year, and about 40% of the world's population lives in areas where malaria is transmitted.

The team of researchers, led by Simon Hay from the Department of Zoology at the University of Oxford, shows that global malaria endemicity is substantially lower than would be predicted from inspection of historical maps. Nevertheless, their map indicates that, in 2007, almost 60% of the 2.4 billion people at any risk of malaria were living in areas where malaria is constantly present – 0.69 billion people in Central and South East Asia, 0.66 billion in Africa, Yemen, and Saudi Arabia, and 0.04 billion in the Americas.



Part of the Malaria Atlas Project, the new map reflects the use of model-based geostatistics to incorporate data obtained across space and time. It provides an important new resource by indicating areas where malaria control can be improved, as well as areas where malaria elimination may be possible. Prior to this study, the

most recent global map of P. falciparum endemicity was published in 1968 and suffered from a number of limitations, such as incomplete description of the input data used and lack of estimates for the uncertainty in its predictions. In contrast, because of the statistical methods used to construct the new map published in PLoS Medicine, it is possible to quantify the uncertainty in the results.

"The state of the P. falciparum malaria world in 2007 represents an enormous opportunity for the international community to act," say the authors. "This cartographic resource will help countries determine their needs and serve as a baseline to monitor and evaluate progress towards interventional goals."

Information about the development of the Malaria Atlas Project can also be found in a previous PLoS Medicine Health in Action paper by Simon Hay and Robert Snow, and a previous PLoS Medicine Research Article by Carlos Guerra and colleagues.

***Citation**: Hay SI, Guerra CA, Gething PW, Patil AP, Tatem AJ, et al. (2009) A world malaria map: Plasmodium falciparum endemicity in 2007. PLoS Med 6(3): e1000048. doi:10.1371/journal.pmed.1000048*
http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.1000048

Alcohol-induced flushing is a risk factor for esophageal cancer from alcohol consumption

Press release from PLoS Medicine

There is growing evidence, say researchers in this week's PLoS Medicine, that people who experience facial flushing after drinking alcohol are at much higher risk of esophageal cancer from alcohol consumption than those who do not.

About a third of East Asians (Japanese, Chinese, and Koreans) show a characteristic physiological response to drinking alcohol that includes facial flushing, nausea, and an increased heart rate. This so-called "alcohol flushing response" is predominantly due to an inherited deficiency in an enzyme called aldehyde dehydrogenase 2 (ALDH2). Although clinicians and the East Asian public generally know about the alcohol flushing response, few are aware of the accumulating evidence that ALDH2-deficient individuals are at much higher risk of esophageal cancer (specifically squamous cell carcinoma) from alcohol consumption than individuals with fully active ALDH2.

Dr Philip Brooks and colleagues from the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Maryland, USA, along with Dr. Akira Yokoyama from the Kurihama Alcohol Center in Japan, say that this lack of awareness is "unfortunate as esophageal cancer is one of the deadliest cancers worldwide, with five-year survival rates of 15.6% in the United States, 12.3% in Europe, and 31.6% in Japan."

"Our goal in writing this article," say the researchers, "is to inform doctors firstly that their ALDH2-deficient patients have an increased risk for esophageal cancer if they drink moderate amounts of alcohol, and secondly that the alcohol flushing response is a biomarker for ALDH2 deficiency."

Clinicians, they say, can determine ALDH2 deficiency simply by asking about previous episodes of alcohol-induced flushing.

"As a result," say Dr Brooks and colleagues, "ALDH2-deficient patients can then be counseled to reduce alcohol consumption, and high-risk patients can be assessed for endoscopic cancer screening."

In view of the approximately 540 million ALDH2-deficient individuals in the world, many of whom now live in Western societies, even a small percent reduction in esophageal cancers due to a reduction in alcohol drinking would translate into a substantial number of lives saved.

***Citation**: Brooks PJ, Enoch M-A, Goldman D, Li T-K, Yokoyama A (2009) The alcohol flushing response: An unrecognized risk factor for esophageal cancer from alcohol consumption. PLoS Med 6(3): e1000050. doi:10.1371/journal.pmed.1000050*
http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.1000050

The legendary Himiko may have lived here

The Asahi Shimbun

NARA--Researchers say they have found evidence of what may be an early third-century palace that could have been part of the Yamatai kingdom ruled by Himiko, the legendary queen.

Excavations at the Makimuku ruins in Sakurai, Nara Prefecture, show there were as many as three buildings facing the same direction in a line, the city's board of education said Friday.

The site is estimated to date from the late second century to early fourth century.

Researchers also uncovered evidence of fortified barriers stretching 40 meters.

Holes for pillars, marked yellow, at the Makimuku ruins in Sakurai, Nara Prefecture, indicate a sophisticated structure stood in ancient times. The white poles denote fortifications. **(TAKAHARU YAGI/ THE ASAHI SHIMBUN)**

It is the first time that such a sophisticated series of structures has been found from that period, said an official of the city education board.

"The site could have been the western end of an important place, such as a palace," said an expert.

In 1978, researchers with the Kashihara Archaeological Institute in Kashihara, Nara Prefecture, discovered evidence of what appeared to have been a shrine measuring 5 meters by 5 meters, along with a 15-meter-long fortified barrier.

Excavations from February by Sakurai city turned up three holes for pillars measuring about 15 centimeters in diameter about 5 meters east of the shrine-like building, as well as a 25-meter barrier which presumably consisted of wooden stakes.

The evidence suggests a building of at least 6 meters in length stood from north to south.

An examination of past discoveries suggests that pillar holes found 10 meters to the west of the shrine-like building may have been part of a separate structure that measured more than 2 meters by 5 meters.

The education board plans to continue digging from the new fiscal year starting April 1 to find out if the site stretches eastward.

Hironobu Ishino, an archaeologist and director of the Hyogo Prefectural Museum of Archaeology, said it may have been the site of a palace for Himiko.

"It is absolutely stunning to find three buildings dating from as early as the third century that were lined up straight," he said. "It is such a beautiful layout. I wonder if it reflects the influence of Chinese culture. "If the site is really from the ancient Yamatai kingdom, then the remains might have been a palace of Himiko's."

Kaoru Terasawa, an official at the Kashihara Archaeological Institute, agrees the site is very significant.

"The fact that it was surrounded by a complex array of barriers would mean the place was very special," he said. "The pillar holes found so far are too small for a central building, but I hope the extended excavation to the eastern area will turn up evidence of a larger building."

Some experts say the Makimuku ruins, which lie 1.5 kilometers north to south and 2 km east to west, was the burial mound for Himiko, who is said to have died in 248.(IHT/Asahi: March 23,2009)

Licorice extract blocks colorectal cancer in mice

Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, and drugs that selectively target a protein known as COX-2 prevent the development of intestinal polyps, the precursors of colorectal cancer. However, these drugs have severe side effects that preclude their routine use in the prevention of colorectal cancer. But now, a team of researchers, at Vanderbilt University School of Medicine, Nashville, has found that inhibiting an enzyme known as 11-beta-HSD2 (both genetically and using an extract from licorice) blocks COX-2 activity in human and mouse colorectal tumor cells, inhibiting their growth and metastasis in experimental models of colorectal cancer. Importantly, long-term inhibition of 11-beta-HSD2 did not have side effects on the heart and blood vessels of mice, as long-term treatment with selective COX-2 inhibitors does. The authors therefore suggest that inhibiting 11-beta-HSD2 might provide a new approach to preventing colorectal cancer.

In an accompanying commentary, Paul Stewart and Stephen Prescott, highlight the importance of these data for the development of a potential new therapeutic option in colorectal cancer.

***TITLE**: Inhibition of 11-beta–hydroxysteroid dehydrogenase type II selectively blocks the tumor COX-2 pathway and suppresses colon carcinogenesis in mice and humans*

Vitamin D supplements associated with reduced fracture risk in older adults

Oral vitamin D supplements at a dose of at least 400 international units per day are associated with a reduced risk of bone fractures in older adults, according to results of a meta-analysis published in the March 23 issue of Archives of Internal Medicine, one of the JAMA/Archives journals.

"The anti-fracture benefits of vitamin D have been questioned by several recent trials, leading to uncertainty among patients and physicians regarding recommendations for vitamin D supplementation," the authors write as background information in the article. "Factors that may obscure a benefit of vitamin D are low adherence to treatment, low dose of vitamin D or the use of less potent ergocalciferol (vitamin D2)."

Heike A. Bischoff-Ferrari, Dr.P.H., of the University of Zurich, University Hospital, Zurich, Switzerland, and colleagues performed a meta-analysis on 12 previously published clinical trials of oral vitamin D supplements among adults age 65 or older. These double-blind randomized controlled trials involved 42,279 participants (average age 78) and looked at non-vertebral (non-spinal) fractures, including eight trials of 40,886 participants specifically studying hip fractures.

When the results of the trials were pooled, vitamin D supplements decreased the risk of non-vertebral fractures by 14 percent and of hip fractures by 9 percent. The authors then pooled the results of only the nine trials in which participants received doses of more than 400 international units per day. At this dosage, vitamin D supplements reduced non-vertebral fractures by 20 percent and hip fractures by 18 percent. Doses of 400 international units per day or lower did not reduce the risk of either fracture type. A greater reduction in risk

was also seen among trial participants whose blood levels of 25-hydroxyvitamin D (a commonly used measure of blood vitamin D levels) achieved a greater increase.

Among individuals taking high doses of vitamin D, additional calcium did not appear to have any further protective effect against fractures. "Physiologically, the calcium-sparing effect of vitamin D may explain why we did not see an additional benefit of calcium supplementation at a higher dose of vitamin D," the authors write.

"The greater fracture reduction with a higher received dose or higher achieved 25-hydroxyvitamin D levels for both any non-vertebral fractures and hip fractures suggests that higher doses of vitamin D should be explored in future research to optimize anti-fracture efficacy," they conclude. "Also, it is possible that greater benefits may be achieved with earlier initiation of vitamin D supplementation and longer duration of use. Our results do not support use of low-dose vitamin D with or without calcium in the prevention of fractures among older individuals."

(Arch Intern Med. 2009;169[6]:551-561. Available pre-embargo to the media at www.jamamedia.org.)

***Editor's Note**: This study was supported by a Swiss National Foundation Professorship grant and a fellowship grant by the Robert Bosch Foundation. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, funding and support, etc.*

Social isolation makes strokes more deadly, study finds

COLUMBUS, Ohio -- New research in mice suggests that social isolation may promote more damaging inflammation in the brain during a stroke.

Researchers at Ohio State University found that all the male mice that lived with a female partner survived seven days after a stroke, but only 40 percent of socially isolated animals lived that long.

In addition, the paired mice suffered much less brain damage than did the surviving solitary mice.

"Under nearly every measure, it seems that there was something about living together that protected the mice by reducing the damaging inflammatory response," said Kate Karelina, lead author of the study and a doctoral student in neuroscience at Ohio State University.

In a series of experiments, Karelina and her colleagues induced experimental strokes in male mice. Some of the mice lived with a female partner for two weeks before the stroke and continuing afterwards. Other mice lived alone before and after the stroke. A control group of mice underwent similar surgery in the brain, but did not have an induced stroke. The research is scheduled to appear this week in the online early edition of the Proceedings of the National Academy of Sciences.

The reasons for the higher survival rate for the socially housed mice were evident when the researchers compared brain tissues of mice after the stroke.

The researchers examined tissue samples in different groups of mice 12 hours, one day, three days or seven days after the stroke to determine the extent of damage.

"We confirmed that that social isolation contributes to the extent of neuronal damage in the brain as early as 24 hours after the stroke," said Courtney DeVries, associate professor of psychology and neuroscience at Ohio State, and a member of the university's Institute of Behavioral Medicine Research.

The amount of tissue damage in the brain was about four times larger in the mice housed alone compared to those housed with another mouse.

"The number of neurons dying is significantly decreased in the pair-housed mice," DeVries said.

In addition, socially housed mice had significantly less edema, or excess water in the brain, when compared to the isolated animals.

"In clinical stroke, edema is a major concern because it can lead to additional neuronal damage, so it is significant that pair housing reduced edema," Karelina said.

The study showed that two genes associated with damaging inflammation in the brain – MAC-1 and glial fibrillary acidic protein, or GFAP – showed decreased activation in the socially housed mice.

In addition, findings revealed that mice that lived with others had significantly higher levels of a cytokine in their brain called interleukin-6 (IL-6) that has an anti-inflammatory response in the brain, helping to limit damage caused by the stroke.

The finding about IL-6 is especially interesting, Karelina said, because IL-6 appears to have opposite effects in the brain than it does in the rest of the body. "IL-6 reduces inflammation in the brain, so it is protective in a stroke, but it is a pro-inflammatory in the periphery of the body," Karelina said.

One practical result of this finding, DeVries said, is to caution researchers as they look for ways to limit damaging inflammation in the body.

For example, if drug developers wanted to develop a medicine to reduce levels of IL-6 in the body in order to minimize its pro-inflammatory response, they would have to take into account that IL-6 actually protects the brain by reducing inflammation there.

Overall, the study provides some early clues as to how social support may protect people who suffer strokes.

"We're learning more about what it is about social support that helps stroke victims have more positive outcomes," Karelina said.

Other co-authors on the study, all from Ohio State, were Greg Norman, a psychology graduate student; Ning Zhang, research associate in psychology; John Morris, a graduate student in psychology; and Haiyan Peng, a graduate student in neuroscience. The work was supported by grants from the American Heart Association, the National Institute of Neurological Disorders and Stroke and the National Heart, Lung, and Blood Institute.

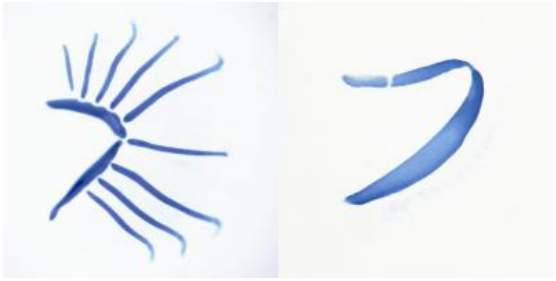
Research links evolution of fins and limbs with that of gills

The genetic toolkit that animals use to build fins and limbs is the same genetic toolkit that controls the development of part of the gill skeleton in sharks, according to research to be published in Proceedings of the National Academy of Sciences on March 23, 2009, by Andrew Gillis and Neil Shubin of the University of Chicago, and Randall Dahn of Mount Desert Island Biological Laboratory.

"In fact, the skeleton of any appendage off the body of an animal is probably patterned by the developmental genetic program that we have traced back to formation of gills in sharks," said Andrew Gillis, lead author of the paper and a graduate student in the Department of Organismal Biology and Anatomy at the University of Chicago. "We have pushed back the evolutionary origin of the developmental genetic program that patterns fins and limbs."

This new finding is consistent with an old theory, often discounted in science textbooks, that fins and (later) limbs evolved from the gills of an extinct vertebrate, Gillis added. "A dearth of fossils prevents us from definitely concluding that fins evolved from gills. Nevertheless, this research shows that the genetic architecture of gills, fins and limbs is the same."

The research builds on the breakthrough discovery of the fossil Tiktaalik, a "fish with legs," by Neil Shubin and his colleagues in 2006. "This is another example of how evolution uses common developmental programs to pattern different anatomical structures," said Shubin, who is the senior author on the PNAS paper and Professor and Associate Dean of Organismal and Evolutionary Biology at the University of Chicago. "In this case, shared developmental mechanisms pattern the skeletons of vertebrate gill arches and paired fins."



***The shark arch gill skeleton (left) shows primitive gill rays that are found only in sharks and other cartilaginous fishes. The gills of other fishes (right) are also arched but lack gill rays. This primitive feature of sharks allowed the researchers to link the developmental genetic program for fins and limbs to the more primitive one for gill rays*. Image by J. Andrew Gillis, University of Chicago**

The research also showed for the first time that the gill arch skeleton of embryonic skates (a living relative of sharks that has gill rays) responds to treatment with the vitamin A derivative retinoic acid in the same way a limb or fin skeleton does: by making a mirror image duplicate of the structure as the embryo develops. According to the researchers, the genetic circuitry that patterns paired appendages (arms, legs and fins) has a deep evolutionary origin that actually predates the origin of paired appendages themselves.

"These findings suggest that when paired appendages appeared, the mechanism used to pattern the skeleton was co-opted from the gills," Gillis said. "Perhaps we should think of shark gills as another type of vertebrate appendage - one that's patterned in essentially the same way as fins and limbs."

The deep structural, functional, and regulatory similarities between paired appendages and developing gill rays, as well as the antiquity of gills relative to paired appendages, suggest that the signaling network that is induced by retinoic acid had a patterning function in gills before the origin of vertebrate appendages, the research concludes. And this function has been retained in the gill rays of living cartilaginous fishes.

New research reveals the earliest evidence for corn in the New World

Among the hundreds of plants that have been domesticated in the New World, none has received as much attention or been subject to as much debate as corn, or maize (Zea mays L.), arguably the most important crop of the Americas. Controversies have existed for years over what the wild ancestor of maize is and where and when it was domesticated.

An international team of scientists led by Dolores Piperno, archaeobotanist at the Smithsonian's National Museum of Natural History, and Anthony Ranere, professor of anthropology at Temple University in

Philadelphia, have discovered the first direct evidence that indicates maize was domesticated by 8,700 years ago, the earliest date recorded for the crop. The research findings will be published March 23 in the journal, Proceedings of the National Academy of Sciences.

It is certain that maize was originally domesticated in Mexico from a wild plant called "teosinte," and genetic studies of modern populations of teosinte and maize suggested this event occurred somewhere in the Central Balsas Valley region of tropical southwest Mexico. However, no research on early prehistoric human settlement and agriculture had been carried out there. Piperno and the team searched this region of Mexico for locations that showed human occupancy for the time period they thought to be critical to maize domestication, from approximately 8,000 to 9,000 years ago. They discovered sites dating to this age, excavated them and analyzed the stone tools and plant remains they retrieved. Microfossil (starch grain and phytolith) analysis from a rock shelter called Xihuatoxtla, conducted in part with Irene Holst at the Smithsonian Tropical Research provide direct evidence for the domestication of maize and a species of squash.

"Our findings confirm an early Holocene age for maize domestication and indicate that it is another important New World crop that had its origins in the tropical forest," said Piperno. "Much more work needs to be done in the Central Balsas region to investigate even earlier periods when teosinte must have been exploited by early human populations and then initially cultivated."

The evidence corroborates a large quantity of previous research carried out in the lowland tropical forest south of Mexico by Piperno and other investigators that indicated maize spread to Panama approximately 7,600 years ago and was well established in northern South America about 6,000 years ago.

The archaeological record establishes tropical southwest Mexico as an important region where early agriculture occurred in the New World and adds maize to the roster of important cereals (others are wheat and barley from the Middle East) that were cultivated and domesticated by 9,000 years ago. The team's findings also contribute to the growing body of evidence that seasonally dry tropical forests were important centers of early human settlement and farming in the Neotropics. Early agriculture in this region of Mexico appears to have involved small groups of cultivators who were shifting their settlements seasonally and engaging in a variety of subsistence pursuits.

New data on cancer survival in Europe show more patients are cured

New data and analyses from a long-running study of cancer survival in Europe have shown that the number of people actually cured of cancer – rather than just surviving for at least five years after diagnosis – is rising steadily.

A special issue of the European Journal of Cancer [1] containing reports from the EUROCARE-4 Working Group, includes, for the first time, an estimate of the proportions of patients who are cured of their cancer in Europe and who, therefore, have a life expectancy equal to that of the rest of the population. The analysis divides patients into two groups – the proportion who may be considered cured of their disease and who are likely to die of something else, and those who will die of their cancer.

The study compared two periods – 1988-1990 and 1997-1999 – and found the proportion of patients estimated to be cured of lung, stomach and colorectal cancers increased from 6% to 8%, from 15% to 18% and from 42% to 49%, respectively.

Dr Riccardo Capocaccia of the National Centre for Epidemiology, Surveillance and Health Promotion (Rome, Italy), who is the guest editor of the EUROCARE-4 special issue, said: "Increases between 1988-1990 and 1997-1999 in the estimated proportion of European patients cured of lung, stomach and colorectal cancers are noteworthy. The proportion cured is not affected by 'lead time' (earlier diagnosis without improvement in life expectancy), so these trends suggest genuine progress in cancer control."

However, as with many other papers in the EJC special issue, the paper on the proportion of cured patients showed there were significant differences between countries in Europe.

For all cancers combined, most men (47%) were cured in Iceland and most women (59%) were cured in France and Finland, while in Poland the least men (21%) and women (38%) were cured.

Dr Capocaccia said: "For all cancers combined, the very wide range in the proportion of patients cured in the contributing countries, ranging from 21% to 47% in men and 38% to 59% in women, also depends on the varying frequency across Europe of the different cancers. This proportion is, therefore, also an indicator of Europe-wide variations in cancer control, because it reflects progress in diagnosis and treatment, as well as success in the prevention of the most fatal cancers.

"Geographic variation in the estimated proportion of patients diagnosed in 1988-1999 who were cured ranged from about 4% to 10% for lung cancer, from 9% to 27% for stomach cancer, from 25% to 49% for colon and rectum cancer, and from 55% to 73% for breast cancer."

For instance, Denmark, Czech Republic and Poland had the lowest proportion of cured lung cancer patients (less than 5%), while France and Spain had the highest (more than 10%). For colorectal cancer, less than 30% were cured in Poland, Czech Republic and Slovenia but 49% were cured in France. In Finland, France, Spain and Sweden, about 73% of breast cancer patients were cured, while the proportion was less than 60% in Czech Republic, Poland and Slovenia.

For prostate cancer, the proportion of men cured was associated more with the intensity of PSA testing activity than with the efficacy of treatments. France led the way with more than 60% of men cured, while only 14% were cured in Denmark. This difference was largely due to cases diagnosed earlier through the PSA test, and many of these prostate cancers would not have killed and might not even have given rise to any symptoms. Indeed, prostate cancer mortality was no higher in Denmark than elsewhere in Northern Europe.

For breast cancer, results showed a gap between Poland, the Czech Republic and Slovenia and more western European countries of about 10%. "Part of this difference has been attributed to the introduction of breast cancer screening from the mid-1990s in several western European countries. If this is true, the implication is that early diagnosis saves the lives of women with breast cancer by rendering their disease more curable," said Dr Capocaccia.

The EUROCARE study has been running since 1990 and is the widest epidemiological study on the survival of cancer patients in Europe. This most recent report, EUROCARE-4, includes data from 93 population-based cancer registries in 23 European countries, covering a total population of about 151,400,000, which represents 35% of the total population in those countries. The EUROCARE-4 database contains the anonymised records for more than 13,500,000 cancer patients diagnosed during the period 1978-2002, with information on their vital status up to 31 December 2003 or later. Preliminary data on survival from EUROCARE-4 were published in 2007.

In addition to the estimates of the proportion of patients cured, data in the EJC special issue that are new since 2007 include comparisons of survival between the elderly and the middle-aged, between men and women and the survival of children.

Survival of the elderly (70-99 years) was lower than for middle-aged patients (55-69 years). Dr Capocaccia said: "This is probably due to more advanced stage of disease at diagnosis, other serious conditions, and more difficult access to, or lack of availability of, appropriate care. The difference was particularly evident for women. During the period 1995-2002 covered by EUROCARE-4, five-year survival improved less for patients aged 70-84 than for those aged 55-69, widening the gap in survival between these two age bands. Survival differences between the oldest and middle-aged patients were mainly concentrated in the first year after diagnosis: five-year survival conditional on survival for the first year after diagnosis varied much less with age than unconditional five-year survival, suggesting that older patients are often diagnosed too late to be efficiently treated."

Women have longer life expectancy than men and better survival from chronic diseases like cardiovascular disease and cancer. Age-adjusted five-year relative survival was higher in women than men for 21 out of 26 types of cancer for which survival was estimated in both sexes. Particularly marked differences were found for cancers of the head and neck, bone, thyroid and stomach, and for melanoma of the skin. Women had significantly lower survival only for cancers of the biliary tract, bladder and larynx. For all cancers combined, and after adjustment for age and for the different patterns of cancer in each sex, women had a two per cent overall advantage in five-year survival (52% vs. 50%). The survival advantage for women younger than 64 was four per cent; this difference decreased with increasing age, becoming negligible in the elderly.

"This suggests that sex hormone patterns may play a role in the consistently higher survival seen for women," said Dr Capocaccia.

In children, adolescents and young adults, five-year survival for all cancers combined was 81% in children (0-14 years) and 87% in adolescents and young adults (15-24 years). From 1995-1999 to 2000-2002, the risk of death within five years of diagnosis fell significantly for young patients, by 8% in children and 13% in adolescents and young adults. International differences in survival also narrowed for children and young adults. Survival improved over time for all the main cancer types affecting the young. The improvement was statistically significant for acute lymphoid leukaemia and central nervous system tumours in children and for non-Hodgkin lymphoma in adolescents and young adults.

"Cancer survival in patients aged less than 25 years is poorly documented in Eastern European countries. Complete cancer registration should be a priority for these countries, as an essential part of a policy for effective cancer control in Europe," said Dr Capocaccia.

Professor Alexander M.M. Eggermont, president of ECCO – the European CanCer Organisation, welcomed the latest data from EUROCARE-4. "EUROCARE-4 provides essential information on the pattern of survival

of cancer patients across Europe. Without this information it would be impossible to assess whether improvements in cancer diagnosis, treatment and care are actually having an effect on the outcome for patients. It also tells us what cancers and which areas of Europe need to be targeted for further research and investment.

"The good news is that, for most cancers, survival has increased during the 1980s and 1990s. There were big differences between countries; however, most of the largest increases in survival have occurred in countries where survival was low at first, and this has contributed to a reduction in the disparities in survival across Europe.

"Europe is changing, with more countries joining the EU, and cancer medicine is also changing and improving. This means that more people have higher expectations of the medical profession. We must do our best to meet these expectations and help both patients and colleagues by disseminating information about better diagnostics, treatments and cures as widely as possible across the whole of Europe, and, indeed, the world. This will be achieved by collaboration and communication, and future EUROCARE studies will, no doubt, chart how successful we have been. Cancer registries play a vital role here, and I would urge all countries to protect and develop them so that information on cancer incidence and survival becomes ever more accurate."

***Notes**: [1] European Journal of Cancer, Vol 45, issue 6 (April 2009), pages 901-1094. "Survival of cancer patients in Europe, 1995-2002: The EUROCARE 4 Study."*

Synthetic blood from embryos bid

UK scientists plan a major research project to see if synthetic human blood can be made from embryonic stem cells.

Led by the Scottish National Blood Transfusion Service, the three year trial could provide an unlimited supply of blood for emergency transfusions. The blood should be free of infections like the human form of mad cow disease. Teams will test human embryos left over from IVF treatment to find those destined to develop into the universal "O-negative" blood donor group.

O-negative blood can be transfused into anyone without fear of tissue rejection and is the only safe option when a patient's blood group is unknown or not immediately available.

This precious blood is in limited supply because only 7% of the population belongs to this blood group.

The Wellcome Trust is understood to have promised £3m towards the cost of the multimillion-pound project, with further funding coming from the blood transfusion services of Scotland, and England and Wales.

The Irish government is also believed to be involved.

The project will be led by Professor Marc Turner of Edinburgh University who is the director of the Scottish National Blood Transfusion Service.

He said the work would begin in the next few weeks after final approval had been gained from the relevant research bodies.

Stem cells are the body's master cells, with the ability to transform into any type of tissue.

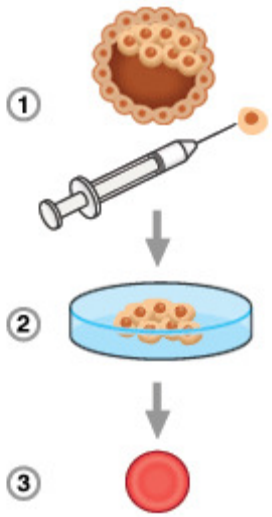
Scientists have already shown it is possible to take a single stem cell from an early human embryo and encourage it to develop into mature blood cells in the laboratory. And a US firm called Advanced Cell Technology has managed to produce billions of red blood cells from embryonic blood cells in this way.

The challenge now is to scale up the production and move the science from the lab to the bedside, which will take years.

Professor Turner said: "We should have proof of principle in the next few years, but a realistic treatment is probably five to 10 years away. "In principle, we could provide an unlimited supply of blood in this way." However, many groups object to the use of embryonic stem cells on the grounds that it is unethical to destroy embryos in the name of science.

Josephine Quintavalle of the public interest group Comment on Reproductive Ethics said: "Like so many of the claims associated with embryonic stem cells, this is first steps research rather than a cure around the corner, and just as hypothetical as the rest of the claims which try to justify destroying the human embryo for the benefit of mankind.

"Associating this controversial research with a National Blood Transfusion service may even end up contaminating the feel-good image of blood banks. "Those who donate blood but who



Making blood from embryos

1. Embryo created from IVF is tested for O-negative blood group, then allowed to develop for several days until stem cells can be extracted
2. Stem cells are cultured in laboratory with nutrients to stimulate red blood cell creation
3. Nuclei are removed in final stage to produce oxygen-carrying mature blood cells. Trillions of these will be needed to build up a blood bank

defend the right to life of the human embryo may be reluctant to continue giving their blood."

New research highlights dramatically reduced risk of developing dementia

Study reveals risk of developing condition is 'widely overestimated' by GPs

People with memory problems are less at risk of developing dementia than previously thought, a new study led by the University of Leicester and Nottinghamshire Healthcare NHS Trust reveals.

The five year research published in Acta Psychiatrica Scandinavica analysed data from 41 studies and dovetails with a Government focus to establish memory clinics in every town in the UK.

The research led by Dr Alex Mitchell from the University of Leicester Department of Cancer Studies and Molecular Medicine was carried out with Dr. Shiri-Feshki of Nottinghamshire Healthcare NHS Trust.

Dr Mitchell said: "This new research suggests that people with mild cognitive impairment (MCI) appear to have a lower risk of progressing to dementia than previously believed. "Mild cognitive impairment (MCI) is an important disorder of memory and related areas found in about 1 in 6 people seen in general practice. The condition can occur in mid or late life and until recently most doctors told people with MCI that their risk of developing dementia was up to 15% per year making deterioration almost inevitable within 5 to 10 years.

"Our research found that the proportion of people who progressed was 10% per year in high risk groups and in fact only 5% per year in low risk groups. Moreover only a minority (20-40%) of people developed dementia even after extended follow-up and the risk appeared to reduce slightly with time.

"These results should be seen as positive for those with memory problems even for those that struggle with the kind of memory tests given by the GP or in a memory clinic. There is a large effort to find out who is most at risk of further decline as well to find strategies that might slow down such progress."

GPs have often been reluctant to give a diagnosis of MCI because of its consequences but this current finding should encourage clinicians to identify people with memory problems. Many such individuals stay stable for a long period and a substantial number also improve.

There are at least 1 million people in the UK with MCI without dementia. In February the government announced funding for a specialised memory clinic in every town giving important focus on this often overlooked condition.

http://www.dh.gov.uk/en/socialcare/deliveringadultsocialcare/olderpeople/nationaldementiastrategy/index.htm

Listening to pleasant music could help restore vision in stroke patients, suggests study

Patients who have lost part of their visual awareness following a stroke can show an improved ability to see when they are listening to music they like, according to a new study published today in the journal Proceedings of the National Academy of Sciences.

Every year, an estimated 150,000 people in the UK have a stroke. Up to 60% of stroke patients have impaired visual awareness of the outside world as a result, where they have trouble interacting with certain objects in the visual world. This impaired visual awareness, known as 'visual neglect', is due to the damage that a stroke causes in brain areas that are critical for the integration of vision, attention and action. Visual neglect causes the patient to lose awareness of objects in the opposite side of space compared to the site of their brain injury.

If the stroke occurs in the right hemisphere of the brain, these patients tend to lose awareness of visual information in the left side of space. This occurs even though the area of the brain associated with sight is not damaged.

The researchers behind the study, from Imperial College London, the University of Birmingham and other institutions, suggest that listening to their favourite music may help stroke patients with impaired visual awareness to regain their ability to see.

The new study looked at three patients who had lost awareness of half of their field of vision as a result of a stroke. The patients completed tasks under three conditions: while listening to their preferred music, while listening to music they did not like and in silence. All three patients could identify coloured shapes and red lights in their depleted side of vision much more accurately while they were listening to their preferred music, compared with listening to music they did not like or silence.

For example, in one task, patients were asked to press a button when they could see a red light appear. One patient could point out the light in 65% of cases while he was listening to music he liked, but could only recognise the light in 15% of cases when there was no music or music he did not like being played.

The researchers believe that the improvement in visual awareness seen in these patients could be as a result of patients experiencing positive emotions when listening to music that they like. The team suggest that when a patient experiences positive emotions this may result in more efficient signalling in the brain. This may then improve the patient's awareness by giving the brain more resources to process stimuli.

The team also used functional MRI scans to look at the way the brain functioned while the patients performed different tasks. They found that listening to pleasant music as the patients performed the visual tasks

activated the brain in areas linked to positive emotional responses to stimuli. When the brain was activated in this way, the activation in emotion brain regions was coupled with the improvement of the patients' awareness of the visual world.

Dr David Soto, the lead author of the study from the Division of Neurosciences and Mental Health at Imperial College London, said: "Visual neglect can be a very distressing condition for stroke patients. It has a big effect on their day-to-day lives. For example, in extreme cases, patients with visual neglect may eat only the food on the right side of their plate, or shave only half of their face, thus failing to react to certain objects in the environment".

"We wanted to see if music would improve visual awareness in these patients by influencing the individual's emotional state. Our results are very promising, although we would like to look at a much larger group of patients with visual neglect and with other neuropsychological impairments. Our findings suggest that we should think more carefully about the individual emotional factors in patients with visual neglect and in other neurological patients following a stroke. Music appears to improve awareness because of its positive emotional effect on the patient, so similar beneficial effects may also be gained by making the patient happy in other ways. This is something we are keen to investigate further," added Dr Soto.

This research was funded by the British Academy, Biotechnology and Biological Sciences Research Council, Economic and Social Research Council, Medical Research Council and Stroke Association.

Groups share information in workplace, but not the 'right' information

Research analysis outlines benefits and drawbacks of working in teams

WASHINGTON – From the operating room to the executive board room, the benefits of working in teams have long been touted. But a new analysis of 22 years of applied psychological research shows that teams tend to discuss information they already know and that "talkier" teams are less effective.

"We're seeing a widespread trend toward a more virtual and globalized world and this is transforming the way people in the workplace communicate," said the article's lead author, Jessica Mesmer-Magnus, PhD, of the University of North Carolina Wilmington. "We need to better understand how teams will perform in this new setting and, to do that, we need to look at how they've worked in the past."

Mesmer-Magnus and Leslie DeChurch, PhD, an organizational psychologist at the University of Central Florida, analyzed research on information sharing in the workplace, consisting of studies of approximately 4,800 groups and more than 17,000 people. Their findings are reported in the March issue of the Journal of Applied Psychology, which is published by the American Psychological Association.

Their analysis showed that teams that spent time sharing new information performed better overall in their tasks. But they also found that most teams spent their time discussing information that was already known by the rest of the group. Groups whose members talked more openly during meetings were on better terms with one another but that did not necessarily mean they performed better.

"What this suggests is that teams who talk more amongst themselves aren't necessarily sharing useful information. Therefore, they're not actually coming to a better result. Rather, it's more important what the teams are talking about, than how much they are talking," said Mesmer-Magnus.

The researchers also found that teams communicate better when they engage in tasks where they are instructed to come up with a correct, or best, answer rather than a consensual solution. For example, teams were more effective when selecting candidates for a job opening or solving a crime when they had been encouraged to share their unique insights and to work to determine the best solution rather than a quicker consensual one. And although team members are often chosen because of their diverse professional and personal backgrounds, teams tended to share more information when the team was composed of members of similar backgrounds, according to the analysis. "This highlights the conundrum surrounding team tasks," said Mesmer-Magnus. "There's a separation in what teams actually do and what they should do in order to be effective."

The authors say their findings show group productivity can be enhanced by:

* Structuring team discussions
* Promoting a cooperative team environment
* Highlighting team members' skills and knowledge
* Focusing on communicating new and unique information

"Teams do have a distinct advantage over individuals in the work setting," said Mesmer-Magnus. "But leaders should be aware of how to effectively maximize their team's potential with effective communication."

***Article**: "Information Sharing and Team Performance: A Meta-Analysis," Jessica R. Mesmer-Magnus, PhD, University of North Carolina Wilmington; Leslie A. DeChurch, PhD, University of Central Florida; Journal of Applied Psychology, Vol. 94, No. 2. (Full text of the article is available from the APA Public Affairs Office and at http://www.apa.org/journals/releases/apl942535.pdf)*

GUMC Researchers Show Adult Human Testes Cells Can Become Embryonic Stem-like, Capable of Treating Disease

Washington, DC – Using what they say is a relatively simple method, scientists at Georgetown University Medical Center have extracted stem/progenitor cells from adult testes and have converted them back into pluripotent embryonic-like stem cells. Researchers say that the naïve cells are now potentially capable of morphing into any cell type that a body needs, from brain neurons to pancreatic tissue.

And because they produced these stem cells without the use of additional genes, the technology should be safe for human use, the researchers say in a paper published online in the journal Stem Cells and Development.

"Given these advances, and with further validation, it is possible that in the not–too-distant-future, men could be cured of disease with a biopsy of their own testes," says the study's senior investigator, Martin Dym, PhD, a professor in the Department of Biochemistry and Molecular & Cellular Biology.

The Georgetown researchers are among the first scientists to show that human testes stem cells can become embryonic-like stem cells, and they have done this work using testis tissue from organ donors, which they say has provided enough valuable tissue to allow them to make their discoveries. While they have published their preliminary results before, they are now disclosing a new and simpler method to isolate the testes stem/progenitor cells than has not been seen in other published procedures in humans and rodents.

Being able to use adult stem cells for this type of cell-based therapy offers a number of advantages over other strategies currently being explored, says Dym. The use of embryonic stem cells is controversial because it necessitates destruction of an embryo, and pushing fully mature cells, such as skin cells, back into a stem-like state requires use of cancer genes, and has therefore been viewed as potentially risky for human treatment, he says.

The idea with this approach is that men with an incurable disorder or disease could have a biopsy of their testes, which Dym says is a common procedure in patients suspected of having testicular cancer. Testes stem/progenitor cells – those cells that can go on to produce sperm – would be removed from the biopsy tissue, and grown in the laboratory with the addition of certain chemicals and growth factors. This causes the cells to revert back into a pluripotent state, which could then be driven into chosen cell types.

"We are taking adult spermatogonial stem/progenitor cells, which in the body are unipotent, capable of only making sperm, and coaxing them back to embryonic stem-like cells, which are pluripotent," Dym says.

Once these new cell types are produced – several weeks after initial collection – they can be frozen and used at any point in the future, the researchers say. He and the research team conducted the study using testes donated to GUMC from four organ donors, aged 16-52 years old.

"This is novel data which strengthens the argument for carrying out further research on pluripotent cells derived from human testes," Dym says.

The next step, he says, is to get differentiated cells to cure disease in animal models and the researchers are now working on a project that uses testes spermatogonial stem/progenitor cells that morphed into pancreatic cells to treat diabetes in mouse models of human diabetes.

The study was funded by a grant from the National Institutes of Health. The authors report no potential financial conflicts.

Co-authors include first author Nady Golestaneh, PhD, Ian Gallicano, PhD, and other Georgetown University Medical Center investigators in the Departments of Oncology and Obstetrics and Gynecology, the Lombardi Comprehensive Cancer Center, and in the Department of Biochemistry and Molecular & Cellular Biology. Colleagues from the Washington Regional Transplant Community also participated in the study.

Astrocytes help separate man from mouse

A type of brain cell that was long overlooked by researchers embodies one of very few ways in which the human brain differs fundamentally from that of a mouse or rat, according to researchers who published their findings as the cover story in the March 11 issue of the Journal of Neuroscience.

Scientists at the University of Rochester Medical Center found that human astrocytes, cells that were long thought simply to support flashier brain cells known as neurons that send electrical signals, are bigger, faster, and much more complex than those in mice and rats.

"There aren't many differences known between the rodent brain and the human brain, but we are finding striking differences in the astrocytes. Our astrocytes signal faster, and they're bigger and more complex. This has big implications for how our brains process information," said first author Nancy Ann Oberheim, Ph.D., a medical student who recently completed her doctoral thesis on astrocytes.

The study is one of the most extensive examinations yet of the astrocyte. Oberheim and co-authors discovered a previously unknown form of the cell, a varicose projection astrocyte, in the human brain but not in the rodent brain. The team also found that the most abundant type of astrocyte, protoplasmic astrocytes, are

approximately 2.6 times larger than their rodent counterparts, and that the human cells have about 10 times as many "processes," or structures designed to connect to other cells.

"We have not really been able to understand why the human brain is so much more capable than that of any other animal," said neuroscientist Maiken Nedergaard, M.D., D.M.Sc., who led the study. "Some people have thought that it's simply that a bigger brain is a better brain, but an elephant's brain is bigger than a person's, for example, but it's not nearly as powerful. So that's not the answer.

"It may be that humans have a much higher brain capacity in large part because our astrocytes are more sophisticated and have more complex processing power," added Nedergaard, who spoke last week at a Gordon Research Conference on glial biology. "Studies in rodents show that non-neuronal cells are part of information processing, and our study suggests that astrocytes are part of the higher cognitive functioning that defines who we are as humans."

Astrocytes had long been considered passive support cells, a means to hold the rest of the brain cells together, like glue. Medical students might spend a few minutes pondering the astrocyte before moving on to their flashy counterparts, the neurons that fire the electrical signals crucial to pretty much everything we do. It's the electrical activity of neurons that constitutes what most scientists have considered to be brain activity, and it's the neurons that are the target of every currently available drug aimed at brain cells. If astrocytes were important, scientists thought, it was most likely because they help create a healthy environment for the neurons.

It turns out that astrocytes, which are 10 times as plentiful as neurons, had been pushed to the boundaries of neuroscience because of a gap in the tools used to study the brain. Scientists measure signaling among brain cells mainly by looking at electrical activity. But astrocytes don't fire in the same way as neurons, and so conventional techniques don't record their activity. So when scientists "listened" with conventional techniques, they witnessed no activity.

Rather than realizing their tools were incomplete, scientists assumed that astrocytes were silent.

So Nedergaard devised a new way to "listen" for astrocyte activity, developing a sophisticated laser system to look at their activity by measuring the amount of calcium inside the cells. Her team has discovered what might be called the secret lives of astrocytes and has made a series of startling discoveries. Astrocytes use calcium to send signals to the neurons, and the neurons respond; neurons and astrocytes talk back and forth, indicating that astrocytes are full partners in the basic working of the brain; and astrocytes are central to conditions like stroke, Alzheimer's, epilepsy, and spinal cord injury.

"Dogma is slow to change, and one of the dogmas of neuroscience is that astrocytes are support cells that don't do much themselves," said Oberheim. "The view is slow to change, but scientists are coming around. Astrocytes are now acknowledged as active participants in brain function and sensory processing."

The brain's two signaling systems – one composed of neurons, and one of astrocytes – complement each other, Nedergaard said. Neurons send signals extremely quickly over long distances – the hand touches a hot stove, for instance, and the brain detects the danger and moves the hand away, instantly. Astrocytes, in contrast, send slower signals whose function is still being worked out by scientists.

"The brain contains two communication networks using different languages," said Nedergaard, director of the Division of Glial Disease and Therapeutics of the Center for Translational Neuromedicine. "You have a highly sophisticated electrical network embodied in the neurons, which send signals instantaneously. And then you have a much slower network composed of astrocytes whose signals are 10,000 times slower but which might be able to process the information in a more sophisticated manner and retrieve memories.

"There is no other tissue in the body that mixes up two different types of cells so completely as how astrocytes and neurons are interspersed throughout the brain," Nedergaard added. "Both comprise extensive signaling networks. Where those networks interface and how they interact makes the brain so interesting."

To do the study, the team studied human brain tissue taken from 30 people who had had surgery, mostly to treat epilepsy or brain tumors. They compared the astrocytes in human brains to those in mice and rats. In addition to the findings above, the team noted additional differences:

* Astrocytes in people signal five times as fast as those in mice and rats.

* Human astrocytes are organized into more complex units known as domains than are rodent astrocytes. A typical rodent domain includes tens of thousands of neuronal synapses, while the team found that a human domain might include up to 2 million synapses. These domains are highly organized groupings of cells that appear to be precisely situated, almost like atoms in a crystal. This organization is likely important for information processing, said Nedergaard, who notes that brain injury is associated with a loss of astrocytic domain organization and a decrease in cognitive function.

* In people, cells known as fibrous astrocytes, which are mainly for structural support, are on average more than twice as large as their counterparts in mice and rats. Also, people have another type of cell known as interlaminar astrocytes, which are not present in rodents.

* Another difference concerns the end feet of protoplasmic astrocytes, which wrap around blood vessels throughout the brain and are thought to play a role in the brain's blood flow. In humans, these end feet cover the walls of blood vessels much more completely than they do in mice and rats, possibly playing a much more important role in keeping agents in the blood from entering the brain and in regulating blood flow.

The authors include Steven Goldman, M.D., Ph.D., professor and chair of Neurology; Webster Pilcher, M.D., professor and chair of Neurosurgery; Jeffrey Wyatt, D.V.M., professor and chair of Comparative Medicine; and research assistant professors Takahiro Takano, Ph.D., Xiaoning Han, Ph.D., Wei He, Ph.D., and Fushun Wang, Ph.D.

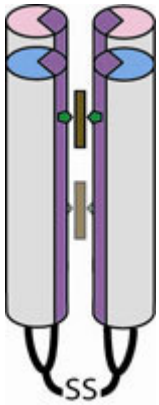
Other authors include technical associate Qiwu Xu; Jane Lin, Ph.D., of New York Medical College; and Jeffrey Ojemann, M.D., and Bruce Ransom, M.D., Ph.D., of the University of Washington, where Oberheim completed part of her doctoral thesis under Nedergaard's supervision.

The work was funded by the G. Harold and Leila Y. Mathers Charitable Foundation and by the National Institute of Neurological Disorders and Stroke.

Proteins by Design: Penn Biochemists Create New Protein from Scratch

Approach could one day be used to make artificial blood

PHILADELPHIA – No doubt proteins are complex. Most are "large" and full of interdependent branches, pockets and bends in their final folded structure. This complexity frustrates biochemists and protein engineers seeking to understand protein structure and function in order to reproduce or create new uses for these natural molecules to fight diseases or for use in industry.



Using design and engineering principles learned from nature, a team of biochemists from the University of Pennsylvania School of Medicine have built – from scratch – a completely new type of protein. This protein can transport oxygen, akin to human neuroglobin, a molecule that carries oxygen in the brain and peripheral nervous system. Some day this approach could be used to make artificial blood for use on the battle field or by emergency-care professionals. Their findings appear in the most recent issue of Nature.

"This is quite a different way of making novel proteins than the rest of the world," says senior author P. Leslie Dutton, PhD, Eldridge Reeves Johnson Professor of Biochemistry and Biophysics. "We've created an unusually simple and relatively small protein that has a function, which is to carry oxygen. No one else has ever done this before."

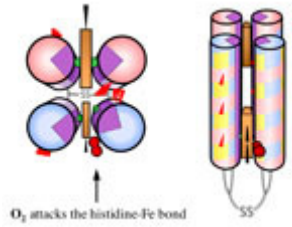
From-scratch design of an oxygen transport protein buries hemes in a bundle of protein columns (alpha helices) linked by loops into a candelabra geometry.

"Our aim is to design new proteins from principles we discover studying natural proteins," explains co-author Christopher C. Moser, PhD, Associate Director of the Johnson Foundation at Penn. "For example, we found that natural proteins are complex and fragile and when we make new proteins we want them to be simple and robust. That's why we're not re-engineering a natural protein, but making one from scratch."

Currently, protein engineers take an existing biochemical scaffold from nature and tweak it a bit structurally to make it do something else. "This research demonstrates how we used a set of simple design principles, which challenge the kind of approaches that have been used to date in reproducing natural protein functions," says Dutton.

The natural design of proteins ultimately lies in their underlying sequence of amino acids, organic compounds that link together to make proteins. In living organisms, this sequence is dictated by the genetic information carried in DNA within chromosomes. This information is then encoded in messenger RNA, which is transcribed from DNA in the nucleus of the cell. The sequence of amino acids for a particular protein is determined by the sequence of nucleotides in messenger RNA. It is the order of the amino acids and the chemical bonds between them that establish how a protein folds into its final shape.

To build their protein, the Penn team started with just three amino acids, which code for a helix-shaped column. From this, they assembled a four-column bundle with loop that resembles a simple candelabra. They added a heme, a chemical group that contains an iron atom, to bind oxygen molecules. They also added another amino acid called glutamate to add strain to the candelabra to help the columns open up to capture the oxygen. Since heme and oxygen degrade in water, the researchers also designed the exteriors of the columns to repel water to protect the oxygen payload inside.



Animation: a schematic view of the functional action of the oxygen transport maquette. Click for full-size movie

Initially, the team used a synthesizer – a robot that chemically sticks amino acids together in a desired sequence – to make the helix-shaped columns. "We do the first reactions with the robot to figure out the

sequence of amino acids that we want," says Moser. When they are satisfied with the sequence, they use the bacterium E. coli as a biological host to make the full protein.

The team used chemical tests to confirm that their protein did indeed capture oxygen. When the oxygen did bind to the iron heme molecule in the artificial protein, the solution in which the reaction took place changed color from dark red to scarlet, a color signature almost identical to natural neuroglobin.

"This exercise is like making a bus," says Dutton. "First you need an engine and we've produced an engine. Now we can add other things on to it. Using the bound oxygen to do chemistry will be like adding the wheels. Our approach to building a simple protein from scratch allows us to add on, without getting more and more complicated."

In addition to Dutton and Moser, co-first authors J.L. Ross Anderson, PhD, a postdoc in the Dutton lab and Ronald L. Koder, PhD, a former postdoc in the Dutton lab now with the Department of Physics at the City College of New York; Lee A. Solomon, a PhD student in the Dutton lab, and Konda S. Reddy, PhD, were also authors on the paper.

This work was funded by the Department of Energy, the National Institutes of Health, and the National Science Foundation.

Early agriculture left traces in animal bones

Washington, D.C. - Unraveling the origins of agriculture in different regions around the globe has been a challenge for archeologists. Now researchers writing in the Proceedings of the National Academy of Sciences* report finding evidence of early human experiments with grain cultivation in East Asia. They gathered this information from an unlikely source - dog and pig bones.

The dog and pig bones, as well as bones of other animals analyzed in the study, come from an archaeological site in a region of northwest China considered to be a possible early center of East Asian agriculture. Chemical traces within the dog bones suggest a diet high in millet, a grain that wild dogs are unlikely to eat in large quantities, but that was a staple of early agricultural societies in northwest China. "If the dogs were consuming that much millet, their human masters were likely doing the same," says Seth Newsome, a coauthor on the study and a post-doctoral associate at the Carnegie Institution's Geophysical Laboratory, where the chemical analysis was performed.

The bones come from a Neolithic site known as Dadiwan, in China's western Loess Plateau, excavated first by a Chinese team in the late 70s and early 80s, and in 2006 by a team from the University of California, Davis, and Lanzhou University in China. Humans occupied the site during two main phases, from 7,900 to 7,200 years ago (Phase 1) and from 6,500 to 4,900 years (Phase 2). Though some fossil remains of millet plants have been found in both of these deposits, the fossils don't directly reveal how much millet contributed to the local diet.

To address this question, the researchers turned to a technique known as stable isotope analysis. Atoms of elements such as carbon come in different forms (isotopes) which are chemically similar, but can be distinguished in the laboratory by minute differences in their mass. Certain kinds of plants known as C4 plants tend to concentrate heavier carbon isotopes as they grow, compared to other plants known as C3 plants. Animals with diets high in C4 plants also tend to concentrate heavier isotopes in their bones. As it turns out, millet is one of the few C4 plants that grow in arid northwest China, making the carbon isotopes in bone a good indicator of a millet-rich diet.

The researchers found that the most of the dog bones from the Phase 1 deposits bore the isotopic signature of a high millet diet. This suggests that these dogs were domesticated and fed by humans who harvested millet. Bones of pigs from the site tell a slightly different story. In the Phase 1 deposits, the pig bones don't show signs of millet in the diet, so they were probably wild pigs hunted and eaten by people. But pig bones from Phase 2 do have the isotopic signature of millet, so they were probably domesticated by this time.

"Our results help fill in the picture of how agriculture arose in this part of the world," says Newsome. "There has been speculation that agriculture spread north from southern rice-farming areas, but the Phase 1 people were likely experimenting with agriculture by cultivating local grains. This simple system was later replaced by people in Phase 2 who had a much more developed agricultural system"

**Loukas Bartona, Seth D. Newsome, Fa-Hu Chen, Hui Wang, Thomas P. Guilderson, and Robert L. Bettinger. Agricultural origins and the isotopic identity of domestication in northern China, Proceedings of the National Academy of Sciences Online Early Edition, March 23-27, 2009*

Licorice may block effectiveness of drug widely used by transplant patients

SALT LAKE CITY - Chemists in Taiwan are reporting that an ingredient in licorice - widely used in various foods and herbal medicines - appears to block the absorption of cyclosporine, a drug used by transplant patients to prevent organ rejection. This drug interaction could potentially result in transplant rejection, causing illness and even death among patients worldwide who take cyclosporine and licorice together, the researchers caution.

The study is the first report of this potential drug interaction, the scientists say. Their findings will be presented here today at the American Chemical Society's 237th National Meeting.

"I would suggest that transplant patients avoid taking licorice," warns Pei-Dawn Lee Chao, Ph.D., a chemist at China Medical University in Taichung, Taiwan.

The researchers say they do not know exactly how much licorice it takes to have a toxic effect in humans. Since licorice-based products vary widely in their content of its main active ingredient, a substance called glycyrrhizin, Chao suggests that patients taking cyclosporine avoid licorice altogether. Thousands of patients also take cyclosporine for rheumatoid arthritis, certain skin conditions, and other diseases.

Licorice may block the effectiveness of cyclosporine, a drug widely used by transplant patients. **American Chemical Society**

Researchers have known for years that certain medications, foods, and herbs can reduce levels of cyclosporine in the body and should be avoided when taking that immunosuppressant drug. These include St. John's wort, quercetin (an ingredient found in onions and other plants that's also a dietary supplement), onions, ginger, and ginkgo. Other studies show that some substances, such as grapefruit juice, can actually boost cyclosporine levels. Now, it appears that licorice will join the growing list of substances that reduce the absorption of cyclosporine, the researchers say.

In the new study, Chao and colleagues fed cyclosporine to laboratory rats with and without various doses of pure glycyrrhizin and natural licorice extract. Much to the scientists' surprise, levels of cyclosporine dropped in the animals fed licorice or glycyrrhizin.

The researchers are trying to find out why licorice interferes with cyclosporine. Chao says there are no known scientific reports linking consumption of licorice to ill effects in transplant patients. Doctors, however, have not been looking for such a link, she added. The government of Taiwan funded the research through the Committee of Chinese Medicine and Pharmacy, Ministry of Health, R.O.C.

Licorice is a popular herb that has been used in food and medicines for thousands of years. Its active ingredient, glycyrrhizin, is 50 times sweeter than sugar, leading to herb's popular use in candy, herbal teas, and other foods. Some alternative health care providers use licorice root to treat a wide range of illnesses, including the common cold, stomach ulcers, and liver disease.

The new study adds to a growing number of reports indicating that licorice can trigger potentially dangerous drug interactions. Other studies have shown that licorice can interfere with the effectiveness of high blood pressure medications, aspirin, anti-inflammatory drugs, insulin and oral contraceptives. Chao and colleagues say patients should check with their doctor before consuming licorice with any critical drugs that might trigger unhealthy interactions.

New form of destructive terrorist material unlikely, chemists report

SALT LAKE CITY - Concerns that terrorists could produce a new and particularly dangerous form of the explosive responsible for airport security screening of passengers' shoes and restrictions on liquids in carryon baggage are unfounded, scientists reported today.

Speaking here at the 237th National Meeting of the American Chemical Society, Gerard Harbison, Ph.D., and colleagues described using computer simulations to analyze a variety of potential peroxide-based explosives in the same chemical class as triacetone triperoxide (TATP). That powerful, easy-to-make explosive was used by the "shoe bomber," Richard Reid, in his failed attempt to blow up a transatlantic airline flight in 2001. TATP has also been used by suicide bombers in the Palestinian Intifada.

Harbison's team became intrigued by "Internet lore," reports circulating on the Web claiming creation of another explosive - tetracetone tetraperoxide (TeATeP) - which is reputedly a more lethal relative to TATP. Initially working on detection methods of peroxide explosives for the Defense Advanced Research Projects Agency, the group instead began to investigate the structure of TeATeP to evaluate likelihood of its use as a terrorist's weapon.

"Our analysis indicates that potentially new and destructive terrorist materials, which would tax our detection capabilities, may be too unstable for a practical synthesis," said Harbison, a chemist at the University of Nebraska-Lincoln. "We consider it unlikely that any of the previous syntheses were actually successful, and the Internet myths about TeATeP are nothing more than that. So the good news is basically this is something we don't have to worry about."

The group investigated 20 molecular structures of various acetone peroxide compounds and found that all substances larger than TATP are likely too sensitive to be used as weapons. "The energies we're seeing in the analysis are extreme enough," Harbison said, adding that a review of previous TeATeP synthesis reports raised many questions. "If you look at the actual literature on people who claim to have made TeATeP, it's very

ambiguous. We think probably what happened when people thought they were making TeATeP was that they were actually making TATP."

This synthesis error is common and often fatal, Harbison said. When trying to make TATP, a less stable relative, diacetone diperoxide, often is created. "The nice thing about doing this on the computer is first it's safe, and our results are so close to what's been experimentally measured that we have a great deal of confidence with what we're doing," Harbison said. "We're really at the stage where we can evaluate threats - potential molecules that might be dangerous - and we can really make some sort of judgment about whether those molecules are going to present a hazard in the future. We can test things with computers at a level of reliability that's comparable to personally doing the synthesis and evaluating material yourself."

There's a lot of research that deals with known threats, Harbison said. But his groups' research focuses on the idea that emerging threats will always exist. "Presumably you'd like to anticipate the threats before they come along. We're now pushing it a little further and discussing potential threats.

"Using computational chemistry, we can narrow down the domain of potential hazards, things that aren't going to be on the horizon. I think we now know so much more about not just what works for improvised-explosive-device detection but also what doesn't work, and we don't have to try it out (experimentally). We did five years ago."

Mayo researchers find link between anesthesia exposure and learning disabilities in children

ROCHESTER, Minn. -- Mayo Clinic researchers have found that children who require multiple surgeries under anesthesia during their first three years of life are at higher risk of developing learning disabilities later. Several studies have suggested that anesthetic drugs may cause abnormalities in the brains of young animals. This is the first study in humans to suggest that exposure of children to anesthesia may have similar consequences. The finding is reported in the current issue of the journal Anesthesiology.

Using data from the long-term Rochester Epidemiology Project, researchers studied the medical records of 5,357 children from Olmsted County who were born between 1976 and 1982.
The research team, led by Robert Wilder, M.D., Ph.D., a Mayo Clinic anesthesiologist, found that although one exposure to anesthesia was not harmful, more than one almost doubled the risk that a child would be identified as having a learning disability before age 19. The risk also increased with longer durations of anesthesia.

"It's very important for parents and families to understand that although we see a clear difference in the frequency of learning disabilities in children exposed to anesthesia, we don't know whether these differences are actually caused by anesthesia," says Randall Flick, M.D., a Mayo Clinic anesthesiologist and co-author of the study. "The problem is that anyone who underwent an anesthetic also had surgery," says Dr. Wilder. "It's unclear whether it's the anesthetic, the physiological stress of surgery or perhaps the medical problems that made surgery necessary that are responsible for the learning disabilities."

Young children's brains are more vulnerable to a variety of problems because they are undergoing dynamic growth. The brain is rapidly forming connections between cells and trimming excess cells and connections, says Dr. Wilder.

The general anesthesia chemicals in use during the study period were primarily halothane and nitrous oxide (laughing gas). Although halothane is no longer used in the U.S., it has been replaced by newer agents that have similar effects on the brain. Nitrous oxide is widely used throughout the U.S. and the world.

Debate exists about the developmental correlation between the animal (rodent) and human studies. Some think that the related exposure period would be perinatal in humans (the last month of pregnancy and first six months after birth), so the researchers repeated their analysis, examining anesthetic exposure before age 2, and found similar results.

"Parents and physicians need to balance this information along with the normal decisions that we all go through when we decide to have surgery for one of our children," says Dr. Flick. "Although alternatives to the use of these medications exist, they are limited. Certainly, performing surgery without appropriate use of anesthesia is unacceptable."

The children in the study were tested as a natural part of the educational process in the Rochester school system. They did not perform as well in reading, writing or math as their IQ tests indicated.

Other studies have linked anesthesia exposure in young children to behavioral problems. Dr. Flick says the Food and Drug Administration (FDA) is aware of the possible problems with anesthesia. "They've been very proactive in trying to gather information as quickly and thoughtfully as possible," Dr. Flick says, "but much more research is needed before we could conclude that anesthesia itself causes problems." He also encourages families with questions to go to the Web sites of the American Society of Anesthesiology and the Society for Pediatric Anesthesia.

The research team is working to obtain funding to extend the database for 10 more years (1982-1992), a period that would include the use of more modern anesthetics. They are also working with the FDA to complete a study that matches children who had an anesthetic with children who have a similar medical problem but did not receive an anesthetic.

The study was funded by grants from the National Institutes of Health and Mayo Clinic Research.
Additional co-authors include Juraj Sprung, M.D., Ph.D.; Slavica Katusic, M.D.; William Barbaresi, M.D.; Christopher Mickelson, M.D.; Darrell Schroeder; Amy Weaver; and David Warner, M.D.; all from Mayo Clinic's campus in Rochester. Another co-author is Stephen Gleich, M.D., of the Primary Children's Medical Center, Salt Lake City.

NYU study finds new risk factor for melanoma in younger women

Genetic test may help identify pre-menopausal women at higher risk

NEW YORK – Researchers may have found a more potent risk factor for melanoma than blistering sunburns, freckling, or family history of the deadly skin disease. In a new study, scientists at NYU Langone Medical Center report that a genetic variation leads to a nearly four-fold increase of melanoma in women under the age of 50. The new study was released online March 24, 2009, in the journal Clinical Cancer Research and will be published in the April 1, 2009, issue of the journal.

"If this number turns out to be reproducible, it is higher than a lot of the other clinical risk factors that we know, such as blistering sunburns, freckling, and family history," said David Polsky, M.D., Ph.D., associate professor of dermatology and director of the Pigmented Lesion Section of the Ronald O. Perelman Department of Dermatology at NYU School of Medicine, and the study's lead author.

"Potentially, we have a genetic test that might identify pre-menopausal women who are at higher risk for melanoma," said Dr. Polsky. "And if that's the case, then we might want to have increased surveillance of those patients including more frequent visits to the doctor, more rigorous teaching of skin self-examination, and other preventive steps."

Melanoma, the most deadly form of skin cancer, was expected last year to strike 62,480 Americans, and kill an estimated 8,420 diagnosed patients, according to the American Cancer Society.

For largely unknown reasons, melanoma is more common among women than men under the age of 40. Between 40 and 50 the incidence is about equal in both sexes, and over the age of 50, melanoma incidence skews markedly toward men. Polsky and his co-authors suspect the difference may be linked to the activity of estrogen, mediated in part by a genetic variant in a gene called MDM2.

When estrogen binds to this gene, it turns on production of MDM2, a potential oncogene (cancer promoting gene) in cells. In the presence of the genetic variation in MDM2, originally identified by the laboratory of Dr. Arnold Levine at the Institute for Advanced Study, Princeton, the estrogen binds more strongly, resulting in far greater production of the MDM2 protein.

Women with higher estrogen levels and who also have the genetic variation would be expected to have higher estrogen-related MDM2 protein that could increase their melanoma risk, explains Dr. Polsky.

The MDM2 genetic variant appears in the gene's promoter, a power switch that determines when the gene is turned on and how many copies are produced within a cell. This promoter region is normally regulated by p53, a tumor suppressor gene implicated in as many of 50 percent of all cancers. Part of MDM2's normal function is to inhibit p53 when its levels get too high in a cell. If MDM2 is turned on independently of p53, it can keep p53 levels low, reducing the cell's protection against turning into a cancer cell.

Scientists have shown that the substitution of a single letter of DNA at a specific point in the MDM2 promoter can significantly ramp up gene production. The new study evaluated the effects of this natural genetic variation in 227 melanoma patients enrolled in NYU's Interdisciplinary Melanoma Cooperative Group between August 2002 and November 2006. Dr. Polsky and colleagues from NYU School of Medicine recorded each patient's MDM2 and p53 genetic variations, as well as age, sex, personal and family history of melanoma, and tumor thickness.

The results showed that more than 40 percent of women diagnosed with melanoma under the age of 50 had the genetic variation in the MDM2 gene promoter. In contrast, only about 16 percent of women diagnosed after the age of 50 had the variation.

The difference in the frequency of the variation corresponded to a 3.89-fold increase in melanoma risk for women under the age of 50 - an elevated risk over background levels that increased more among even younger women, according to the study. When the researchers compared the MDM2 genotypes to patients' ages at diagnosis, they found that about 38 percent of women with the variation had been diagnosed between the relatively young ages of 30 to 39 - a much higher melanoma incidence than among older women patients with the variation.

Beyond validating the risk in a larger group of patients, Dr. Polsky hopes to begin formulating a stronger model of cancer risk that incorporates genetic information and other factors. "Can we look at people's sun exposure history, hormonal status and a panel of genetic markers in addition to MDM2 and ask, 'Does this help identify more high-risk people?'" he said.

Among the study investigators are Elnaz F. Firoz, a medical student from the College of Physicians and Surgeons at Columbia University; and Richard Shapiro, Russell Berman, Anna Pavlick, Prashiela Manga, Harry Ostrer, Hideko Kamino, Farbod Darvishian, Linda Rolnitzky, Judith D. Goldberg, and Iman Osman from NYU Langone Medical Center.

The study was supported by a grant from the Marc Jacobs Campaign to Support Melanoma Research, with partial support by a grant from the National Cancer Institute to Linda Rolnitzky and Judith D. Goldberg. The NYU Interdisciplinary Melanoma Cooperative Group is supported by the NYU Cancer Institute and NYU School of Medicine's Ronald O. Perelman Department of Dermatology.

Herbal medicines for treatment of gastrointestinal disease

Herbal medicines could benefit patients suffering from gastrointestinal (GI) motility disorders that cannot be treated using conventional drug therapy. In a study published in Neurogastroenterology and Motility, researchers reviewed data on Japanese herbal medicines and found them to be effective in reducing the symptoms of GI disorders such as functional dyspepsia, constipation, and postoperative ileus.

"Japanese herbal medicines have been used in East Asia for thousands of years," says lead researcher Hidekazu Suzuki, Associate Professor at the Keio University School of Medicine. "Our review of the world medical literature reveals that herbal medicines serve a valuable role in the management of patients with functional gastrointestinal disorders."

Many of the drugs used to treat GI motility disorders are ineffective or cause unwanted side effects and, in some cases, this has led to drugs being withdrawn from the market. Herbal medicine is an attractive alternative.

The researchers reviewed data from studies looking at the effect of several different Japanese herbal medicines including the use of Rikkunshi-to, Dai-Kenchu-to, and other herbal medicines. Rikkunshi-to, which is prepared from eight crude herbs, was effective in reducing discomfort caused by functional dyspepsia. Dai-Kenchu-to, a mixture of ginseng, ginger, and zanthoxylum fruit, was beneficial for constipation in children and patients suffering from post-operative ileus – disruption of normal bowel movements following an operation. Another herbal medicine, hangeshashin-to, reduced the severity and frequency of diarrhoea caused by anti-cancer drugs.

In Japan, herbal medicine is manufactured in standardised form with regards to quality and quantity of ingredients. The researchers say the health benefits of standardised formulations of herbal medicines require more rigorous examination, particularly in the Western world.

"There is a mandate to provide accurate data regarding the effectiveness of non-traditional therapy, not only to our patients but also to healthcare providers who face the dilemma of recommending or opposing management strategies that incorporate herbal medicine," says Suzuki.

Really?

The Claim: Fish Oil Supplements Can Contain Mercury

By ANAHAD O'CONNOR

THE FACTS Fish oil supplements are increasingly popular with people who don't like seafood but are attracted by claims of cardiac benefits. But could they also expose you to the harmful pollutants found in some species of fish?

The concern is a common one, but studies have found that most of the widely available supplements contain little or no mercury, dioxins or PCBs. For one thing, most companies use species of fish that are lower on the food chain, like cod and sardines, which accumulate less mercury. And many companies distill their oils to help remove contaminants.

A report by ConsumerLab.com, which conducts independent tests of supplements, examined 41 common fish oil products and found none contaminated with mercury or PCBs.

Leif Parsons

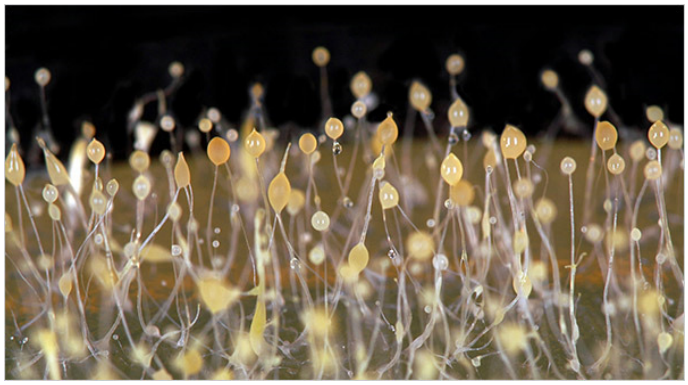
Another report, by researchers at Harvard Medical School and at Massachusetts General Hospital, studied five popular brands of fish oil, including Nordic Ultimate, Kirkland and CVS. They found that the brands had "negligible amounts of mercury, suggesting either that mercury is removed during the manufacturing of purified fish oil or that the fish sources used in these commercial preparations are relatively mercury-free."

Test results for various fish oils can also be found on the International Fish Oil Standards Web site.

THE BOTTOM LINE Studies suggest that fish oil products contain little or no contaminants.

Oozing Through Texas Soil, a Team of Amoebas Billions Strong

By CAROL KAESUK YOON



After producing superlatives like the world's biggest statue of a jackrabbit and the nation's most unpopular modern-day president, Texas can now boast what may be its most bizarre and undoubtedly its slimiest topper yet: the world's largest known colony of clonal amoebas.

Scientists found the vast and sticky empire stretching 40 feet across, consisting of billions of genetically identical single-celled individuals, oozing along in the muck of a cow pasture outside Houston.

"It was very unexpected," said Owen M. Gilbert, a graduate student at Rice University and lead author of the report in the March issue of Molecular Ecology. "It was like nothing we'd ever seen before."

AS ONE A field of genetically identical amoebas in Texas raises the possibility that cells might organize on much larger scales than once thought. **Owen Gilbert/Rice University**

Scientists say the discovery is much more than a mere curiosity, because the colony consists of what are known as social amoebas. Only an apparent oxymoron, social amoebas are able to gather in organized groups and behave cooperatively, some even committing suicide to help fellow amoebas reproduce. The discovery of such a huge colony of genetically identical amoebas provides insight into how such cooperation and sociality might have evolved and may help to explain why microbes are being found to show social behaviors more often than was expected.

"It is of significant scientific interest," said Kevin Foster, an evolutionary biologist at Harvard University who was not involved with the study. Though amoebas would seem unlikely to coordinate interactions with one another over much more than microscopic distances, the discovery of such a massive clonal colony, he said, "raises the possibility that cells might evolve to organize on much larger spatial scales."

Thoughts of a giant organized amoeba colony can conjure up visions of the 1958 horror classic "The Blob," but these social amoebas, a species known as Dictyostelium discoideum, a kind of slime mold, are infinitely more subtle. Microscopic and tucked away in the dirt, the billions of amoebas would have gone unnoticed by anyone driving past the pasture. Joan Strassmann, an author on the paper along with another evolutionary biologist at Rice University, David Queller, said she and a team of undergraduates searched for the species by sticking drinking straws into dirt and cow dung to retrieve materials where the amoebas might be living. In the laboratory, they spread the samples on Petri dishes and waited to see what would grow. DNA analyses later showed that the huge numbers of amoebas collected from the pasture were genetically identical.

Bernard Crespi, an evolutionary biologist at Simon Fraser University in Canada, said the study was the first to clearly demonstrate "the extreme of relatedness" in social microbes, a population of genetically identical individuals. Such a colony provides the ideal conditions to foster the evolution of behaviors like cooperation, because the more genetically similar two organisms are, the more natural selection will favor their assisting each other.

Dictyostelium, for example, can carry out stunning feats of cooperation, engaging in what's known as suicidal altruism, a behavior in which individual amoebas come together to form a single body, with some amoebas sacrificing themselves to allow for more effective reproduction of amoebas in other parts of the body.

Scientists said that if other species were also found to have such clonal colonies, that could help explain the surprisingly widespread finding of social behaviors among microbes. But just what conditions prompt the flourishing of clones remains unclear. Scientists said it was odd to find the slime molds thriving in an open field, as they prefer enclosed forest soils. It is possible that the lumbering cows fostered the growth of the giant clone colony by spreading the amoebas through the muck, said John Bonner, professor emeritus of ecology and evolutionary biology at Princeton University.

Meanwhile, as impressive (or even threatening) as a colony of a couple billion amoebas might sound, it has turned out to be surprisingly fragile.

"Just one week later, it had rained a lot and then it basically was gone," Mr. Gilbert said.

Apparently, such is the fleeting nature of grand amoebic phenomena, for the Texas clone is not the first to dwindle inexplicably into nothingness. Scientists say that the last traces of what at one point may have been the world's largest individual amoeba - and the star of a highly productive research program - shriveled in their laboratory last summer until it disappeared.

Manfred Schliwa, a cell biologist at the University of Munich, first came across the organism, known as Reticulomyxa, quite by accident as it spread as a white slime across the fish tank in his office at the University of California at Berkeley where he was then a professor. The amoeba, a blob with no defined shape, bits of which could break off to take up a life of their own, fed so heartily off stray morsels of fish food that it eventually attained the status of giant among microbes, its body reaching more than an inch across.

A single enormous cell, the amoeba was studied by Dr. Schliwa and colleagues to understand movement from one part of a cell to another, a process that was both easily visualized and carried out extremely rapidly in the big Reticulomyxa, which at its largest could house a billion or more nuclei as it constantly shuttled cell parts and whatnot across its titanic form.

Dr. Schliwa, still mystified by the demise of the big-amoeba-that-couldn't, said he hoped at some point to obtain a new wild Reticulomyxa, though under natural conditions the organism is much smaller and lives in the soil, making it difficult to spot. In fact, like the colony of social amoebas, the giant amoebas could be everywhere underfoot without anyone's noticing.

"I used to joke," Dr. Schliwa said, "that there might be a giant organism in the soil spanning the entire continent and whenever you dig up a shovelful you get a piece of it."

So where will the next giant amoeba be found hiding? Dr. Schliwa points out that the original discovery of the amoeba-to-end-all-amoebas was made in the 1940s by a researcher named Ruth N. Nauss. She discovered the species in a New York City park.

Botox Frees Muscles for Stroke Patients in the Know

By DONALD G. McNEIL Jr.

After her stroke, Francine V. Corso, a software engineer who worked on NASA's lunar lander, was housebound from 1992 to 2001.

Her left arm was twisted up near her neck, making it difficult to pull on a blouse, and her fingers curled so rigidly that her nails buried themselves in her palm. When she finally learned to rise from her wheelchair, her contorted left leg had the so-called horse gait of many brain-injury victims - she stepped toe-downward, and then fought to keep her foot from rolling over.

Now, with injections of botulinum toxin every three months, she says, "I'm completely transformed - I drive, I volunteer, I take art classes." Her fingers are so relaxed that a manicurist can lacquer her nails red.

Botulinum toxin, the wrinkle smoother best known by the brand name Botox, has many medical uses, some official and some off label. It helps dystonia victims regain control of spasming muscles, actors who struggle with flop sweat slow down the flow, and children with clubfoot avoid surgery.

Its use in stroke victims is still off label - that is, it is not approved for that purpose by the Food and Drug Administration. But it is so widely accepted that Medicare and other insurers will usually reimburse for its use.

Nonetheless, said Dr. David M. Simpson, a professor of neurology at Mount Sinai Medical Center in New York and a leading botulinum researcher, only about 5 percent of the stroke patients who could benefit from its use ever get it.

Primary care doctors who oversee nursing homes often do not know about it, he said. Relatively few doctors are trained to do the injections, which go much deeper than dermatologists do to erase frown lines. And most neurologists are in the habit of prescribing antispasticity drugs like tizanidine and baclofen, which are oral and inexpensive, but which cause drowsiness and weaken every muscle in the body, not just the target ones.

Ms. Corso, 66, never heard about the treatment from her first neurologist, whom she called "Dr. Bad News" because he told her family she would die and then kept telling her she would never walk. "I heard about it from Dr. Max Gomez on NBC," she added. "That's when I came into the city and found you people."

In a Mount Sinai classroom with a broad view over Manhattan, Dr. Simpson stands behind two disembodied arms mounted on rocker joints. One looks pasty but muscular and is covered with needle tracks. Its partner is bright red and nothing but muscle; it is an anatomical model with all the skin and fat removed.

Dr. Simpson, who gets financing from three botulinum toxin producers - Allergan, which makes Botox; Solstice Neurosciences, which makes Myobloc; and Merz Pharmaceuticals, which makes Xeomin - is teaching residents how to find the harder-to-reach muscles, like the flexor pollicus brevis, which bends the thumb, and the pronator quadratus, which rotates the wrist.

The rubber arms have sensors that beep when the tip of his needle enters the right muscle. Human arms do not beep, of course, but Dr. Simpson had used a variant of the technology on Ms. Corso only an hour before.

TEST A rubber arm with sensors that beep when a needle hits the proper muscle. "I think it's valuable to make sure you're in the right place," Dr. Simpson said. **Alex di Suvero for The New York Times**

Just before the first needle sank in, she let visitors know how she felt about electromyography, which she calls “the stim.”

“This,” announced Ms. Corso, who is almost 5 feet tall, “is what separates the men from the boys.”

The syringe was wired to an electric stimulator that pulsed a charge - up to a tenth of an amp - twice a second. When Dr. Simpson believed he had pierced the right muscle, he dialed it up. If the correct finger began twitching in sync, he knew he was there, and pressed the plunger. If not, he moved the needle and tried again.

He did that several times in Ms. Corso’s arm and then in her leg. Within 45 minutes, Ms. Corso said her foot was hitting the floor more evenly.

Botulinum cannot restore the use of muscles when stroke has destroyed the brain region that controls them. But patients look and feel better and often find it easier to dress, hold objects and bathe themselves.

Dr. Mark Hallett, chief of the motor control section of the National Institute of Neurological Disorders and Stroke, says he uses both electromyography and ultrasound when injecting patients.

“A number of authorities feel that if they get close, that’s good enough,” Dr. Hallett said. “I don’t agree. I think it’s valuable to make sure you’re in the right place.”

So does Ms. Corso. For a while, she said, she was seeing another neurologist nearer her home in Fort Salonga, on Long Island, who injected botulinum but did not use electromyography.

It did not work as well, she said. Now she has a friend drive her to the border of New York City, then takes a car service to the hospital. “It’s a long way from Long Island,” she said. “But it’s worth it.”

New study set to change how critically ill patients are treated

Brussels - The current practice of intensively lowering blood glucose in critically ill patients increases the risk of death by 10%. Results of the largest trial of intensive glucose lowering in critically ill patients published today in The New England Journal of Medicine indicate that international clinical guidelines need urgent review.

Intensive blood glucose lowering has been widely recommended and embraced to control hyperglycemia (high blood sugar) which is extremely common among acutely ill patients and linked with serious complications such as organ failure and death. These new findings reveal that current practice to intensively lower blood glucose increases the risk of death among patients in the intensive care unit (ICU).

"Intensively lowering blood glucose in critically ill patients is not beneficial and may be harmful. Based on our findings, we do not recommend pursuing a normal blood glucose level in critically ill patients. We found that intensively lowering blood glucose levels increased a patient's risk of dying by 10%," said Chief Investigator, Professor Simon Finfer from The George Institute for International Health, which is affiliated with the University of Sydney.

Researchers from The Australian and New Zealand Intensive Care Society Clinical Trials Group, The George Institute for International Health, The Canadian Critical Care Trials Group and Vancouver Coastal Health Research Institute set out to clarify the target range for blood glucose levels in critically ill patients. They followed 6104 ICU patients in Australia, New Zealand, Canada and the USA for up to 90 days to assess whether the treatment would improve patients' chance of survival.

"Previous, smaller research studies have produced conflicting results and overall suggested that intensive blood glucose control didn't affect death rates in critically ill adults. This new study gives us more powerful information, based on this larger study with stronger evidence, we can conclude that targeting very low levels of blood glucose is not safe," said North American Chief Investigator Dr Dean Chittock of Vancouver Coastal Health and University of British Columbia, Vancouver, Canada.

There are over six million admissions each year to ICU's in North America. The new evidence suggests that current guidelines must be reviewed.

"It's essential that international guidelines reflect this new evidence. Many professional organizations recommend very tight glucose control for ICU patients – they will now need to take this new evidence into consideration and adjust recommendations accordingly," added Dr Chittock.

The study, NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) randomly assigned patients to one of two target ranges for blood glucose; an intensive control target (81-108mg/dL; 4.5-6.0 mmol/L) or a conventional control target (180mg/dL; 10.0 mmol/L or less). Control of blood glucose was achieved by the use of an intravenous infusion of insulin.

A unique feature of the NICE-SUGAR study was standardized complex blood glucose management, which was accessed by multiple centres as a computerized algorithm.

Researchers Studying Hearing Loss in Adult Animals Find that Auditory Regions of the Brain Convert to the Sense of Touch

Virginia Commonwealth University School of Medicine researchers have discovered that adult animals with hearing loss actually re-route the sense of touch into the hearing parts of the brain.

In the study, published online in the Early Edition of the Proceedings of the National Academy of Sciences the week of March 23, the team reported a phenomenon known as cross-modal plasticity in the auditory system of adult animals. Cross-modal plasticity refers to the replacement of a damaged sensory system by one of the remaining ones. In this case, the sense of hearing is replaced with touch.

About 15 percent of American adults suffer from some form of hearing impairment, which can significantly impact quality of life, especially in the elderly.

"One often learns, anecdotally, that 'grandpa' simply turned off his hearing aid because it was confusing and no longer helped. Our study indicates that hearing deficits in adult animals result in a conversion of their brain's sound processing centers to respond to another sensory modality, making the interpretation of residual hearing even more difficult," said principal investigator Alex Meredith, Ph.D., a professor in the VCU Department of Anatomy and Neurobiology.

"Whether this becomes a positive feedback cycle of increasing hearing difficulty is currently under investigation, but these findings raise the possibility that even mild hearing loss in adult humans can have serious and perhaps progressive consequences," Meredith said.

The findings provide researchers and clinicians with insight into how the adult brain retains the ability to re-wire itself on a large scale, as well as the factors that may complicate treatment of hearing loss with hearing aids or cochlear implants.

The study was supported by a grant from the National Institutes of Health.

Meredith worked with postdoctoral fellows Brian L. Allman and Leslie P. Keniston, both in the Department of Anatomy and Neurobiology.

Deep-sea rocks point to early oxygen on Earth

Red jasper cored from layers 3.46 billion years old suggests that not only did the oceans contain abundant oxygen then, but that the atmosphere was as oxygen rich as it is today, according to geologists. This jasper or hematite-rich chert formed in ways similar to the way this rock forms around hydrothermal vents in the deep oceans today.

This is a banded rock formation in Pilbara Craton, West Australia. **Hiroshi Ohmoto/Yumiko Watanabe**

"Many people have assumed that the hematite in ancient rocks formed by the oxidation of siderite in the modern atmosphere," said Hiroshi Ohmoto, professor of geochemistry, Penn State. "That is why we wanted to drill deeper, below the water table and recover unweathered rocks."

The researchers drilled diagonally into the base of a hill in the Pilbara Craton in northwest Western Australia to obtain samples of jasper that could not have been exposed to the atmosphere or water These jaspers could be dated to 3.46 billion years ago.

"Everyone agrees that this jasper is 3.46 billion years old," said Ohmoto. "If hematite were formed by the oxidation of siderite at any time, the hematite would be found on the outside of the siderite, but it is found inside," he reported in a recent issue of Nature Geoscience.

The next step was to determine if the hematite formed near the water's surface or in the depths. Iron compounds exposed to ultra violet light can form ferric hydroxide, which can sink to the bottom as tiny particles and then converted to hematite at temperatures of at least 140 degrees Fahrenheit.

"There are a number of cases around the world where hematite is formed in this way," says Ohmoto. "So just because there is hematite, there is not necessarily oxygen in the water or the atmosphere."

The key to determining if ultra violet light or oxygen formed the hematite is the crystalline structure of the hematite itself. If the precursors of hematite were formed at the surface, the crystalline structure of the rock would have formed from small particles aggregating producing large crystals with lots of empty spaces between. Using transmission electron microscopy, the researchers did not find that crystalline structure.

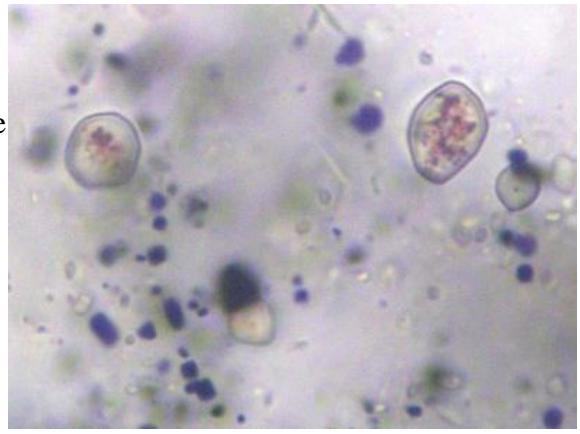
"We found that the hematite from this core was made of a single crystal and therefore was not hematite made by ultra violet radiation," said Ohmoto.

This could only happen if the deep ocean contained oxygen and the iron rich fluids came into contact at high temperatures. Ohmoto and his team believe that this specific layer of hematite formed when a plume of heated

water, like those found today at hydrothermal vents, converted the iron compounds into hematite using oxygen dissolved in the deep ocean water.

"This explains why this hematite is only found in areas with active submarine volcanism," said Ohmoto. "It also means that there was oxygen in the atmosphere 3.46 billion years ago, because the only mechanism for oxygen to exist in the deep oceans is for there to be oxygen in the atmosphere."

In fact, the researchers suggest that to have sufficient oxygen at depth, there had to be as much oxygen in the atmosphere 3.46 billion years ago as there is in today's atmosphere. To have this amount of oxygen, the Earth must have had oxygen producing organisms like cyanobacteria actively producing it, placing these organisms much earlier in Earth's history than previously thought.



Pictured is a micrograph of siderite crystals with the red showing hematite inside. The dark blue is magnetite and pyrite. **Hiroshi Ohmoto/Yumiko Watanabe**

"Usually, we look at the remnant of what we think is biological activity to understand the Earth's biology," said Ohmoto. "Our approach is unique because we look at the mineral ferric oxide to decipher biological activity."

Ohmoto suggests that this approach eliminates the problems trying to decide if carbon residues found in sediments were biologically created or simply chemical artifacts.

Other researchers on the study included who included Masamichi Hoashi, graduate student at Kagoshima University, Japan; Arthur H. Hickman, geologist with the Geological Survey of Western Australia; Satoshi Utsunomiya, Kyushu University, Japan, and David C. Bevacqua and Tsubasa Otake, former Penn State master's and doctoral students, Penn State; and Yumiko Watanabe, research associate, Penn State.

The NASA Astrobiology Institute supported this work.

Alarming new data shows TB-HIV co-infection a bigger threat

Disease experts raise alarm amid concerns global health funding will be shortchanged

WASHINGTON—The World Health Organization released staggering new data about the threat of tuberculosis and the toll it takes on people with HIV/AIDS today, in recognition of World TB Day.

The TB-HIV co-infection crisis is twice as big as previously thought, the new WHO figures show. In 2007, there were at least 1.37 million cases of HIV-positive TB - or nearly 15 percent of the total incident cases. That's double the previous WHO estimates.

"A global health catastrophe is unfolding," said Gerald Friedland, a professor of Medicine, Epidemiology and Public Health at Yale University School of Medicine and a leading expert on the emerging threat.

In addition, the WHO data shows that drug-resistant TB is on the rise. There were more than 500,000 cases of MDR-TB in 2007, the WHO reported. And by the end of 2008, at least 55 countries and territories had identified at least one case of extensively drug-resistant TB.

In light of the new WHO figures and increasing concern about the threat of drug-resistant TB, leading physicians and scientists are urging the Obama administration to triple the U.S. donation to the Global Fund to Fight AIDS, Tuberculosis and Malaria and to dramatically ramp up the U.S.'s own vastly-underfunded global TB programs.

Right now, nearly 60 countries are seeking new Global Fund grants for anti-TB programs. But the Fund, facing a $5 billion donation shortfall, may not be able to finance any of these desperately needed efforts.

Five world-renown experts on TB and HIV are available to discuss the new WHO data - set to be released on March 24th, World TB Day. They can address the scope of the TB-HIV co-infection crisis and talk about how U.S. policy makers should respond.

Tuberculosis is sometimes a forgotten and neglected disease. But an estimated one-third of the world's population is infected with the bacterium that causes TB, and the disease kills nearly 1.7 million people each year. Now, virulent new drug-resistant strains of TB are on the rise across the globe. HIV-positive patients are highly vulnerable to TB, because of their weakened immune systems, and tuberculosis is now the No. 1 killer of people with HIV. These twin epidemics present a stark new global health threat and raise the prospect of a global pandemic of extensively-drug-resistant TB, which is extremely difficult to treat.

The new WHO figures come amid deep concern among global health advocates that the Obama administration will flatline vital HIV/AIDS and TB programs, as the global recession deepens. The president is expected to release his detailed request for global health and other programs in the coming weeks. Advocates are urging full funding for PEPFAR, so the initiative can tackle the growing crisis of HIV-TB co-infection, and a tripling of the U.S. contribution to the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Briny pools 'may exist on Mars'

By Paul Rincon Science reporter, BBC News, The Woodlands, Texas

Pools of salty water might be able to exist just below the surface of Mars, planetary scientists believe.

Researchers previously thought water existed largely as ice or as vapour on Mars, because of the low temperatures and atmospheric pressure. But Nasa's Phoenix lander has shown the presence in Martian soil of perchlorate salts, which can keep water liquid at temperatures of minus 70C. Pockets of brine might form when soil interacted with ice.

Researchers have been discussing the idea at the 40th Lunar and Planetary Science Conference (LPSC), here in The Woodlands, Texas. They were presenting some of the first scientific results from Phoenix, which touched down on Mars's northern plains on 25 May 2008.

"I do think those pools might exist. But there's still more to know about the properties of these perchlorate solutions, such as what their vapour pressure is," Dr Mike Hecht, from Nasa's Jet Propulsion Laboratory (JPL) in Pasadena, California, explained.

Soil dampness

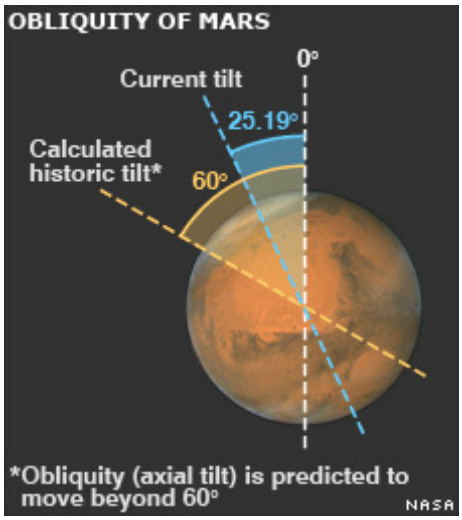
Phoenix used thrusters to slow its descent to the surface. And these blew away topsoil, exposing water-ice just centimetres beneath. Dr Hecht said: "Here are all these perchlorate salts right under them, by a few centimetres, is a slab of [water ice]. It doesn't take much of a stretch of the imagination to say that those two materials will interact. "And once you get dampness, the perchlorate is very soluble and it will become mobile."

On Earth, perchlorates - salts derived from perchloric acid - are used in solid rocket fuel, fireworks and airbags. Scientists are just starting to understand the important roles they may play on Mars. Dr Hecht said that forming pockets of liquid on Mars would require just the right concentrations of perchlorate salts. He commented: "In this case we have very little perchlorate and vast slabs of ice, so I can imagine we have an excess of water. This means you would form a pool of low temperature brine if the two ever interacted."

Other researchers cautioned that the concentrations of these salts found at the Phoenix landing site remained a small component of the overall soil chemistry, and that more had to be done to test the idea.

Nevertheless, Dr Hecht said the discovery of these compounds made the Red Planet seem more Earth-like in several respects.

Big tilt



Perchlorates might be controlling the amount of water vapour in the midday atmosphere, according to separate evidence presented by Dr Troy Hudson of JPL.

And their presence might also explain why neither Phoenix nor the 1970s Viking landers found any firm evidence for "organics" - molecular compounds which contain carbon (though excluding carbonates for historic reasons).

These molecules are a crucial component in the search for possible biology on the Red Planet. “The perchlorates, as you heat them in the oven (onboard Phoenix), release their oxygen and combust the organics," Peter Smith, the mission's chief scientist, told the conference. "It's ironic: the two compete as you heat them. We did see CO2 release, but we're not sure whether that was from organics or not."

Professor Smith said several lines of evidence pointed to the past action of liquid water on the northern plains. These included the presence of aqueous minerals, cloddy, cemented soil and the discovery that some of the ice was "segregated", as if it had melted.

"It's probable that in a warmer, wetter climate, as when the obliquity (the extent to which Mars is tilted on its axis) changes, this could be a place where liquid water is found. That doesn't mean it's a lake. It just means that the soil is wet," Professor Smith, from the University of Arizona, explained.

The discovery of calcium carbonate in the soil is also suggestive of the past action of liquid water. The substance is found in rocks all over Earth and is the main component in limescale. Peter Smith said it occurred at levels of 3-5% at the Phoenix landing site, probably forming as carbon dioxide from the Martian atmosphere dissolved into liquid water, forming a weak acid which leached calcium out of the soil.

But Dr Nilton Renno, from the University of Michigan, US, presented evidence that droplets of liquid water could actually be seen in photographs of a strut of the spacecraft's landing leg. "The (spheroids) move, drip and merge," Dr Renno explained.

But Mike Hecht and Dr Tom Pike, from Imperial College London, UK, believe the droplets are more likely to be frost. "The photographs are clipped from the corners of relatively low resolution images, so the number of pixels across those droplets is very small. Trying to ascribe shapes to them, to say they are spheres - which are characteristic of liquid - is going beyond the quality of the images," said Mike Hecht.

Secondly, he thought the thermodynamics of the Martian environment were not consistent with the relatively large changes in the sizes of droplets seen in the images.

Eventual demise

Dr Renno told the conference that ice particles were usually not just spheroidal, and did not move in the way the droplets did.

Mike Hecht said frost was able to move more readily in the Martian environment than it did on Earth because of the thin air.

However, the JPL scientist emphasised his agreement with Dr Renno on most areas concerning the properties of perchlorates at the Phoenix landing site.

Launched from Earth in August 2007, Phoenix landed further north than any previous mission to the Martian surface. It conducted science operations for more than five months before succumbing to the cold and dark of the Martian winter. The robot dug, scooped, baked, sniffed and tasted the Martian soil to test whether it has ever been capable of supporting life. It became the first mission to Mars to sample the water-ice it found just centimetres below the topsoil. Chunks of ice were seen to vaporise before the lander's cameras.

Five classic examples of gene evolution

* 16:56 24 March 2009 **by Michael Le Page**

As the genomes of more and more species are sequenced, geneticists are piecing together an extraordinarily detailed picture of the molecules that are fundamental to life on Earth.

With modern techniques, we can not only trace how the bodies of animals have evolved, we can even identify the genetic mutations behind these changes and, as we recently reported, genes sometimes evolve in surprising ways. Here though, in celebration of the versatility of DNA, New Scientist presents five classic examples of gene evolution.

1. Collecting colours

Ever noticed how dogs sometimes seem unable to spot a brightly coloured ball that's obvious to you? That's because most mammals have just two colour-sensitive retina pigments, or opsins, compared to our three. This means they effectively have a form of colour blindness.

So why do we have three? In the ancestors of apes and some monkeys, the gene MWS/LWS – which codes for one of the two pigments found in most mammal eyes – was duplicated. Spare gene copies usually degenerate quickly as they acquire mutations, but in this case mutations in one copy resulted in an opsin that could detect a different spectrum of light. In this way, we gained better, trichromatic colour vision.

There is, however, a twist to this tale. The ancestors of vertebrates actually had even better colour vision than we do, thanks to their four colour-sensitive opsins. Unlike us, they could see ultraviolet, as well as the other colours. This ability has been inherited by most amphibians, reptiles and birds, so how come mammals lost two of the colour-sensitive opsin genes?

The answer is probably that because some of the earliest mammals were nocturnal, they had no little need for colour-sensitive opsins that only worked during daylight. As a result, these genes acquired mutations and some were lost – if you don't use it, you lose it.

Our vision could have evolved along very different lines. When the ancestors of geckos became nocturnal, they evolved colour night vision.

2. Crystal clear

You wouldn't be able to read these words without the crystallin proteins in your eye. These transparent proteins can bend light thanks to their high refractive index, enabling the lens of the eye to focus light on the retina.

So where did evolution find transparent proteins with a high refractive index when the eye was evolving? All over the place, it turns out.

Take alpha-crystallin, which is found in a variety of animal eyes, including ours. It was originally a heat-shock protein – a type of protein that keeps other proteins in shape. In fact, it still is a heat shock protein. In some tissues in the body, where only small amounts of the protein is made, it still carries out this role – in the lens, though, it is produced at high levels and its main function is optical.

There is only one gene, HspB5 that codes for alpha-crystallin. So the evolution of a new function – such as bending light – does not always require the evolution of an entire new gene encoding a novel protein. Sometimes, all it takes are a few mutations in the sequences that determine how much of an existing protein is made in a particular tissue type. Sometimes evolution takes the easy path.

3. Fishy smell

Over hundreds of millions of years, a single gene can give rise not just to one new gene, but to hundreds via gene duplication. We humans have around 400 genes coding for smell receptors, for instance, all of which derive from two original genes in a very early fish living around 450 million years ago.

The evolution of this gene "family" has been a messy process. Genome studies show that, rather than steadily acquiring genes for new smell receptors, there have also been extensive losses of genes during the evolution of mammals – a process dubbed "birth-and-death evolution".

This has led to great variation between mammals. You would expect dogs to have more receptors than humans, with around 800 working smell-receptor genes – but why do cows have even more, with over 1000?

Masatoshi Nei of Pennsylvania State University, University Park, has suggested that mammals only need a certain minimum number of different olfactory receptors to have a good sense of smell. What animals do with the ones they have – the wiring of the brain during development, in other words – may matter more when it comes to a keen sense of smell.

As long as animals have more olfactory receptor genes than they need, he suggests, there is no natural selection and genes are gained and lost randomly. In other words, genetic drift might explain why the numbers and type of smell receptors vary so widely among mammals.

4. Double for nothing

The HOX genes are a family of closely related genes that control embryonic development in animals. They are the "master switches", the proteins that coordinate the activation of other sets of genes during development.

All HOX genes evolved from a "protoHOX" gene in a very early animal. This protoHOX gene was repeatedly duplicated, creating a cluster of 13 HOX genes in the ancestor of vertebrates. Then the entire genome in this ancestral line got duplicated. And then it got duplicated again, creating the four clusters of HOX genes that control the development of all living vertebrates.

In the lineage leading to mammals, 13 of the 52 genes created by genome duplications were lost, leaving mammals with 39 HOX genes. The real mystery, though, is why so many of the gene copies created by the genome duplications survived? Why didn't they just degenerate and disappear? It might make sense to keep spare copies of genes handy, but evolution does not plan for the future.

The same phenomenon has been seen in the African clawed frog, Xenopus laevis, whose entire genome got duplicated 40 million years ago. The vast majority of all these extra gene copies should have croaked long ago. Yet even after all this time, up to half of the duplicate genes have been preserved.

In remarkable 2006 study, Mario Capecchi of the Howard Hughes Medical Institute in Salt Lake City, for instance, reversed the process that gave rise to the HOX gene family. He merged two existing HOX genes, HOXA1 and HOXB1, to recreate the HOX1 gene from which they evolved. Mice given this ancestral gene instead of the two modern ones still developed normally.

His work suggests that the two new genes together do no more than the ancestral gene did. In other words, both the gene copies did degenerate after being duplicated. No advantage has been gained by swapping one gene for two: the process was neutral.

This phenomenon, proposed a decade ago, is known as subfunctionalisation: when a gene is duplicated, the functions of the original gene can end up divided among the copies. Studies of the clawed frog suggest subfunctionalisation can explain the preservation of at least a third of gene copies.

What this shows is that greater genomic complexity – having more genes – can evolve as a result of genetic drift, as well as by natural selection. Once organisms have acquired extra genes, of course, there is more chance of those genes acquiring new beneficial new functions that will be selected for.

5. Enigmatic enzyme

Nylon was first made in 1935. Just 40 years later, in 1975, a bacterium was discovered that is able to digest and live off not nylon itself, but waste chemicals from its manufacture – chemicals that had not existed before nylon production began. It was later shown this bacterium, now known as Arthrobacter KI72, has evolved several types of enzymes capable of utilising these waste products. One type, 6-aminohexanoic acid hydrolase, encoded by genes called nylBs, has become known popularly as "nylonase".

As a dramatic example of evolution in action, nylonase has attracted a lot of attention over the years. But there has also been a great deal of confusion about how it evolved.

In 1984, geneticist Susumu Ohno suggested that one way in which new genes could evolve is through a "frameshift" mutation – one that alters the way in which the genetic code is read and thus completely alters the amino acid sequence of a protein. And nylonase evolved this way, he claimed.

Then in 1992, another team claimed that nylB genes are unique and had evolved by a rather complicated and special mechanism.

They are both wrong, says Seiji Negoro of the University of Hyogo, Japan, whose team has published many studies on the structure and evolution of nylon-related enzymes. "I believe that the above two hypotheses can be excluded," he told New Scientist.

His team's study of the protein structure show that nylonase is very similar to a common type of enzyme that breaks down beta-lactamases – natural antibiotics produced by many organisms. Just two amino-acid changes – two mutations, in other words – are required to change the beta-lactamase binding site to one capable of binding the nylon by-product.

However, while Ohno was wrong about nylonase, he was right about frameshift mutations being one way in which genes evolve. Hundreds of examples have now been discovered in humans alone.

How speeding cancer growth offers hope of cure

* 11:16 25 March 2009 **by Linda Geddes**

Certain cancer therapies may make tumours grow more aggressively depending on the dose given, new research shows. While this may not sound particularly reassuring, the finding could actually speed the way towards a cure.

Andrew Reynolds at the Institute of Cancer Research (ICR) in London and his colleagues looked at a class of anti-angiogenesis drug called integrin inhibitors, which are designed to stop the growth of new blood vessels that supply the tumour. Without a fresh supply of oxygen and nutrients, the tumour should wither and die.

Yet despite some promising results in patients with a type of brain cancer called glioma, these drugs haven't been successful in treating other types of cancer.

Reynolds and colleagues wondered if the dosage and delivery of the drug had anything to do with it. Integrin inhibitors are usually administered to patients every 3 days, so they get a big initial dose, but the concentration in the body diminishes after around 16 hours.

"Could it be that the drug is having different effects at high doses and low doses?" asks Kairbaan Hodivala-Dilke at Queen Mary, University of London, who supervised the work.

Enhanced growth

They used osmotic mini pumps, designed to deliver a constant dose of drug into the body, to test the effects of different concentrations of an integrin inhibitor called cilengitide on mice implanted with human tumours.

Although high doses of the drugs reduced tumour growth, at low doses they appeared to enhance growth. "It was completely unexpected," says Hodivala-Dilke.

But rather than giving up on integrin inhibitors altogether, she thinks that gaining a better understanding of how they work could enable researchers to make them work better. One possibility might be to use osmotic minipumps to administer the drugs to people – although we don't yet know whether consistently high doses of the drugs would have additional side effects. Another alternative might be to combine them with different types of anti-cancer drug.

"The take-home message is that we need to be to be careful about the dose of the drug that our cells are exposed to because it is having effects that we didn't predict," says Hodivala-Dilke. "These drugs have a dark side."

"This study is important because it may help to explain the mixed results previously seen in patients and turn around disappointing results so people may still benefit from the drug without the potential harm," adds Lesley Walker, of Cancer Research UK.

"Other anti-angiogenesis drugs like sunitinib (Sutent) and bevacizumab (Avastin) have proven effective enough for use, but there is still need to understand why they can sometime fail. It may be that there are similar mechanisms at work." ***Journal reference: Nature Medicine, DOI:10.1038/nm.1941***

Desire to amputate healthy limbs shows up in brain scans

* 14:02 25 March 2009 **by Ewen Callaway**

It's a bizarre and rare disorder, but its consequences can be horrific. One man with body integrity identity disorder (BIID) dumped his lower leg in dry ice for several hours until doctors were forced to amputate. Others have resorted to wood chippers and gunshots to do away with healthy limbs they never wanted.

Now a study of four men with BIID suggest their condition is linked to reduced activity in a brain area involved in forming a mental body map. "They can feel the body being touched, but it does not integrate into their sense of body image," says Paul McGeoch, a neuroscientist at the University of California, San Diego, who presented the study at a recent conference on the condition in Frankfurt-am-Main, Germany.

"They know the limb is part of their body, but it's 'more' than it should be. It should be gone," he adds.

Sexual oddity

The disorder, also known as apotemnophilia, was first described in 1977 by the American sexologist John Money. He classified it as an intense sexual desire to have an amputation, hence its original name, which is Greek for love of amputation. Most patients, however, don't describe their desire to be amputees as sexual, says

Michael First, a psychiatrist at Columbia University in New York who has conducted extensive interviews with dozens of patients. “It's very, very rare," First says of all forms of the disorder. "I've been working on this condition now, researching it for 8 years, and I almost never get calls from therapists saying 'I have somebody with this. I need your advice.' "

Brain malfunction

Explanations for how BIID develops have run the gamut, from a cry for attention to early childhood exposure to an amputee, McGeoch notes. Those explanations "seemed absolute nonsense to us", he says.

Instead, he and co-author David Brang theorise that the disorder is caused by a malfunction in a brain area called the right parietal lobe. Other studies have linked this region to people's representation of their own body: stroke patients who suffer damage to this area sometimes fail to recognise a limb as their own.

"We suggest that perhaps apotemnophillia, or BIID or whatever you want to call it, is a cognitive variation on this – there's something cognitively wrong with their right parietal lobe," McGeoch says.

To test this hypothesis, McGoech's team recruited four men with BIID via internet support groups. Though precise numbers are hard to come by, the disorder is about 10 times more common in men than in women.

Scanning evidence

The team tested subjects using a non-invasive brain imaging technology called magnetoencephalography (MEG), which measures the tiny magnetic fields created when neurons fire.

When researchers touched the limb that BIID subjects perceived as normal, their right parietal lobe kicked into action. When they touched the limb subjects wanted gone, activity in the right parietal lobe didn't change.

One patient who wanted both his legs amputated registered no increased activity at all, McGeoch's team found. Meanwhile, four volunteers with no desire to hack off a limb cranked up their right parietal lobes when researchers touched either leg.

"The fact that they're able to scan anybody is amazing," given the rarity of BIID, says First. He guesses that no more than a few thousand people worldwide have the disorder.

Warped body image

He is, however, not yet convinced that a deficit in the right parietal lobe causes BIID. It's also possible that a strong desire to amputate a limb could transform neural circuitry in a brain region responsible for body image, he says. "There's a chicken-and-egg problem here." The limb that patients want amputated can change throughout their lifetime, First notes. "That can't be explained by a cognitive mismapping [of the limb]."

Deeper insight into the causes of BIID could offer insight into how to treat the condition. Drugs that alleviate symptoms of obsessive compulsive disorders are one possibility worth testing, First says.

Yet many patients see an actual amputation as the best treatment possible. "I have never heard of them regretting it," McGeoch says. "They're always delighted."

Journal reference: Nature Precedings (DOI: 10101/npre.2009.2954.1)

Beneficial Alzheimer's gene can be perilous in pairs

WHERE protection against Alzheimer's is concerned, you can have too much of a good thing. If you inherit one copy of a particular gene mutation it seems to protect you from Alzheimer's. With a copy from each parent, you may be in trouble.

Fabrizio Tagliavini of the Carlo Besta National Neurological Institute in Milan, Italy, and colleagues discovered the mutation in a 44-year-old man with signs of early-onset Alzheimer's who didn't have the usual gene mutations.

Both he and a younger sister with mild cognitive problems, have two copies of a mutation in a gene called APP, while relatives with just one copy of the mutation, including an 88-year-old aunt, seemed to be actively protected against the disease (Science, DOI: 10.1126/science.1168979).

APP makes the protein A-beta, which can form clumps in the brain, blocking neurons from firing. But experiments showed that a mix of normal and mutant A-beta is less likely to clump than mutant protein or normal protein alone, which may explain why one copy of APP is protective.

Germany's stone age cannibalism

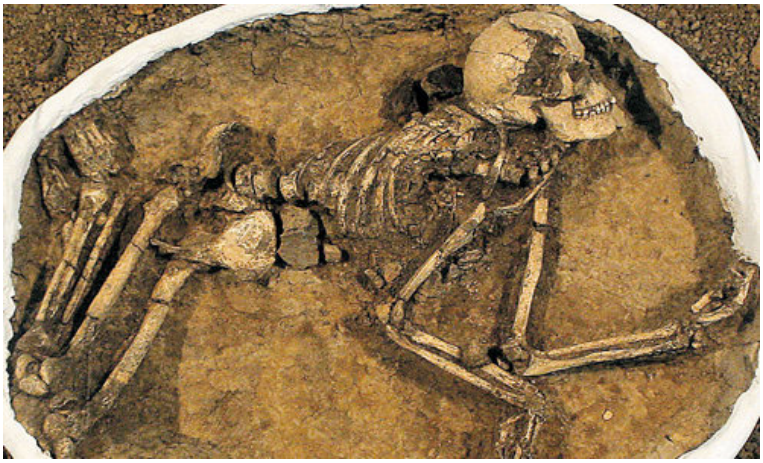
Tens of thousands of ancient human bones found in Germany suggest that victims were not killed just to satisfy hunger, writes Pierre Le Hir in Le Monde

The German city of Speyer, in Rheinland-Palatinate, well known for its -Romanesque cathedral, also boasts some much more macabre relics. A collection of skulls, shin bones and vertebrae might not seem unusual in an archaeology museum, but these particular remains are special. They all show signs of having been cut, scraped or broken, indicating that their owners were cannibalised.

"Look at these grooves, running from the base of the nose to the back of the neck, or here on the temples," says Andrea Zeeb-Lanz, the regional head of archaeology, holding up a skull. "The grooves show, beyond all

possible doubt, that the flesh was torn off." It takes good eyesight to catch the fine parallel incisions made by the cutting edge of the flint stone. She then shows me a piece of thigh-bone the end of which has been crushed. Judging by the state of the bone tissue, it was smashed shortly after the victim was killed.

All these human remains were found at the stone-age site at Herxheim, near Speyer. About 7,000 years ago farmers, who grew wheat and barley, raised pigs, sheep and cattle, settled here, building a village of four to 12 houses, the post holes of which have survived. At the time the first farmer-stockherders were moving into Europe, supplanting their hunter-gatherer predecessors. The Herxheim settlers came from the north (between 5,400 and 4,950BC) and belonged to the Linear Pottery culture.



Some skeletons show signs of cannibalism. **Photograph: Nikolay Doychinov/Reuters**

Two lines of ditches were dug around the settlement. They can't have been defensive because they weren't continuous. Nor were they intended for use as an ossuary, as the Linear Pottery people generally buried or burned their dead. However, during a rescue dig just before the area was developed as an industrial estate, in some of the ditches archaeologists uncovered tens of thousands of -human bones.

During the first series of excavations, at the end of the 1990s, the numerous injuries visible on the skeletons were taken as evidence that the victims had been massacred. But in 2008 Bruno Boulestin, an anthropologist at Bordeaux University, examined the fragments recovered from one of the trenches, pointing out that nearly 2,000 samples belonged to fewer than 10 individuals.

"It is impossible to establish direct proof of cannibalism. But here we have systematic, repetitive gestures, which suggest that the bodies were eaten," says Boulestin. The marks of breaking, cutting, scraping and crushing indicate that the bodies were dismembered, the tendons and ligaments severed, the flesh torn off, the bones smashed. The vertebra were cut up to remove the ribs, just as butchers do today with loin chops. The tops of skulls were opened to extract the brains. Another telling clue is that there are proportionately fewer bones containing marrow, particularly vertebrae and short bones, suggesting they were set aside.

A quick investigation of the bones in neighbouring ditches showed that they had suffered the same fate. Extrapolating to the whole site, only half of which was excavated, about 1,000 people must have been butchered. There is no other example in prehistory of a mass grave of this size. "We are dealing with an exceptional event," says Zeeb-Lanz. Other cases of neolithic cannibalism have certainly been identified, in particular in France, at the caves at Fontbrégoua and Adaouste, near the south coast, or at Les Perrats, further west, but never on this scale.

What can this bloodbath mean? The potsherds found among the human remains suggest it must have occurred over a period of no longer than 50 years. There is nothing to imply the victims were killed for food. Only under extreme conditions would 100 or so farmers have been able to overcome about 10 times their number. The archaeologists have therefore concluded that this was some form of ritual killing. In some cases the tops of skulls were arranged to form a nest, scattered with pottery fragments, broken adzes, jewellery made of shells, the paws and jawbones of dogs.

There are two main types of ritual cannibalism, as the historian Jean Guilaine and palaeopathologist Jean Zammit explain in The Origins of War: Violence in Prehistory. Exocannibalism targets people outside the community: by eating a conquered enemy the aim was not so much to feed on their body as to make them disappear for ever, appropriating their strength, energy and valour.

Endocannibalism, within a community, was a token of affection, the recognition of a bond that needed to be maintained. The scientists have also excluded this possibility, given the small size of the village. But wartime exocannibalism also seems unlikely, as it would have involved raids on remote communities to bring back hordes of prisoners and their pottery.

The team that discovered the site have come up with another hypothesis. Members of the Linear Pottery culture deliberately gathered here, with their prisoners and pottery, to take part in sacrificial ceremonies.

"At this time, the Linear Pottery culture was undergoing a crisis, which led to its disappearance," says Zeeb-Lanz. "Perhaps they hoped to prevent the end of their world through some ceremony, of which cannibalism was just a part."

New drug agent knocks out multiple enzymes in cancer pathway

A team of 24 researchers from the U.S., Europe, Taiwan and Japan and led by University of Illinois scientists has engineered a new anti-cancer agent that is about 200 times more active in killing tumor cells than similar drugs used in recent clinical trials.The study appears this week in the Journal of the American Chemical Society.

The new agent belongs to a class of drugs called bisphosphonates. These compounds were originally developed to treat osteoporosis and other bone diseases, but were recently found to also have potent anti-cancer and immune boosting properties.

Drug developers have tried for years to design drugs to inhibit cell survival pathways in tumor cells, focusing on a protein called Ras since nearly a third of all human cancers involve a mutation in the Ras gene that causes cell signaling to go awry. These efforts have met with limited success.

Bisphosphonates act on other enzymes, called FPPS and GGPPS, which are upstream of Ras in the cell survival pathway. Inhibiting these enzymes appears to be a more effective strategy for killing cancer cells.

When used in combination with hormone therapy in a recent clinical trial, the bisphosphonate drug zoledronate significantly reduced the recurrence of breast cancer in premenopausal women with estrogen-receptor-positive breast cancer. Similar results were reported previously for hormone-refractory prostate cancer.

But zoledronate quickly binds to bone, reducing its efficacy in other tissues.

"We're trying to develop bisphosphonates that will be very active but won't bind to the bone, because if they bind to the bone they're not going to go to breast, lung or other tissues," said University of Illinois chemistry professor Eric Oldfield, who led the new study. Oldfield's team also wanted to design a compound that would inhibit multiple enzymes in the tumor cell survival pathway, rather than just one, an approach analogous to the use of multi-kinase inhibitors in cancer therapy.

Andrew Wang, of Academia Sinica, Taipei, and Illinois chemist Rong Cao began by producing crystallographic structures of the target enzymes and drug candidates, allowing the researchers to identify those features that would enhance the drugs' ability to bind to the enzymes. Using this and other chemical data, Illinois chemistry department research scientist Yonghui Zhang engineered new bisphosphonate compounds that bound tightly to multiple enzyme targets, but not to bone.

One of the new compounds, called BPH-715, proved to be especially potent in cell culture and effectively inhibited tumor cell growth and invasiveness. Tadahiko Kubo, of Hiroshima University, then found that BPH-715 also killed tumor cells in mice. And Socrates Papapoulos, of Leiden University, the Netherlands, showed that the compound had a very low chemical affinity for bone.

In humans, compounds like BPH-715 and zoledronate have an added benefit in fighting cancer: They spur the proliferation of immune cells called gamma delta T-cells, which aid in killing tumor cells.

"The new drugs are about 200 times more effective than the drugs used in recent clinical trials at killing tumor cells and in activating gamma delta T-cells to kill tumor cells," Oldfield said. "They also prevent tumor progression in mice much better than do existing bisphosphonate molecules."

A new approach to prostate cancer detection

Sarcosine may distinguish between slow-growing and aggressive prostate cancers

On Friday 20 March, US researcher Dr. Chris Beecher from the University of Michigan gave a well attended lecture about sarcosine, an N-methyl derivative of the amino acid glycine, at the 24th Annual EAU Congress in Stockholm, Sweden. Dr Beecher is a colleague of lead author Dr. Arun Sreekumar. The research of Sreekumar, Beecher and their team looked at more than 1,000 small molecules in tissues associated with prostate cancer. These findings suggest that not only is sarcosine a marker of cancer aggressiveness, it also has a role in endowing a cancer with malignant properties.

Sreekumar´s publication in Nature (457, 12 February 2009: 910-914) has attracted a lot of scientific and also popular attention. The EAU Scientific Congress Office inserted a special breaking news session in the congress programme in order to present the most updated scientific information in Stockholm.

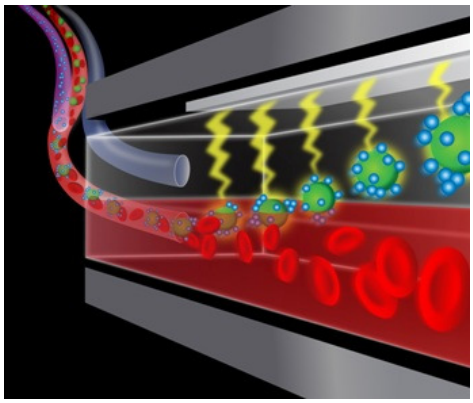
Sarcosine may distinguish slow-growing prostate cancers from those likely to spread and become lethal. Conveniently, sarcosine can be identified in urine, a less invasive test than the blood analysis needed for the standard prostate-specific antigen (PSA), a protein produced by the cells of the prostate gland. PSA is present in small quantities in the serum of healthy men, and is often elevated in the presence of prostate cancer. Quite often men have PSA scores that fall into a grey area. Therefore, invasive biopsy is needed to clarify a diagnosis. But even when a biopsy reveals cancer, it often remains unclear whether the cancer is aggressive and at risk of spreading, or indolent and likely to stay put. Rather than looking for genes or proteins, Dr. Arun Sreekumar and his team of the University of Michigan measured the levels of chemical by-products of the reaction inside the human cells. These chemicals are called metabolites. They looked into 42 tissue samples, 110 blood samples and the same number of urine samples from patients with advanced prostate cancer, early prostate cancer and

men with benign disease. Ten of these chemicals were found at much higher levels in prostate cancer than normal samples. One of these metabolites stood out: sarcosine.

According to Dr. Beecher, the results are promising: "Sarcosine continues to predict the aggressiveness of the tumours". The metabolomic analysis yielded the observation that sarcosine was highly associated with tumour development. The scientific data support a correlation and provide biological insights.

A fast magnetic fix for sepsis?

Micromagnetic-microfluidic device could quickly pull pathogens from the bloodstream



Sepsis, an infection of the blood, can quickly overwhelm the body's defenses and is responsible for more than 200,000 deaths per year in the U.S. alone. Premature newborns and people with weakened immune systems are especially vulnerable. Since most existing treatments are ineffective, researchers in the Vascular Biology Program at Children's Hospital Boston have come up with a first line of defense--using magnetism to quickly pull pathogens out of the blood.

Their blood-cleansing device, developed by Chong Wing Yung, PhD, a researcher in the laboratory of Don Ingber, MD, PhD, is described in the journal Lab on a Chip. (The article can be accessed here, and is scheduled for formal online publication on April 13).

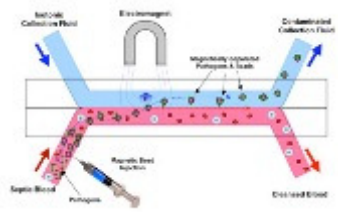
***In the micromagnetic-microfluidic blood cleansing device, saline collection fluid and contaminated blood with opsonized pathogens flow together without mixing under laminar conditions. As the fluids pass the external magnetic field concentrator, opsonized pathogens and excess beads are selectively pulled from the blood across the boundary between laminar streams and into the collection fluid where it exits as waste. A multiplexed, 4-channel prototype can continuously cleanse over 80% of pathogens from contaminated human whole blood at a rate of 20 mL/hr in a single pass*. (Credit: Kristin Johnson and Chong Wing Yung, PhD, Children's Hospital Boston)**

The system they envision will work like this: The patient's blood is drawn, and tiny magnetic beads, pre-coated with antibodies against specific pathogens (such as the fungus Candida albicans) are added. The blood is then run through a microfluidic system in which two liquid flow streams run side by side without mixing -- one containing blood, the other a saline-based collection fluid. The beads bind to the pathogens, and a magnet then pulls them (along with the pathogens) into the collection fluid, which is ultimately discarded, while the cleansed blood in reintroduced into the patient.

Tested with contaminated human blood, a device with four parallel collection modules achieved over 80 percent clearance of fungi in a single pass, at a flow rate and separation efficiency that would be viable for clinical applications. Yung and Ingber estimate that a scaled-up system with hundreds of channels could cleanse the blood of an infant within several hours.

"This blood-cleansing microdevice offers a potentially new weapon to fight pathogens in septic infants and adults, that works simply by removing the source of the infection and thereby enhancing the patient's response to existing antibiotics," says Ingber.

Slideshow



A magnetic fix for sepsis

Yung, Ingber and physicians Mark Puder, MD, PhD, and Jay Wilson, MD. from the Department of Surgery at Children's Hospital Boston, with collaborators from Draper Laboratories, recently won a $500,000 grant from the Center for Integration of Medicine and Innovative Technology (CIMIT) to further the work. The next phase will be to test the device in an animal model.

The study was funded by CIMIT, with additional resources from Harvard University's Center for Nanoscale Systems (CNS) and the National Nanotechnology Infrastructure Network (NNIN) initiative. The article can be accessed here.

Mending a broken heart: Study offers closer look at 'broken heart syndrome'

Overall outcomes, prognosis excellent following quick medical treatment

PROVIDENCE, RI – "Broken heart syndrome" is still a mystery to many in the medical community, but new data from researchers at The Miriam Hospital may shed some light on the clinical characteristics and outcomes of this relatively rare, life-threatening condition.

Researchers created a registry of 70 patients with the syndrome, known medically as Takotsubo cardiomyopathy, who were diagnosed between July 2004 and April 2008. Two-thirds of the patients – almost all post-menopausal women – had experienced a very stressful physical or emotional event just before arriving at the hospital with heart attack-like symptoms. Although 20 percent were critically ill and required emergency

treatment to keep them alive, all patients survived the first 48 hours and experienced a full and complete recovery. The report is published in the April 1 issue of the American Journal of Cardiology.

"It can be difficult for cardiologists and emergency room physicians to diagnose and manage patients with broken heart syndrome. However, this data will helps us better understand the disease process and could play a major role in developing and tailoring more effective short and long-term treatment strategies," says lead author Richard Regnante, MD, an interventional cardiology fellow at The Miriam Hospital and a teaching fellow in medicine (cardiology) at The Warren Alpert Medical School of Brown University.

Broken heart syndrome was first described by Japanese researchers in the early 1990s. Symptoms typically mimic a heart attack and tend to follow exposure to an intense physical or emotional event. Experts believe these symptoms may be brought on by the heart's reaction to a surge of stress hormones, like adrenaline, causing a part of the heart to temporarily weaken or become stunned (cardiomyopathy), although the exact mechanism is unknown. However, it appears that broken heart syndrome is temporary and completely reversible.

All patients in the Rhode Island Takotsubo Cardiomyopathy Registry arrived at the hospital with heart attack-like symptoms, including chest pain and shortness of breath. Because of those similarities, patients underwent emergency cardiac catheterization. Approximately 67 percent of patients had been exposed to some sort of physical or emotional distress – such as bad news about a family member, a domestic argument, severe physical illness or a car accident – just before the onset of symptoms. All were eventually diagnosed with broken heart syndrome during their hospital stay.

Researchers identified a wide spectrum of disease severity among patients in the registry. Six patients presented with cardiogenic shock and three patients experienced sustained ventricular arrhythmias, requiring emergency defibrillation or cardioversion. Overall, the majority of those in the registry were prescribed aspirin, beta blockers, ACE inhibitors and statins during their hospitalization, consistent with treatment protocol for patients with acute coronary syndrome. Similarly, most patients left the hospital on a cardiac regimen very similar to that prescribed for heart attack patients.

Looking at long-term prognosis, researchers say patients tended to do well from a cardiac standpoint, with only two patients experiencing a recurrence of broken heart syndrome, while the remaining patients did not appear to have any other cardiac issues during the four-year follow-up. "Although there is much we're still learning about broken heart syndrome, we do know that it is rarely fatal as long as patients are fully supported with medications, respirators and other critical devices in the first 48 hours," says Regnante.

The registry also revealed an interesting and unexpected discovery that researchers say is not easily explained: the majority of broken heart syndrome cases occurred during the spring and summer months. Regnante points out that this is in complete contrast to the seasonal timing of heart attacks, which tend to occur during the winter months, and says this finding fuels the debate about what actually causes the weakened muscle in broken heart syndrome.

"Some believe it is simply a form of a heart attack that 'aborts' itself early and therefore doesn't leave any permanent heart muscle damage. Others say that the syndrome has nothing to do with the coronary arteries and is simply a problem with the heart muscle," he says. "Since the seasonal pattern of broken heart syndrome that we observed is opposite of what it seen with heart attack patients, our findings suggest – but certainly does not prove – the latter theory may be correct."

As a next step, Regnante and colleagues are currently enrolling patients with broken heart syndrome for a new study in which intravascular ultrasound (IVUS) will be used during cardiac catheterization. This imaging technique can uncover evidence of ruptured plaque in the artery or a small blood clot, which happens when a patient suffers a heart attack, but cannot be seen well on angiography alone. Researchers say this important study may help answer the ongoing question about the mechanism that causes broken heart syndrome.

The study was conducted at The Miriam Hospital and Rhode Island Hospital. Study co-authors from The Miriam Hospital, Rhode Island Hospital and/or Alpert Medical School include Immad Sadiq, MD, Ryan W. Zuzek, MD; Steven B. Weinsier, MD; Syed R. Laif, MD; Russell A. Linsky, MD; and Hanna N. Ahmed, MD, MPH.

Artificial cartilage performs better than the real thing

* 18:00 26 March 2009 **by Colin Barras**

The smooth cartilage that covers the ends of long bones provides a level of lubrication that artificial alternatives haven't been able to rival – until now. Researchers say their lubricating layers of "molecular brushes" can outperform nature under the highest pressures encountered within joints, with potentially important implications for joint replacement surgery.

With every step we take, bones at the knee and hip rub against each other. That would quickly wear them away if it wasn't for the protection afforded by the thick layer of smooth and slippery cartilage that covers their ends.

No amount of polishing can remove all of the small imperfections from the stainless steel used in artificial joints. Any raised areas that are left grind against each other and release debris particles that soften the bone, explains Jacob Klein at the Weizmann Institute of Science in Rehovot, Israel.

Like bone, artificial joints must be covered with a cartilage-like layer. However, while it's possible to match cartilage's slick properties at low pressure, at the high pressures found in joints synthetic alternatives "seize up".

Under pressure

Now Klein has discovered a possible solution. Working with colleagues in the UK, he's developed molecular brushes that slide past each other with friction coefficients that match those of cartilage. In some respects, they perform even better: the brushes remain highly effective even at pressures of 7.5 megapascals. Cartilage performs well only up to around 5 megapascals – a natural limit because joint pressure only rarely exceeds that level.

Each 60-nanometre-long brush filament has a polymer backbone from which small molecular groups stick out. Those synthetic groups are very similar to the lipids found in cell membranes, says Klein – although they're neutral overall, they are positively charged at one end and negatively charged at the other.

In a watery environment, each of these molecular groups attracts up to 25 water molecules through electrostatic forces, so the filament as a whole develops a slick watery sheath. These sheathes ensure that the brushes are lubricated as they rub past each other, even when firmly pressed together to mimic the pressures at bone joints.

Klein's team produced a similar set of molecular brushes six years ago, but the friction between those brushes increased sharply at pressures of just 0.3 megapascals. The new brushes work better because their filaments attract more water, giving them a thicker sheath.

Stronger bonds

There's another reason for the huge improvement in performance, however. The previous generation of brush filaments were weakly anchored by shared water-repelling properties with the artificial joint surface below – a sheet of the mineral mica in these simulations.

When two of the mica sheets were rubbed against each other under pressure, the filaments simply tore away from the mica surface and their lubricating properties were lost. In the latest experiments, the mica is first coated with a chemical to encourage polymer growth. The team can then grow the filaments directly from the mica surface and each forms strong covalent bonds to the surface that are less likely to shear away.

Jennifer Elisseeff, a professor of engineering and orthopaedic surgery at Johns Hopkins University in Baltimore, who was not involved with the study, says the new material is an "important step forward" for joint lubrication studies.

Bone damage risk

Farshid Guilak, a professor of orthopaedic surgery at Duke University in North Carolina agrees. "It is very exciting to see that artificial polymer brushes can be designed to provide such low frictional properties," he says.

However, Elisseeff and Guilak both wonder how well the brushes will perform in the real world. Guilak points out that Teflon was initially used in joints, thanks to its low-friction properties, but proved to be a "disaster" because it wore out rapidly to leave bone-damaging debris.

Klein responds that Hiroshi Kawaguchi's team at the University of Tokyo has already grafted earlier forms of his brushes onto a plastic-metal joint and tested it in a hip-joint simulator. "A large reduction in the wear of the [plastic] was achieved," says Klein. He adds that it's not yet clear when the new brushes might be used in a clinical setting. *Journal reference: Science (DOI: 10.1126/science.1169399)*

Ironware piece unearthed from Turkey found to be oldest steel

Tokyo (PTI): A piece of ironware excavated from a Turkish archaeological site is about 4,000 years old, making it the world's oldest steel, Japanese archaeologists said on Thursday.

Archaeologists from the Middle Eastern Culture Center in Japan excavated the 5-centimetre piece at the Kaman-Kalehoyuk archaeological site in Turkey, about 100 kilometers southeast of Ankara, in 2000. The ironware piece is believed to be a part of a knife from a stratum about 4,000 years old, or 2100-1950 B.C., according to them.

An analysis at the Iwate Prefectural Museum in Morioka showed that the ironware piece was about 200 years older than one that was excavated from the same site in 1994 and was believed to be the oldest steel so far made in 20th-18th centuries B.C. The ironware is highly likely to have been produced near the Kaman-Kalehoyuk site as a 2-cm-diameter slag and two iron-containing stones have also been excavated, Kyodo news agency quoted the archaeologists as saying.

Hideo Akanuma, an archaeologist at the Iwate Prefectural Museum, said the fresh finding led to a change in the history of iron and steel production, noting that such production was earlier thought to have begun in the Hittite kingdom dating in the 14th to 12th centuries B.C.

Drinking very hot tea can increase the risk of throat cancer

Tea drinking habits and oesophageal cancer in a high risk area in Northern Iran: Population based case-control study

People are advised to wait a few minutes before drinking a cup of freshly-boiled tea today as a new study, published on bmj.com, finds that drinking very hot tea (70°C or more) can increase the risk of cancer of the oesophagus, the muscular tube that carries food from the throat to the stomach.

The study was carried out in northern Iran, where large amounts of hot tea are drunk every day. But an accompanying editorial says these findings are not cause for alarm and the general advice is to allow foods and beverages to cool a little before swallowing.

Cancers of the oesophagus kill more than 500,000 people worldwide each year and oesophageal squamous cell carcinoma (OSCC) is the commonest type. In Europe and America, it is mainly caused by tobacco and alcohol use and is more common in men than in women, but drinking hot beverages is also thought to be a risk factor.

Golestan Province in northern Iran has one of the highest rates of OSCC in the world, but rates of smoking and alcohol consumption are low and women are as likely to have a diagnosis as men. Tea drinking, however, is widespread, so researchers set out to investigate a possible link between tea drinking habits and risk of OSCC.

They studied tea drinking habits among 300 people diagnosed with OSCC and a matched group of 571 healthy controls from the same area. Nearly all participants drank black tea regularly, with an average volume consumed of over one litre a day.

Compared with drinking warm or lukewarm tea (65°C or less), drinking hot tea (65-69°C) was associated with twice the risk of oesophageal cancer, and drinking very hot tea (70°C or more) was associated with eight-fold increased risk. Likewise, compared with drinking tea four or more minutes after being poured, drinking tea less than two minutes after pouring was associated with a five-fold higher risk. There was no association between the amount of tea consumed and risk of cancer.

To minimise errors between reported and actual tea temperatures, the researchers then measured the actual temperature that tea was consumed by nearly 50,000 residents of the same area. This ranged from less than 60°C to more than 70°C and there was a moderate agreement between reported tea drinking temperature and actual temperature measurements. Our results show a strong increase in the risk of oesophageal squamous cell carcinoma associated with drinking hot or very hot tea, say the authors.

Previous studies from the United Kingdom have reported an average temperature preference of 56-60°C among healthy populations. They suggest that informing the population about the hazards of drinking hot tea may be helpful in reducing the incidence of oesophageal cancer in Golestan and in other high risk populations where similar habits are prevalent.

These results provide persuasive evidence that drinking tea at temperatures greater than 70°C markedly increases the risk of oesophageal squamous cell carcinoma, says David Whiteman from the Queensland Institute of Medical Research in Australia in an accompanying editorial.

This report also lends support to the notion that thermal injury may be a cause of epithelial cancers, though he points out that the way in which heat promotes tumour development is not clear and warrants further investigation.

However, he stresses that these findings are not cause for alarm, and they should not reduce public enthusiasm for the time honoured ritual of drinking tea. Instead he suggests waiting at least four minutes before drinking a cup of freshly boiled tea, or more generally allowing foods and beverages to cool from "scalding" to "tolerable" before swallowing.

Vindictiveness doesn't pay

Study shows: The guiding motto of 'an eye for an eye, and a tooth for a tooth' brings neither success nor happiness

This release is available in German.

Vindictiveness doesn't pay. This has been demonstrated by a current study at Bonn and Maastricht Universities. According to this study, a person inclined to deal with inequity on a tit-for-tat basis tends to experience more unemployment than other people. Vindictive people also have less friends and are less satisfied with their lives. The study appears in the current edition of the Economic Journal.

We tend to live by the motto "tit for tat". We repay an invitation to dinner with a counter-invitation; when a friend helps us to move house, we help to move his furniture a few months later. On the other hand, we repay meanness in the same coin. Scientists speak here of reciprocity. A person who repays friendly actions in a like manner is said to behave with positive reciprocity, and one who avenges unfairness acts with negative reciprocity.

Positive and negative reciprocity are interdependent traits: many people incline to positive reciprocity, others more to negative; others, again, incline to both. The researchers from Bonn and Maastricht wanted to discover what influence these traits of character have on parameters such as "success" or "satisfaction with life". For this, they resorted to data from the so-called "socio-economic panel". This contains information gathered by the Deutsche Institut für Wirtschaftsforschung (German Institute for economic Research) in its annual surveys. These involve around 20,000 respondents from all over Germany and cover a diversity of topics.

The researchers in Bonn used this instrument to discover something about the attitudes to reciprocity of the participants in the study. They were to state, for example, to what extent they would repay a favour or, on the other hand, an insult on a tit-for-tat basis. "Both positive and negative reciprocity are widespread in Germany", declares Professor Dr. Armin Falk of Bonn University, summarising the results.

Positively reciprocal People perform more Overtime

The researchers then related these data to other results of the survey, whereby they stumbled upon a number of interesting correlations: "Thus, positively reciprocal people tend on average to perform more overtime, but only when they find the remuneration fair", declares Professor Dr. Thomas Dohmen of Maastricht University. "As they are very sensitive to incentives, they also tend to earn more money".

This is in stark contrast to vindictive people. With these people, the equation "more money = more work" does not always apply. Even pay cuts are not an effective means of bringing negatively reciprocal people back into line. Ultimately the danger arises that they will take revenge – for example, by refusing to work, or by sabotage. "On the basis of these theoretical considerations it would be natural to expect that negatively reciprocal people are more likely to lose their jobs", Falk explains: "A supposition which coincides with our results. Consequently, negatively reciprocal people experience a significantly higher rate of unemployment".

And in other respects, too, vindictiveness is not a maxim to be recommended. Anyone who prefers to act according to the Old Testament motto of "An eye for an eye, and a tooth for a tooth" has on average less friends – and is clearly less than satisfied with his or her life.

Do Americans have an identity crisis when it comes to race and ethnicity?

Say goodbye to Italian-Americans and German-Americans and say hello to Vietnamese-Americans, Salvadoran-Americans and a bunch of other hyphenated Americans.

The way people identify themselves in the United States is changing, and the way the federal census classifies them by race or ethnicity isn't painting a clear portrait of America, according to new research.

University of Washington demographers who analyzed 2000 census data contend that because of the way the census was structured many Hispanics or Latinos were eventually lumped into a category called "some other race." So many were placed in that category that it was the third-largest group behind whites and blacks in the census. This led to mistaken reports last year that whites, as opposed to non-Hispanic whites, were projected to be a minority in the U.S. by 2050. Actually, whites – including Hispanic whites – are expected to comprise upwards of 70 percent of the population in 2050.

"The truth is many people probably can't accurately report the origins of their ancestors," said Anthony Perez, lead author of a new study and a UW post-doctoral fellow in sociology and the university's Center for Studies in Demography and Ecology. His co-author is Charles Hirschman, a UW professor of sociology and former president of the Population Association of America. The research appears in the March issue of the journal Population and Development Review.

"We have a fair degree of knowledge about where our parents and grandparents came from," said Perez. "But with every generation the number of our ancestors doubles and it is difficult to know the ethnic and racial details of all of them. Many people might have more ethnic or racial groups in their backgrounds than they imagine."

Most Americans, except for recent immigrants, probably descended from multiple geographic, ethnic and racial origins, and the United States was multi-ethnic and multi-racial from the start, the researchers contend.

"With the exception of indigenous people, everyone came from somewhere else. They were immigrants," said Perez. "Frontier societies absorbed many indigenous people and we also have a long history of interracial unions between Americans of European and African descent. It is not just Barack Obama, but most of us are a bunch of 'mutts' from different cultures and backgrounds."

All of this led to what is called Americanization, or the blending away of the specific ancestries that people brought with them. Typically Americanization begins with immigrants coming to the U.S., settling in neighborhoods with their compatriots and retaining their ethnic roots. But within a generation, they or their children learn English, intermarry with other Americans of different backgrounds and their ancestral ties begin to fade. With several more generations, most Americans begin to lose track of their increasingly complex family trees.

This blending has dramatically transformed Native Americans and Hawaiian-Pacific Islanders, most of whom acknowledge multiracial heritage. At the same time, very few whites and blacks acknowledge common ancestry on censuses and surveys.

"The low levels of racial mixture reported by whites and blacks represent an astounding loss of memory or a reluctance to acknowledge such mixing," said Perez. "One-fifth of African-Americans identified multiracial origins in the 1910 census and researchers think that number probably is low. Yet in Census 2000, just 2 percent of blacks and 0.4 percent of white acknowledge shared ancestry. The blurring of memories over many generations, the stigma of race mixing and a long history of segregation and political polarization have probably contributed to the amnesia of shared ancestry among many white and black Americans.

"Whites are notoriously inconsistent about the specifics of ethnic identity. We don't put a lot of stock in their answers because they often change their minds on follow-up questions. There also is inconsistency between parents and their children. The majority of whites have multiple ancestries and some will pick theirs on the basis of cuisine, a favorite relative or trends. And who isn't Irish on St. Patrick's Day?" he said.

What will Americans look like in another 50 years? Perez isn't sure.

"The future face of America is uncertain. It's like predicting the weather 50 years from now. If current rates of intermarriage continue, there is likely to be continued blurring of race and ethnic divisions. Even the race and ethnic categories used in the census may change, as they have in the past. For Asians and Hispanics, there is likely to be continued blending, as with previous generations of immigrants." If intermarriage between blacks and whites continues to increase in the coming year, perhaps there will be greater acknowledgement of their shared ancestry. But this will likely depend also on how well we bridge the social and economic gaps between groups." *The research was supported by the National Institute of Child Health and Human Development.*

Hire a Dwight Schrute for a better-performing team, says study co-authored by BYU biz prof

Adding a socially unique outsider increases both group discomfort and quality of results

Nobody wants to share a cubicle with a new hire like Dwight Schrute. The beet-farming volunteer sheriff's deputy/paper salesman creates many awkward moments because of his differences with co-workers on NBC's "The Office."

But according to new research co-authored by a Brigham Young University business professor, better decisions come from teams that include a "socially distinct newcomer." That's psychology-speak for someone who is different enough to bump other team members out of their comfort zones.

Researchers noticed this effect after conducting a traditional group problem-solving experiment. The twist was that a newcomer was added to each group about five minutes into their deliberations. And when the newcomer was a social outsider, teams were more likely to solve the problem successfully.

The research is published in the Personality and Social Psychology Bulletin.

"One of the most-cited benefits of diversity is the infusion of new ideas and perspectives," said study co-author Katie Liljenquist, assistant professor of organizational leadership at BYU's Marriott School of Management. "And while that very often is true, we found the mere presence of a newcomer who is socially distinct can really shake up the group dynamic. That leads to discomfort, but also to a better process that ultimately yields superior outcomes."

The key factor is simply whether newcomers are distinct in some way from the other group members.

"Remember, socially 'distinct' doesn't necessarily mean socially 'inept,'" says Liljenquist, whose co-authors on the paper are Northwestern's Katherine Phillips and Stanford's Margaret Neale. "Dwight's upbringing and past work history - in addition to his bobblehead doll collection - all contribute to the measure of diversity he brings to 'The Office' melting pot."

The paper adds a new wrinkle to the wealth of research on teams, says Melissa Thomas-Hunt, associate professor at Cornell's Johnson School of Management.

"[This research] is groundbreaking in that it highlights that the benefits of disparate knowledge in a team can be unleashed when newcomers actually share opinions of knowledge with old-timers but are socially different," Thomas-Hunt says. "It is the tension between social dissimilarity and opinion similarity that prompts heightened effectiveness in diverse teams."

What explains the results?

According to Liljenquist, newcomers in the experiment didn't necessarily ask tougher questions, possess novel information, or doggedly maintain a conflicting point of view. Just being there was enough to change the dynamic among old-timers who shared a common identity.

When a member of the group discovered that he agreed with the new outsider, he felt alienated from his fellow old-timers - consequently, he was very motivated to explain his point of view on its merits so that his peers wouldn't lump him in with the outsider.

The person who found himself disagreeing with the in-group - and instead agreeing with an outsider - felt very uncomfortable. An opinion alliance with an outsider put his social ties with other team members at risk.

"Socially, that can be very threatening," Liljenquist says. "These folks are driven to say, 'Wait, the fact that I disagree with this outsider doesn't make me weird. Something more is going on here; let's figure out what's at the root of our disagreement.' The group then tends to analyze differing opinions and critical information much more thoroughly, and that facilitates much better decision-making results."

Another revelation

The experiment also revealed a fallacy in the assumptions we make about our own effectiveness in groups. The subjects in the experiment were members of different fraternities and sororities. In general, when the newcomer was from the same sorority or fraternity as the other team members, the group reported that it worked well together, but was less likely to correctly solve the problem.

In contrast, when the newcomer was a member of a rival sorority or fraternity, the opposite was true - these groups felt they worked together less effectively, yet they significantly outperformed socially homogenous groups.

"What's really distinct about this research is that, from a self-reporting perspective, what people perceive to be beneficial turns out to be dead wrong," Liljenquist says. "The teams that felt they worked least effectively together were ironically the top performers!"

In the workplace

Common "social distinctions" in today's workplace, Liljenquist says, would include:

* One employee from accounting working on a team in which everyone else is from sales
* An employee of a company that had just been bought out finding herself on a team of people from the acquiring firm
* An out-of-stater finding himself on a team full of natives of the company's home state

To help employees in those situations cope, managers would be wise to explain that such conflict can actually generate better results.

"Without that information people just assume, 'This is really uncomfortable. My team obviously must not be working effectively,'" Liljenquist says. "The experience in diverse teams may not always be a feel-good session, but if employees know that from the outset, they can better deal with inevitable conflicts and recognize the potential benefits - that the affective pains can translate to real performance gains."

Although Liljenquist acknowledges many other cases for diversity in the workplace, she contends that "reaping the benefits of diverse workgroups doesn't necessarily require that newcomers bring unique perspectives or expertise to the table. Simply having people around us who differ on some dimension -- whether it is functional background, education, race or even a different fraternity - drives a very different decision-making process at a group level because of the social and emotional conflict we experience in their presence."