GUMC discovery highlights new direction for drug discovery

Researchers did what others thought was not possible by finding a small molecule to stop 'slippery' protein from binding to another, causing Ewing's Sarcoma

Washington, DC - In a discovery that rebuffs conventional scientific thinking, researchers at Georgetown University Medical Center (GUMC) have discovered a novel way to block the activity of the fusion protein responsible for Ewing's sarcoma, a rare cancer found in children and young adults.

In the paper published online July 5 in Nature Medicine, they report discovering and successfully testing a small molecule that keeps the fusion protein from sticking to another protein that is critical for tumor formation. The researchers say this interaction is unique - and is especially surprising since the Ewing's sarcoma fusion protein is extremely flexible, which allows it to change shape constantly.

"Most targeted small molecule cancer drugs inhibit the intrinsic activity of a single protein, but our agent stops two proteins from interacting. This has never been shown before with a cancer-causing fusion protein and represents a potentially novel medical therapy in the future," says the study's lead investigator, Jeffrey Toretsky, MD, a pediatric oncology physician and researcher at GUMC's Lombardi Comprehensive Cancer Center.

The study could provide a model upon which to design treatment for other disorders caused by the interaction between two proteins, and may be especially useful in cancers caused by translocations of genes, such as sarcomas and leukemias, the researchers say. Agents in use now that work against fusion proteins inhibit a single protein to stop intrinsic enzymatic activity; one example is Gleevec, used for chronic myelogenous leukemia (CML). The Ewing's sarcoma fusion protein, known as EWS-FLI1, lacks enzymatic activity, "and this difference is why our work is significant," Toretsky says.

In the United States, about 500 patients annually are diagnosed with the cancer, and they are treated with a combination of five different chemotherapy drugs. Between 60-70 percent of patients survive over time, but with side effects from the treatment. Few additional treatment options are available for patients whose cancer progresses, Toretsky says.

Ewing's sarcoma is caused by the exchange of DNA between two chromosomes, a process known as a translocation. The new EWS-FLI1 gene is created when the EWS gene on chromosome 22 fuses to the FLI1 gene on chromosome 11, and its product is the fusion protein responsible for cancer formation. It is a so-called disordered protein, which means it does not have a rigid structure. A number of cancer-causing proteins are disordered.

In their 15-year search for a new treatment for Ewing's sarcoma, Toretsky and his colleagues were the first to make a recombinant EWS-FLI1 fusion protein. They used it to discover that the fusion protein stuck to another protein, RNA helicase A (RHA), a molecule that forms protein complexes in order to control gene transcription. "We believe that when RHA binds to EWS-FLI1, the combination becomes more powerful at turning genes on and off," says the study's first author, Hayriye Verda Erkizan, PhD, a postdoctoral researcher in Toretsky's lab.

Then, from a library of 3,000 small molecules loaned to Georgetown from the National Cancer Institute, the researchers searched for a small molecule that would bind on to EWS-FLI1. They found one, and further discovered the same molecule, NSC635437, could stop EWS-FLI1's fusion protein from sticking to RHA.

This was a wonderful discovery, Erkizan says, because the notion long accepted among scientists is that it is not possible to block protein-protein interactions given that the surface of many of these proteins are slippery - much too flexible for a drug to bind to.

They tested the agent in laboratory cell culture, and with the help of GUMC's Drug Discovery Program, the researchers designed a stronger derivative compound they called YK-4-279. In this study, they tested YK-4-279 in two different animal models of Ewing's sarcoma and found that the agent significantly inhibited the growth of tumors. There was an 80% reduction in the growth of treated tumors compared to untreated tumors.

Toretsky says that while the agent needs to be "optimized," these results serve as a proof of principle that inhibiting protein-protein interaction can work as a novel therapeutic that will target only cancer cells. "We may be able to use this strategy to attack proteins we thought to be impervious to manipulation," he says.

The study was funded by grants from the National Institutes of Health, Children's Cancer Foundation of Baltimore, MD, Go4theGoal Foundation, Dani's Foundation of Denver, the Liddy Shriver Sarcoma Initiative, the Amschwand Sarcoma Cancer Foundation, the Burroughs-Wellcome Clinical Scientist Award in Translational Research, and the GUMC Drug Discovery Program.

Toretsky and co-authors Milton L. Brown, Aykut Üren and Yali Kong are inventors on a patent application that has been filed by Georgetown University related to the technology described in this paper. The other authors report no related financial interests.

Variations in 5 genes raise risk for most common brain tumors

Genomewide study finds first genetic factors in development of gliomas

HOUSTON - Common genetic variations spread across five genes raise a person's risk of developing the most frequent type of brain tumor, an international research team reports online in Nature Genetics.

Genetic risk factors identified by the research team, led by scientists at The University of Texas M. D. Anderson Cancer Center and the Institute of Cancer Research in the United Kingdom, also are the first glioma risk factors of any type identified in a large study.

"This is a ground-breaking study because it's the first time we've had a large enough sample to understand the genetic risk factors related to glioma, which opens the door to understanding a possible cause of these brain tumors," said co-senior author Melissa Bondy, Ph.D., professor in M. D. Anderson's Department of Epidemiology.

Bondy and colleagues expect their findings eventually to help identify people most at risk for the disease and to provide potential targets for treatment or prevention.

Gliomas, deadly tumors that form in the supportive tissue of the brain and spine, account for about 80 percent of all primary malignant brain tumors, with about 22,000 new cases annually in the United States and 13,000 deaths. They include astrocytomas, oligodendrogliomas and glioblastoma multiforme, the most aggressive, deadly and common glioma in adults.

Risk rises with each variation

The top variations in each of the five genes individually raise a person's glioma risk by 18, 24, 27, 28 and 36 percent over someone without the variations. The team found the effects are independent of one another, so risk escalates with the number of genes involved. People with eight or more of the 14 risk variations discovered on the five genes have a three-fold risk of developing glioma.

Even though this is the largest genetic study of a rare cancer, and thus provides a high degree of statistical confidence in the findings, co-first author Sanjay Shete, Ph.D., associate professor of epidemiology at M. D. Anderson, cautions that it's too early to screen people for risk using these variations alone.

Additional research is needed on the genes involved and how variation affects their function and contributes to development of gliomas. And the disease is not solely genetic. A more comprehensive model that includes demographic and behavioral factors and environmental exposures will be needed to identify those at risk.

Bondy will be principal investigator on a multi-center research project that will examine the complex interplay of all of those factors in 6,000 glioma patients and 6,000 controls beginning next year. "We will be able to look at all of the potential risk and protective factors we've identified in much smaller studies over the years, such as exposure to ionizing radiation, allergies, infections, and use of non-steroidal anti-inflammatory drugs, in a much larger study that will include the genes involved," Bondy said.

Combing through 521,571 variations to find 14

Researchers from M. D. Anderson and the Institute of Cancer Research analyzed 521,571 single nucleotide polymorphisms (SNPS) - points in the genome known to commonly vary from person to person - in 1,878 glioma patients and 3,670 controls. They discovered 34 SNPS with evidence of association with glioma.

These 34 were then analyzed in independent case-control studies in Germany, France and Sweden that examined 2,545 cases of glioma and 2,973 controls. The combined analysis winnowed the candidates down to 14 SNPS that mapped to five addresses in the genome.

The five genes identified, listed in descending order by their strongest effect, are:

* CCDC26, located on chromosome 8, modulates retinoic acid, which in turn increases programmed cell death in glioblastoma cells and reduces telomerase activity (see next).
* TERT, found on chromosome 5, is essential for telomerase activity that preserves telomeres, which are found on the ends of chromosomes and prevent them from unraveling. TERT expression in tumors has been associated with tumor grade and prognosis.
* CDKN2A, located on chromosome 9, regulates p14, which activates the tumor-suppressor p53. It also regulates cyclin-dependent kinases vital to the cell cycle. At least one copy of the gene is deleted in half of brain tumors, and loss of CDKN2A expression is associated with poor prognosis.
* RTEL1, found on chromosome 20, maintains genomic stability. Its chromosomal address is amplified in 30 percent of gliomas.
* PHLDB1, on chromosome 11, is commonly deleted in neuroblastoma but there is no evidence to date of a role for the gene in glioma.

The fact that four of the genetic variations found in a person's genome point to a gene that has been associated in some way with the genome of the tumors is an encouraging sign, Shete said.

"I've been collecting families and case studies since the early 90s," Bondy said. "We have only just begun to understand the causes of brain tumors. Our findings give reasons for hope for those who might be affected and an incentive for a more comprehensive investigation of what has been a mysterious disorder."

The Wellcome Trust provided principal funding for the study. Additional sources include Cancer Research UK, the European Union, grants from the U.S. National Cancer Institute, the American Brain Tumor Association and the National Brain Tumor Society.

Co-authors with Bondy and Shete are co-senior author Richard Houlston and co-first author Fay Hoskings, Lindsay B Robertson, Sara E Dobbins, and Amy Price, all of Section of Cancer Genetics, Institute of Cancer Research, Sutton, Surrey. U.K.; Georgina Armstrong, Yanhong Liu, and Xiangjun Gu of M. D. Anderson's Department of Epidemiology; Marc Sanson, Yannick Marie, Blandine Boisselier, Jean-Yves Delattre, Khe Hoang-Xuan, Soufiane El Hallani and Ahmed Idbaih, all of Service de Neurologie Mazarin et INSERM, Hôpital de la Salpêtrière in Paris; Beatrice Malmer, Ulrika Andersson and Roger Henriksson, of Department of Radiation Sciences, Oncology, Umeå University, Sweden; Matthias Simon and Johannes Schramm of Neurochirurgische Universitätsklinik, Bonn, Germany; Diana Zelenika and Mark Lathrop of Centre National de Génotypage, Evry Cedex, France; Lathrop also is affiliated with Foundation Jean Dausett-CEPH, Paris; A Tommy Bergenheim, and Anders Ahlbom of Department of Clinical Neuroscience, Umeå University, Sweden; Maria Feychting of Institute of Environmental Medicine, Karolinska Institutet, Sweden; Stefan Lönn of the Department of Medical Epidemiology and Biostatistics Karolinska Institutet, Sweden; Michael Linnebank of the Department of Neurology, University Hospital Zurich, Switzerland; Kari Hemminki and Rajiv Kumar both of the Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany; Sarah Hepworth of Centre for Epidemiology and Biostatistics, Faculty of Medicine and Health, University of Leeds, UK; Kenneth Muir of the Division of Epidemiology and Public Health, University of Nottingham Medical School, Queen's Medical Centre, Nottingham, UK; Minouk Schoemaker Section of Epidemiology, Institute of Cancer Research, Sutton, UK; and Ching Lau of Texas Children's Cancer Center, Baylor College of Medicine, Houston.

Researchers find possible environmental causes for Alzheimer's, diabetes

Call for reducing nitrate levels in fertilizer and water, detoxifying food and water

Providence, RI - A new study by researchers at Rhode Island Hospital have found a substantial link between increased levels of nitrates in our environment and food with increased deaths from diseases, including Alzheimer's, diabetes mellitus and Parkinson's. The study was published in the Journal of Alzheimer's Disease (Volume 17:3 July 2009).

Led by Suzanne de la Monte, MD, MPH, of Rhode Island Hospital, researchers studied the trends in mortality rates due to diseases that are associated with aging, such as diabetes, Alzheimer's, Parkinson's, diabetes and cerebrovascular disease, as well as HIV. They found strong parallels between age adjusted increases in death rate from Alzheimer's, Parkinson's, and diabetes and the progressive increases in human exposure to nitrates, nitrites and nitrosamines through processed and preserved foods as well as fertilizers. Other diseases including HIV-AIDS, cerebrovascular disease, and leukemia did not exhibit those trends. De la Monte and the authors propose that the increase in exposure plays a critical role in the cause, development and effects of the pandemic of these insulin-resistant diseases.

De la Monte, who is also a professor of pathology and lab medicine at The Warren Alpert Medical School of Brown University, says, "We have become a 'nitrosamine generation.' In essence, we have moved to a diet that is rich in amines and nitrates, which lead to increased nitrosamine production. We receive increased exposure through the abundant use of nitrate-containing fertilizers for agriculture." She continues, "Not only do we consume them in processed foods, but they get into our food supply by leeching from the soil and contaminating water supplies used for crop irrigation, food processing and drinking."

Nitrites and nitrates belong to a class of chemical compounds that have been found to be harmful to humans and animals. More than 90 percent of these compounds that have been tested have been determined to be carcinogenic in various organs. They are found in many food products, including fried bacon, cured meats and cheese products as well as beer and water. Exposure also occurs through manufacturing and processing of rubber and latex products, as well as fertilizers, pesticides and cosmetics.

Nitrosamines are formed by a chemical reaction between nitrites or other proteins. Sodium nitrite is deliberately added to meat and fish to prevent toxin production; it is also used to preserve, color and flavor meats. Ground beef, cured meats and bacon in particular contain abundant amounts of amines due to their high protein content. Because of the significant levels of added nitrates and nitrites, nitrosamines are nearly always detectable in these foods. Nitrosamines are also easily generated under strong acid conditions, such as in the stomach, or at high temperatures associated with frying or flame broiling. Reducing sodium nitrite content reduces nitrosamine formation in foods.

Nitrosamines basically become highly reactive at the cellular level, which then alters gene expression and causes DNA damage. The researchers note that the role of nitrosamines has been well-studied, and their role as a carcinogen has been fully documented. The investigators propose that the cellular alterations that occur as a

result of nitrosamine exposure are fundamentally similar to those that occur with aging, as well as Alzheimer's, Parkinson's and Type 2 diabetes mellitus.

De la Monte comments, "All of these diseases are associated with increased insulin resistance and DNA damage. Their prevalence rates have all increased radically over the past several decades and show no sign of plateau. Because there has been a relatively short time interval associated with the dramatic shift in disease incidence and prevalence rates, we believe this is due to exposure-related rather than genetic etiologies."

The researchers recognize that an increase in death rates is anticipated in higher age groups. Yet when the researchers compared mortality from Parkinson's and Alzheimer's disease among 75 to 84 year olds from 1968 to 2005, the death rates increased much more dramatically than for cerebrovascular and cardiovascular disease, which are also aging-associated. For example, in Alzheimer's patients, the death rate increased 150-fold, from 0 deaths to more than 150 deaths per 100,000. Parkinson's disease death rates also increased across all age groups. However, mortality rates from cerebrovascular disease in the same age group declined, even though this is a disease associated with aging as well.

De la Monte notes, "Because of the similar trending in nearly all age groups within each disease category, this indicates that these overall trends are not due to an aging population. This relatively short time interval for such dramatic increases in death rates associated with these diseases is more consistent with exposure-related causes rather than genetic changes." She also comments, "Moreover, the strikingly higher and climbing mortality rates in older age brackets suggest that aging and/or longer durations of exposure have greater impacts on progression and severity of these diseases."

The researchers graphed and analyzed mortality rates, and compared them with increasing age for each disease. They then studied United States population growth, annual use and consumption of nitrite-containing fertilizers, annual sales at popular fast food chains, and sales for a major meat processing company, as well as consumption of grain and consumption of watermelon and cantaloupe (the melons were used as a control since they are not typically associated with nitrate or nitrite exposure).

The findings indicate that while nitrogen-containing fertilizer consumption increased by 230 percent between 1955 and 2005, its usage doubled between 1960 and 1980, which just precedes the insulin-resistant epidemics the researchers found. They also found that sales from the fast food chain and the meat processing company increased more than 8-fold from 1970 to 2005, and grain consumption increased 5-fold.

The authors state that the time course of the increased prevalence rates of Alzheimer's, Parkinson's and diabetes cannot be explained on the basis of gene mutations. They instead mirror the classical trends of exposure-related disease. Because nitrosamines produce biochemical changes within cells and tissues, it is conceivable that chronic exposure to low levels of nitrites and nitrosamines through processed foods, water and fertilizers is responsible for the current epidemics of these diseases and the increasing mortality rates associated with them.

De la Monte states, "If this hypothesis is correct, potential solutions include eliminating the use of nitrites and nitrates in food processing, preservation and agriculture; taking steps to prevent the formation of nitrosamines and employing safe and effective measures to detoxify food and water before human consumption."

Other researchers involved in the study with de la Monte include Alexander Neusner, Jennifer Chu and Margot Lawton, from the departments of pathology, neurology and medicine at Rhode Island Hospital and The Warren Alpert Medical School of Brown University.

The study was funded through grants from the National Institutes of Health. Two subsequent papers have been accepted for publication in the near future that demonstrate experimentally that low levels of nitrosamine exposure cause neurodegeneration, NASH and diabetes.

De la Monte, Suzanne M., Alexander Neusner, Jennifer Chu and Margot Lawton. "Epidemilogical Trends Strongly Suggest Exposures as Etiologic Agents in the Pathogenesis of Sporadic Alzheimer's Disease, Diabetes Mellitus, and Non-Alcoholic Steatohepatitis." Journal of Alzheimer's Disease, 17:3 (July 2009) pp 519-529.

Ready for relapse: Molecule helps breast cancer cells to survive in the bone marrow

Patients who survive an initial diagnosis of breast cancer often succumb to the disease years later when the cancer shows up in a different part of the body. Now, scientists have identified key signals that support the long term survival of breast cancer cells after they have spread to the bone marrow. The research, published by Cell Press in the July issue of the journal Cancer Cell, may lead to development of treatment strategies that decrease the likelihood of breast cancer recurrence in the bone and other organs.

Metastasis, the ability of cancer cells to spread from the initial site of origin to other parts of the body, occurs frequently in breast cancer. Although it is clear that the majority of late-onset relapses after breast cancer arise in the bone, the mechanisms that contribute to cancer cell survival in the bone marrow environment are unknown.

"We sought to identify signaling pathways that support the survival of metastasized breast cancer cells and thereby extend the period during which metastasis may emerge after the diagnosis and removal of a breast tumor," explains senior study author Dr. Joan Massague from the Cancer Biology and Genetics Programs at Memorial Sloan-Kettering Cancer Center and the Howard Hughes Medical Institute.

Dr. Massague and colleagues used a sophisticated gene profiling technique link specific signaling pathways with late-onset relapse after breast cancer. In an investigation of samples from over 600 breast tumors, the researchers discovered that activity of a cancer-related enzyme called Src was associated with late-onset bone metastasis. Interestingly, this link was independent of breast cancer subtype and was selective and specific for cell survival in the bone marrow.

The researchers went on to identify Src-regulated signaling molecules that were expressed in the bone marrow and promoted cell survival. Further, Src increased the resistance of metastasized breast cancer cells to a key cell death-inducing signal that was abundantly expressed in bone metastasis tissue. These results demonstrate that Src hyperactivity provides breast cancer cells with a superior ability to survive in the bone marrow.

"The link between Src-dependent signaling and metastatic cell survival provides mechanistic insights into metastasis latency, and suggests strategies to hasten the attrition of disseminated breast cancer cells," concludes Dr. Massague. "Recently, a number of pharmacological Src inhibitors have been developed that may be worthy of consideration in this respect."

The researchers Xiang H.-F. Zhang, Memorial Sloan-Kettering Cancer Center, New York, NY; Qiongqing Wang, Memorial Sloan-Kettering Cancer Center, New York, NY; William Gerald, Memorial Sloan-Kettering Cancer Center, New York, NY; Clifford A. Hudis, Memorial Sloan-Kettering Cancer Center, New York, NY; Larry Norton, Memorial Sloan-Kettering Cancer Center, New York, NY; Marcel Smid, Erasmus Medical Center Rotterdam, Josephine Nefkens Institute and Cancer Genomics Centre, Rotterdam, the Netherlands; John A. Foekens, Erasmus Medical Center Rotterdam, Josephine Nefkens Institute and Cancer Genomics Centre, Rotterdam, the Netherlands; and Joan Massague´, Memorial Sloan-Kettering Cancer Center, New York, NY, Howard Hughes Medical Institute, Chevy Chase, MD.

Health food supplement may curb compulsive hair pulling

Patients with the disorder, known as trichotillomania, reported feeling much improved after taking the supplement

MINNEAPOLIS/ ST. PAUL (July 6, 2009) - University of Minnesota Medical School researchers have discovered that a common anti-oxidant, widely available as a health food supplement, may help stop the urges of those with trichotillomania, a disorder characterized by compulsive hair-pulling.

Fifty people enrolled in a double-blind 12 week study; half were given N-Acetylcysteine, an amino acid commonly found in health food supplements. The average age of patients who enrolled was about 34, and most started pulling hair compulsively by the age of 12. Patients were given 1,200 mg of N-Acetylcysteine every day for six weeks. For the following six weeks, the dosage was increased to 2,400 mg per day. After nine weeks, those on supplement had significantly reduced hair-pulling. By the end of the 12 week study, 56 percent reported feeling much or very much improved, while only 16 percent on the placebo reported less pulling.

The study is published in the July, 2009 issue of the Archives of General Psychiatry.

"Trichotillomania is compulsive in the sense that people can't control it. People feel unable to stop the behavior even though they know it is causing negative consequences," said Jon Grant, M.D., J.D., a University of Minnesota associate professor of psychiatry and principal investigator of the study. "Some people don't even know they are doing it."

Those who have trichotillomania compulsively or habitually pull their hair to the point of noticeable loss. It is most commonly associated with women, but men can also be affected, and pulling can occur anywhere on the body. Grant believes 2 to 4 percent of the general population is impacted by trichotillomania on some level.

"These are people who have tried all kinds of things that have never worked," Grant said. "The reality is that if you pull hair and it is on a noticeable part of the body, people are really disabled by this. It's not easy to go out in public if people are noticing your bald spots. Self esteem is a huge problem. This supplement may offer hope."

The study is significant on another level because it's one of the first studies of compulsive behaviors to look at lowering levels of glutamate - a chemical that triggers excitement - in the brain to curb harmful behavior rather than serotonin, a naturally occurring chemical most commonly linked to compulsive behavior. This supplement affects levels of glutamate in a specific area of the brain, making it easier for patients to put the breaks on their harmful behavior.

For that reason, Grant believes glutamate modulators such as N-Acetylcysteine may be applicable to other disorders, addictions, and compulsive behaviors.

The study is funded by The University of Minnesota Medical School.

New Study Pinpoints Difference in the Way Children With Autism Learn New Behaviors

Kennedy Krieger and Johns Hopkins Researchers Examine the Brain Basis of Motor Control, Imitation and Social Function Deficits

Baltimore, MD - Researchers from the Kennedy Krieger Institute and Johns Hopkins University School of Medicine have collaborated to uncover important new insights into the neurological basis of autism. Their new study, published in the journal Nature Neuroscience, examined patterns of movement as children with autism and typically developing children learned to control a novel tool. The findings suggest that children with autism appear to learn new actions differently than do typically developing children. As compared to their typically developing peers, children with autism relied much more on their own internal sense of body position (proprioception), rather than visual information coming from the external world to learn new patterns of movement. Furthermore, researchers found that the greater the reliance on proprioception, the greater the child's impairment in social skills, motor skills and imitation.

Previous research has shown that children with autism have difficulty with motor skills, which appears to be associated with abnormalities in how the brain learns motor actions. To study the models formed in the brain when children with autism learn a new movement, researchers measured patterns of generalization as 14 children with autism and 13 typically developing children learned to reach using a novel tool. They then examined how well children were able to generalize what they learned in two separate ways - one that detected how much they relied on visual information to guide learning and one that detected how much they relied on proprioceptive information to guide learning.

"These findings can lead to important advances in methods for treating autism. Applying the knowledge gained in the current study, targeted interventions can be developed that enhance visuo-motor associations in children with autism as they learn new skills," said Dr. Stewart H. Mostofsky, study author and a pediatric neurologist in the Department of Developmental Cognitive Neurology at the Kennedy Krieger Institute. "If done early enough, this could help to improve development of motor, social and communicative skills in children with autism. Further, it could also improve their ability to understand social cues because the brain systems critical to forming internal models of behavior that guide our actions are also critical to developing an understanding of the meaning of those actions."

The study findings also provide support for observations from previous studies suggesting that autism may be associated with abnormalities in the wiring of the brain; specifically, with overdevelopment of short range white matter connections between neighboring brain regions and underdevelopment of longer distance connections between distant brain regions. The findings from this study are consistent with this pattern of abnormal connectivity, as the brain regions involved in proprioception are closely linked to motor areas, while visual-motor processing depends on more distant connections.

"These findings not only demonstrate why children with autism have difficulty learning motor skills, but also provide real insight into why these children have difficulty learning to interact with the world around them," said Dr. Reza Shadmehr, senior study author and Professor of Biomedical Engineering and Neuroscience at the John Hopkins University School of Medicine. "If the way their brain is wired is not allowing them to rely as much as typically developing children on external visual cues to guide behavior, they may have difficulty learning how to interact with other people and interpret the nature of other people's actions."

Potential next steps include the use of neuroimaging to investigate whether or not proprioceptive versus visual feedback is actually associated with abnormal patterns of structural and functional connectivity in the brain of children with autism. Additionally, researchers may study if patterns of motor learning can be altered to increase visual connections in specific regions of the brain. Through interventions such as cortical stimulation, biofeedback and behavioral approaches, researchers are looking to investigate if there is an improvement in children with autism's ability to rely on visual input to guide how they learn a range of behavioral skills.

This research was funded by grants from the National Alliance for Autism Research/Autism Speaks, the National Institutes of Health, and the Johns Hopkins University School of Medicine Institute for Clinical and Translational Research.

CU-Boulder study shows brain's immune system may cause chronic seizures

Chronic seizures caused by traumatic head injuries may result from chemicals released by the brain's immune system attempting to repair the injured site, according to a study led by the University of Colorado at Boulder.

The findings could help prevent one of the most common forms of adult epilepsy, called acquired epilepsy, which is often found in people who have suffered a brain injury or infection, according to CU-Boulder psychology and neuroscience Professor Daniel Barth, the study's chief author.

For decades researchers have focused on neurons as the culprits in seizures, which can be characterized as debilitating "electrical storms" in the brain.

However, recent research has shown that micro-glial cells may play a major role in seizures. Researchers have found that glial cells, which are supportive cells that also constitute a major part of the brain's immune system, cluster within areas in the brain when a severe brain injury has occurred.

"When there has been serious damage to the brain, such as a head injury or infection, the immune system is activated and tries to counteract the damage and repair it," Barth said. "These glial cells migrate to the damaged area and release chemicals called cytokines that, unfortunately, also profoundly increase the excitability of the neurons that they are near.

"In our new study, we showed for the first time that glial cells moving in and secreting these cytokines cause the neurons in the area to become excitable enough to cause seizures."

The results of the study appear in the July issue of the journal Brain. Barth co-authored the paper with CU-Boulder professors of psychology and neuroscience Linda Watkins and Steven Maier, CU-Boulder graduate students Krista Rodgers and Alexis Northcutt and Professor Mark Hutchinson of the University of Adelaide in Australia. The National Institutes of Health funded the study.

Acquired epilepsy is one of the few forms of epilepsy that has the potential for being prevented, because known head injuries are often followed by latent periods when changes in the brain lead to the development of chronic seizures.

The findings are extremely promising, according to Barth, because if the brain's initial immunity reaction could be temporarily shut down, this could prevent the development of acquired epilepsy.

"After a traumatic brain injury, there is often a period of several months where nothing seems to be happening," Barth said. "And then suddenly the person may start having seizures, which often develop into chronic epilepsy."

What the research team believes is happening is that the initial immune response to the brain injury causes the first seizures. Then the adaptive immune system, which works on a longer-term basis, kicks in and makes structural changes in the brain, which could perpetuate epilepsy as a life-long condition, said Barth.

Drugs are available on the market that suppress the immune system temporarily, Barth said. Even more promising are drugs currently under Food and Drug Administration trials for human use that cross the blood-brain barrier, which in simple terms means patients can take a pill which will effectively suppress the glial cells and stop them from reacting.

"The thought is that maybe there is a window of opportunity where we could go in after an injury and administer one of these immune response inhibitors and stop a process that we think is going to lead to epilepsy," Barth said. "So instead of giving anti-seizure drugs, which have no effect in preventing or subsequently treating post-traumatic epilepsy, we could give some anti-immune drugs which may actually stop the process of developing epilepsy in the first place."

The research team came to its conclusions through a series of experiments with rats in which they applied a bacteria called lipopolysaccharide, or LPS, to the brain, activating the micro-glial cells. The glial cells very rapidly clustered around the area where the LPS was applied and created an immune reaction in that locale.

The glial cells then released their cytokines, causing the neurons to become excitable enough to cause seizures. By directly applying other drugs that either blocked the activation of glial cells or the effect of cytokines on neurons, all signs of increased brain excitability and seizures were abolished, Barth said.

Ancient fossils shed light on anatomical changes accompanying evolution of first land vertebrates

Durham, NC - Cartoon depictions of the first animals to emerge from the ocean and walk on land often show a simple fish with feet, venturing from water to land. But according to Jennifer Clack, a paleontologist at the University of Cambridge who has studied the fossils of these extinct creatures for more than two decades, the earliest land vertebrates - also known as tetrapods - were more diverse than we could possibly imagine.

"Some looked like crocodiles, some looked like little lizards, some like moray eels, and some were snake-like," said Clack. "They occupied all sorts of niches and habitats. And they varied tremendously in size - from about 10 cm long to 5 meters."

Long before mammals, birds, and even dinosaurs roamed the Earth, the first four-legged creatures made their first steps onto land, and quickly inhabited a wide range of terrestrial environments. These early land vertebrates varied considerably in size and shape, said Clack.

To understand the anatomical changes that accompanied this diversity, Clack teamed up with two biologists who work on living fishes - Charles Kimmel of the University of Oregon, and Brian Sidlauskas of the National Evolutionary Synthesis Center in North Carolina.

The researchers focused on 35 early tetrapods that lived between 385 and 275 million years ago. As a proxy for body size and shape, they examined the dimensions of a number of bones in a region of the skull known as the palate. By tracing changes in the length and width of interlocking bones in this part of the skull, the researchers hoped to get a more fine-grained picture of skeleton evolution as a whole.

"I tend to think the genetic instructions for making a skeleton come from how you make individual bones first, and then how you fit those bones together as a refinement of that," said developmental biologist Charles Kimmel, who was the first author on the paper.

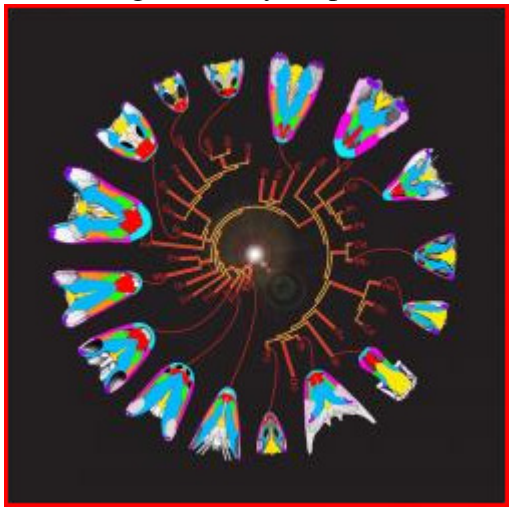
This is a photograph of a museum reconstruction of Acanthostega, an early tetrapod. Acanthostega measured about 2 feet (0.6m) in length. **Photo courtesy of Jennifer Clack**

When they mapped the changes in bone length and width onto the tetrapod family tree, the researchers discovered that not all bones changed size at the same rate or in the same direction. This phenomenon can result in an overall reshaping from one lineage to the next, explained Sidlauskas. "Sometimes a change in size can have indirect consequences for the shape of the animal," said Sidlauskas. "When different parts of an animal's body change size at different rates over evolutionary time, that can generate changes in body shape from one species to another."

Moreover, some changes are consistent with an evolutionary quirk known as paedomorphosis, in which species retain in adulthood the youthful dimensions that their ancestors had as juveniles. "Paedomorphosis is definitely there - the descendents of some groups are retaining the proportions that their juveniles had in the past," said Clack.

These results not only help explain why early tetrapods were so diverse in size and shape, but also shed light on an important chapter in the evolution of life on land - the transition from fish to amphibians.

"One of the big questions at the moment is: where did modern amphibians come from?" said Clack. "One of the hypotheses is that they have evolved by paedomorphosis and miniaturization from early tetrapods. This study lends weight to that idea."



This is an artist's depiction of the tree-of-life for early tetrapods, showing 100 million years of palate evolution and diversification. The outer edges of the diagram represent the diversity of palate size and shape. **Artwork by Brian Sidlauskas**

The team's findings will appear in the 16 July 2009 online issue of the Journal of Anatomy.
CITATION: Kimmel, C., B. Sidlauskas, and J. Clack. (2009). "Linked morphological changes during palate evolution in early tetrapods." Journal of Anatomy 215(2). doi: 10.1111/j.1469-7580.2009.01108.x. For full data see Dryad Digital Repository: http://hdl.handle.net/10255/dryad.488

Stanford study bolsters case for preventive prostate cancer treatment

STANFORD, Calif. - For the last six years, doctors have faced a dilemma about whether to treat men at risk of prostate cancer with the drug finasteride. On one hand, the drug had been shown to prevent cancer in about one of every four patients who received it. On the other, those who did develop cancer while on the drug were 25 percent more likely to have a more aggressive form of the disease.

Now new research from Stanford University School of Medicine appears to show that the drug did not cause those more aggressive forms of prostate cancer but simply made them easier to diagnose. The findings, which are to be published July 7 in Clinical Cancer Research, suggest that doctors can be less cautious in use of finasteride.

The questions about finasteride treatment can be traced to 2003 when researchers published results from the Prostate Cancer Prevention Trial, a 7-year study that tracked 18,882 healthy men over age 55. That study assigned some of the participants to take finasteride and some to take a placebo. Finasteride, which reduces levels of the male hormone dihydrotestosterone and shrinks the prostate, was found to decrease the prevalence of prostate cancer by about 25 percent. But the drug also seemed to increase the chances that if a cancer was found, it would be fast-growing and likely to spread, again by about 25 percent. As a result, doctors rarely prescribe the drug as a preventive measure.

In reviewing this study, however, a number of researchers, including Stanford's Joseph Presti Jr., MD, noticed that the initial analysis failed to detect a subtlety in the data: The increase in fast-spreading "high-grade" cancers wasn't consistent across all groups and occurred disproportionately in those men who had developed warning signs of the disease.

In men who went through the study without developing any cancer warning signs, finasteride use made no difference in the rate of high-grade cancers diagnosed upon an exit biopsy. But the results were quite different for men who were biopsied after an abnormal digital rectal exam or because of a test showing elevated levels of prostate-specific antigen, a protein also known as PSA that can be unusually high in prostate cancer. Of those men, the ones on finasteride had an 11.5 percent rate of high-grade cancer, compared with 7.7 percent in the placebo group.

That inconsistency suggested something wrong with the initial study analysis, not the drug. Others, including the original study authors, had found evidence that prostate-specific antigen screening works better in men taking finasteride, but no one knew why.

Presti, the Thomas A. Stamey Research Professor in Urology and director of the urologic oncology program at Stanford, and other researchers wondered if it was because of finasteride's propensity to shrink the prostate. A malignant growth in a large, mostly non-cancerous prostate would be easier to miss, they reasoned. If the rest of the prostate tissue was smaller, biopsies would more easily pick up on the cancer tissue left behind.

To test the idea, Presti and his colleagues analyzed a database of 1,304 men who had been referred to Stanford after an abnormal digital rectal exam or high PSA test results - the same conditions as in the original study, except none were on finasteride. Nearly 500 of them were eventually diagnosed with prostate cancer, 247 of which had the aggressive, high-grade disease.

The team found that the smaller the prostate, the more likely a biopsy would result in a diagnosis of high-grade cancer - and the more likely a high PSA level would predict the disease. In men with prostates between 20 cubic centimeters and 29.9 cubic centimeters, for example, the diagnostic rate for one level of high-grade cancer was 29.7 percent. For men with prostates larger than 80 cubic centimeters, it was just 6.5 percent.

"We're showing that this is all related to size," said Presti, who is a member of Stanford's Cancer Center.

The original cancer trial researchers reached similar conclusions after analyzing their own results, said Catherine Tangen, DrPH, the statistical principle investigator for the Prostate Cancer Prevention Trial and a member at Fred Hutchinson Cancer Research Center in Seattle. Tangen warned that without removing and analyzing the prostates of the men in Presti's study, the true prevalence of undetected prostate cancer remains unknown, leaving the actual sensitivity of the prostate-specific antigen test open to question. But, she said, "Their observations are consistent with everything we found," and suggest that men "should be given the opportunity" to take finasteride if they and their doctors deem it necessary. Prostate cancer affects one in 15 men ages 60 to 69, and one in six men overall will someday get the disease.

The co-authors on the paper were Christopher Elliott, MD, PhD, a resident in urology at Stanford, and Rajesh Shinghal, MD, associate chief of urology at Santa Clara Valley Medical Center.

Single gene mutation responsible for 'catastrophic epilepsy'

HOUSTON -- (July 8, 2009) - Catastrophic epilepsy - characterized by severe muscle spasms, persistent seizures, mental retardation and sometimes autism - results from a mutation in a single gene, said Baylor College of Medicine (www.bcm.edu) researchers in a report that appears in the current issue of the Journal of Neuroscience.

The BCM department of neurology team replicated the defect in mice, developing a mouse model of the disease that could help researchers figure out effective treatments for and new approaches to curing the disease, said Dr. Jeffrey Noebels (http://www.bcm.edu/neurology/faculty/noebels.html), professor of neurology, neuroscience and molecular and human genetics at BCM and director of the Blue Bird Circle Developmental Neurogenetics Laboratory at BCM, where the research was performed.

"While many genes underlying various forms of childhood epilepsy have been identified in the past decade, most cause a disorder of 'pure' seizures," said Noebels. Why some children have a more complicated set of disorders beginning with major motor spasms in infancy followed by cognitive dysfunction and developmental disorders such as autism remained a mystery until the discovery by the BCM team that a mutation in only a single gene explains all four features of catastrophic epilepsy.

A gene known as Aristaless-related homeobox or ARX has a specific mutation called a triplet repeat, which means that a particular genetic (in this case, GCG) is repeated many times in the gene. When the researchers duplicated this particular mutation in specially bred mice, the animals had motor spasm similar to those seen in human infants. Recordings of their brain waves showed that they had several kinds of seizes, included absence epilepsy and general convulsion. They also had learning disabilities and were four times more likely to avoid

contact with other mice than their normal counterparts. This behavior is similar to that seen in children with autism or similar disorders in the same spectrum.

"The new model is an essential tool to find a cure for the disorder," said Noebels.

"Mutation of the ARX gene was previously known to affect interneurons, a class of cells that inhibit electrical activity in the brain," said Dr. Maureen Price (http://www.bcm.edu/neurology/faculty/price.html), the report's lead author and an instructor in neurology at BCM.

When researchers evaluated the brains of the adult mice with the mutated gene, they found that a special class of interneurons had never developed in specific brain regions.

"Further study will allow use to pinpoint which brain region is liked to the autistic-like behavior," said Price.

Two members of the research team - Dr. James Frost, professor of neurology at BCM (http://www.bcm.edu/neurology/faculty/frost.html), who developed the concept of the special mouse, and Dr. Richard Hrachovy (http://www.bcm.edu/neurology/faculty/hrachovy.cfm), also a professor of neurology at BCM - are pioneers in the study of human infantile spasms.

"At present there is no proven cure to offer children with this specific epilepsy", said Noebels. "We now have new clues into the mechanism and have already initiated studies with a new class of drugs not previously explored for this disorder." The new drug testing is supported by the private foundation People Against Childhood Epilepsy.

Others who took part in this work include Jong W. Yoo, Daniel L. Burgess and Fang Deng, all of BCM.
Funding for this work came from the Peter Kellaway Memorial Research Fund, the Blue Bird Circle Foundation, the National Institutes of Health Intellectual and Developmental Disabilities Research Center, and the PACE Foundation.
When the embargo lifts, this report will be available at http://www.jneurosci.org/

Erythropoietin boosts brainpower

Healthy young mice treated with erythropoietin show lasting improved performance in learning and other higher brain functions. Researchers writing in the open access journal BMC Biology tested the cognitive effects of the growth factor, finding that it improved the sequential learning and memory components of a complex long-term cognitive task.

Hannelore Ehrenreich led a team of researchers from the Max Planck Institute of Experimental Medicine in Göttingen, Germany, who studied the mice. She said, "Erythropoietin has been in clinical use for over 20 years to treat patients with anemic conditions, ranging from renal failure to cancer. It has recently received attention for its apparent ability to improve cognitive function in people with schizophrenia and multiple sclerosis. Here, we sought to investigate erythropoietin's effects in healthy mice".

Ehrenreich and her colleagues tested the effects of erythropoietin on the ability of the mice to learn how to exploit an experimental set-up to receive sugared water. Over a series of learning stages, the mice were trained to get their treat by poking their noses into holes lit by LEDs, rather than into unlit holes, within a time limit. The mice that had been treated with recombinant human erythropoietin were significantly more likely to master the task than those that had not. According to Ehrenreich, "Treated mice showed superior performance in associative, operant and discriminant learning as well as in the initial training phases. Moreover, erythropoietin-treated mice demonstrated better task adaptation and higher performance stability".

The researchers conclude, "Further untangling of molecular mechanisms of erythropoietin action on higher cognitive functions may ultimately open new avenues for prevention strategies and therapeutic interventions in neuropsychiatric diseases".

Notes to Editors

1. Erythropoietin improves operant conditioning and stability of cognitive performance in mice
Ahmed El-Kordi, Konstantin Radyushkin and Hannelore Ehrenreich BMC Biology
During embargo, article available here:
http://www.biomedcentral.com/imedia/3376926122535758_article.pdf?random=119865
After the embargo, article available at journal website: http://www.biomedcentral.com/bmcbiol/

Muscle rubs: Use for pain is questionable

There is not enough evidence to support using gels and creams containing rubefacients for chronic and acute pain, according to a systematic review by Cochrane Researchers. Rubefacients cause irritation and reddening of the skin, due to increased blood flow. The review focused on formulations containing salicylates, which are widely prescribed or sold over the counter as topical treatments for sports injuries and muscle pain.

"At present, due to a lack of high quality evidence, we can't say exactly how effective rubefacients are for acute injuries and there are certainly other more effective treatments which could be prescribed for use in chronic conditions like osteoarthritis," says lead researcher Andrew Moore, of the Nuffield Department of Anaesthetics at the University of Oxford in the UK.

There are over a million prescriptions each year for rubefacient gels and creams such as Movelat

. As with Movelat, the rubefacient compounds in many of these products are salicylates, which, while they are related to aspirin, may not work in the same way, especially when applied to the skin. They are referred to as "counter-irritants" because it is thought that they offset localised pain through local skin irritation.

The review analysed data from 16 trials for acute and chronic pain, which together included 1,276 people. Only salicylates were studied and trials were generally small. Results from four studies showed topical salicylates performed better than placebos against acute pain, but excluding lower quality studies meant the results were not statistically significant. When used for chronic conditions, salicylates performed better than placebos. However, only one in six patients with chronic pain benefited substantially from using the muscle rubs compared to one in three using non-steroidal anti-inflammatory drugs.

"Larger and higher quality controlled trials of topical rubefacients are needed to establish whether these treatments really work. We also need more studies on other rubefacients as we were only able to assess the effectiveness of the salicylate formulations in this review," says Moore. "But it is important to remember that not all analgesic gels or creams are the same, and for others there is very good evidence of effectiveness. Those will be dealt with in other reviews presently being finalised."

Chinese herbs for endometriosis

May have comparable benefits with fewer side effects than conventional drug treatment

Chinese herbal medicine (CHM) may relieve symptoms in the treatment of endometriosis. A systematic review by Cochrane Researchers found some evidence that women had comparable benefits following laparoscopic surgery and suffered fewer adverse effects if they were given Chinese herbs compared with conventional drug treatments.

Endometriosis is a gynaecological disorder affecting as many as one in six women of reproductive age. It can cause pelvic pain, irregular and painful periods, and infertility. Surgical treatments do not always lead to long-term improvement in symptoms and drug treatments can have unpleasant side effects such as hot flushes, acne and weight gain.

The researchers conducted the first English language systematic review of CHM for treatment of endometriosis. Two trials, which together focused on a total of 158 women, were included in the review. In one trial, CHM provided symptomatic relief comparable to that provided by the hormonal drug gestrinone, but with fewer side effects. In the other trial, CHM was more effective than the hormonal drug danazol, and also resulted in fewer side effects.

"These findings suggest that Chinese herbs may be just as effective as certain conventional drug treatments for women suffering from endometriosis, but at present we don't have enough evidence to generalize the results," says lead researcher Andrew Flower of the Complementary Medicine Research Unit at the University of Southampton in the UK.

110 studies were originally considered for review but most were of poor methodological quality and had to be excluded. The researchers stress the need for Chinese researchers to adopt more rigorous methods in carrying out trials and reporting them. "Poor quality reporting has the potential to confuse and undermine research in Chinese herbal medicine," says Flower.

Vital Signs

Regimens: Licorice May Curb a Postoperative Hurt

By NICHOLAS BAKALAR

One annoying consequence of surgery is the painful sore throat that follows recovery from anesthesia, but a small study suggests a simple and cheap way to reduce the risk: gargle with licorice just before going under.

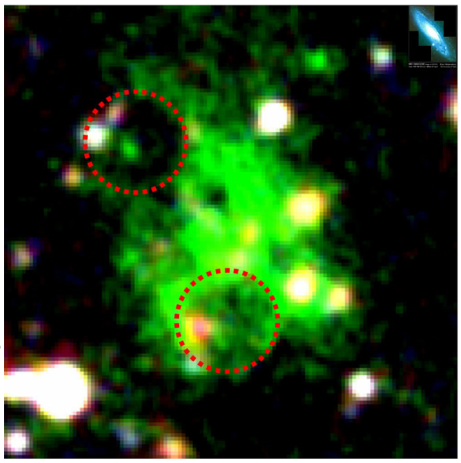
Licorice has been used for thousands of years to treat inflammation and allergies, so a group of Indian doctors decided to test it for treating postoperative sore throat. In their study, in the July issue of Anesthesia & Analgesia, they divided 40 patients undergoing an elective spinal operation into two groups. Twenty patients gargled with a licorice solution five minutes before anesthesia, and 20 gargled with plain water.

There was no difference between the groups in age, sex, weight or duration of anesthesia, but only 4 of the licorice group reported soreness on swallowing right after waking, compared with 15 from the group that gargled with water. By the end of 24 hours, nine water garglers, but only two in the licorice group, still found it painful to swallow.

The authors acknowledge that the study was not double-blinded - that is, the patients knew what they were gargling with, even though the operating room personnel did not - and that as a practical matter, gargling just before anesthesia could be problematic. Still, they conclude, the risks of the practice are very small, and the benefits may be significant.

Black Holes, a Riddle All Their Own, May Be Fueling the Blobs

By DENNIS OVERBYE



Black holes, dead stars and other objects so dense that not even light can escape them might seem like the most inwardly focused denizens of the universe. Space and time have effectively closed around them, leaving no exit.

But astronomers have found growing evidence that black holes can be extroverts, reaching out across millions of light-years and controlling the destinies of galaxies and even clusters of galaxies. The ultimate control freaks, the black holes seem to be able to regulate other objects' cosmic growth by a fiery feedback of light and other radiation from material on its way to oblivion.

And now, researchers have found evidence that black holes may also be the key to mysterious glowing clouds of gas lurking in the early universe.

Over the last 10 years, astronomers patrolling the distant reaches of space have discovered dozens of these clouds, which are technically called blobs. One, named Himiko after a mythical Japanese queen by the Japanese astronomers who found it, dates to only 840 million years after the Big Bang.

The blobs inhabit places and times in which galaxies and stars were being built like gangbusters, but astronomers have been divided about what these blobs have to say about how galaxies are born, and what makes them glow.

A group of astronomers, brandishing results from NASA's Chandra X-ray Observatory, are now pointing a finger at black holes. The blobs, they reported at a recent news conference and in a paper to be published on Friday in The Astrophysical Journal, are being blasted and lighted up from inside by the radiation spilling from the lips of supermassive black holes, weighing in at perhaps a billion times the mass of the Sun, at the centers of newly forming galaxies.

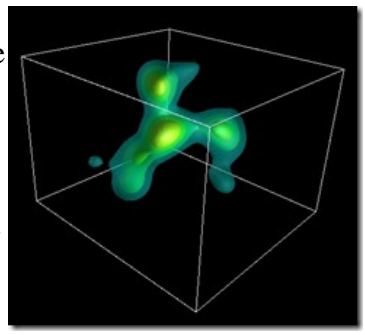
The blobs themselves were probably "leftovers," as one scientist put it, from the initial growth spurts of these galaxies. "The blobs," said James Geach of Durham University in England, might be "the signatures of galaxies coming of age."

Mario Livio, an astronomer at the Space Telescope Science Institute in Baltimore who was not involved in the research, said "it is a bit like understanding the teenage years in the life of humans."

Training the Chandra satellite on a field of 29 blobs in the constellation of Aquarius that lived about two billion years after the Big Bang, Dr. Geach and his colleagues from Durham found the telltale signature of X-rays from a supermassive black hole in five of them.

Dr. Geach and his colleagues said that the X-rays from other blobs might have just been too weak to be seen by Chandra, which was operating at its observational limits during a five-day exposure.

Galaxies grow, and grow and grow, so the accepted story goes, from small lumps left in the primordial gravy after the Big Bang that attract gas and the so-called dark matter permeating space. At some point - and theorists still debate this - a black hole forms in the middle of this growing lump.



Indeed, black holes are thought to live in the centers of most galaxies, gulping the occasional unlucky star or gas cloud that falls too close, spilling X-rays and other fireworks in a fit of sloppy digestion. The more the galaxy grows, the more its central black hole feeds and spits fire.

At some point radiation from the black hole and new stars forming in waves in the galaxy will be so strong that it will push back on the falling material. The galaxy will stop growing. That is what Dr. Geach and his colleagues claim to have seen. The infant galaxies Chandra observed, the astronomers said, are today probably among the most massive in the universe.

"The blobs look to be leftovers from the formation of giant galaxies," said Bret Lehmer, also of Durham. Too hot to fall any farther into the new galaxy, they are destined to wind up as intergalactic gas, he said.

This is not the first time that black holes have been seen to reach back out and influence the cosmos around them. In 2003, astronomers also using the Chandra observatory discovered that a supermassive black hole in the constellation Perseus was blowing bubbles 30,000 light-years in diameter across the Perseus cluster of galaxies, with periodic outbursts every 10 million years. The effect in the case of Perseus is to keep intergalactic gas in the cluster too hot to fall into the center of the cluster and condense into stars.

Martin Rees, a cosmologist at the University of Cambridge, in England, said there seemed to be a spooky correlation between the masses of black holes and the galaxies in which they are embedded, leading

astronomers to suspect some feedback mechanism. Speaking of the new Chandra results, Dr. Rees said, “I think in these observations we are seeing when that is actually happening.”

But that conclusion was not unanimous.

In April, at the same time that Dr. Geach and his colleagues first posted their results on the Internet, Abraham Loeb and Mark Dijkstra of Harvard submitted their own paper to the Monthly Notices of the Royal Astronomical Society, with a different explanation of the blobs. They pointed out that cold gas streaming into a massive protogalaxy would heat up from the gravitational energy gained by falling in and would glow of its own accord as a way of cooling off.

Asked about Dr. Geach’s results by e-mail, Dr. Loeb said that it was too soon to conclude that all the blobs were powered by black holes, noting that “the hard evidence is only 17 percent of all blobs, and the rest is speculations.” The inflow of cold gas necessary to build up a black hole and all those stars, he said, would glow even in the absence of any black-hole fireworks.

Dr. Livio said Dr. Geach had made a strong case that black holes can heat blobs. There could be different answers for other objects, he said by e-mail, “but physics rarely works this way.”

Essay

A Doctor by Choice, a Businessman by Necessity

By SANDEEP JAUHAR, M.D.

To meet the expenses of my growing family, I recently started moonlighting at a private medical practice in Queens. On Saturday mornings, I drive past Chinese takeout places and storefronts advertising cheap divorces to a white-shingled office building in a middle-class neighborhood.

I often reflect on how different this job is from my regular one, at an academic medical center on Long Island. For it forces me, again and again, to think about how much money my practice is generating.

A patient comes in with chest pains. It is hard not to order a heart-stress test when the nuclear camera is in the next room. Palpitations? Get a Holter monitor - and throw in an echocardiogram for good measure. It is not easy to ignore reimbursement when prescribing tests, especially in a practice where nearly half the revenue goes to paying overhead.

Sean Kelly

Few people believed the recent pledge by leaders of the hospital, insurance and drug and device industries to cut billions of dollars in wasteful spending. We’ve heard it before. Without fundamental changes in health financing, this promise, like the ones before it, will be impossible to fulfill. What one person calls waste, another calls income.

It is doubtful that doctors and other medical professionals would voluntarily cut their own income (even if some of it is generated by profligate spending). Most doctors I know say they are not paid enough. Their practices are like cars on a hill with the parking brake on. Looking on, you don’t realize how much force is being applied just to maintain stasis.

I recently spoke with a friend who dropped out of medical school 20 years ago to pursue investment banking. Whenever we meet, he finds a way to congratulate me on what he considers my professional calling. He often wonders whether he should have stuck with medicine. Like many expatriates, he has idealistic notions of the world he left.

At our most recent meeting, we talked about the tumult on Wall Street. Like many bankers, he was worried about the future. “It is a good time to be a doctor,” he said yet again, as I recall. “I’d love a job where I didn’t have to constantly think about money.”

I didn’t bother to disillusion him, but the reality is that most doctors today, whether in academic or private practice, constantly have to think about money. Last January, Dr. Pamela Hartzband and Dr. Jerome Groopman, physicians at Beth Israel Deaconess Medical Center in Boston, wrote in The New England Journal of Medicine that “price tags are being applied to every aspect of a doctor’s day, creating an acute awareness of costs and reimbursement.” And they added, “Today’s medical students are being inducted into a culture in which their profession is seen increasingly in financial terms.”

The rising commercialism, driven in part by increasing expenses and decreasing reimbursement, has obvious consequences for the public: ballooning costs, fraying of the traditional doctor-patient relationship. What is not so obvious is the harmful effects on doctors themselves. We were trained to think like caregivers, not

businesspeople. The constant intrusion of the marketplace is creating serious and deepening anxiety in the profession.

Not long ago, a cardiology fellow who had been interviewing for jobs came to my office, clearly disillusioned. “I was naïve,” he said. “I never thought of medicine as a business. I thought we were in it to take care of patients. But I guess it is.”

I asked him how he felt about going into private practice. “I’ll be too busy vomiting for the first six months - I won’t have much time to think about it,” he replied.

Of course, there has always been a profit motive in medicine. Doctors who own their own imaging machines order more imaging tests; to take an example from my moonlighting work, a doctor who owns a scanner is seven times as likely as other doctors to refer a patient for a scan. In regions where there are more doctors, there is more per capita use of doctors’ services and testing. Supply often dictates demand.

But financial considerations have never been as prominent as they are today, probably because so many hospitals and doctors, especially in large metropolitan areas, are in financial trouble. More and more doctors are trying to sell their practices, or are negotiating with hospitals for jobs, equipment or financial aid.

At hospitals, uncompensated care is increasing as patients suffering from the economic downturn lose health insurance. Admissions and elective procedures - big moneymakers - are declining. Hospitals are cutting administrative costs, staff and services.

“More and more you’ll see people in medicine get M.B.A.’s,” a doctor told me at a seminar, in a prediction borne out in my experience. “We are in a total crisis, and I don’t know the answer.”

I must admit that part of me wants to see doctors master the business side of our profession. When I hear about executives at health companies getting tens of millions of dollars in bonuses, I am nauseated by the blatant profiteering. As a loyal member of my guild, I want to see doctors exert more control over our financial house.

And yet the consequences of this commercial consciousness are troubling. Among my colleagues I sense an emotional emptiness created by the relentless consideration of money. Most doctors went into medicine for intellectual stimulation or the desire to develop relationships with patients, not to maximize income. There is a palpable sense of grieving. We strove for so long, made so many sacrifices, and for what? In the end, for many, the job has become only that - a job.

Until I went into practice, I never had an interest in the business side of medicine. I sometimes yearn to be a resident or fellow again, discussing the intricacies of a case rather than worrying about the bottom line. “You need to learn a little of the private-practice mind-set,” a doctor friend recently advised me. “You can’t survive with your head in the clouds.”

But something fundamental is lost when doctors start thinking of medicine as a business. In their essay, Dr. Hartzband and Dr. Groopman talk about the erosion of collegiality, cooperation and teamwork when a marketplace environment takes hold in the hospital. “The balance has tipped toward market exchanges at the expense of medicine’s communal or social dimension,” they write.

How this battle plays out will determine to a great extent what medicine will look like in 20 years. This is about much more than dollars and cents. It is a battle for the soul of medicine.

Sandeep Jauhar is a cardiologist on Long Island and the author of the recent memoir “Intern: A Doctor’s Initiation.”

Progressive resistance strength training helps older people in daily life

Progressive resistance strength training not only helps older adults become stronger but also makes their everyday life easier, a Cochrane Review suggests.

Muscle strength decreases naturally as people age. This reduction in muscle strength could affect older adults carrying out daily activities. Progressive resistance strength training is a type of strength training that uses free weights, exercise machines, or elastic bands to strengthen muscles. Key to this type of this exercise is adjusting the resistance, or weight, according to the person's progress. This exercise can be prescribed to help older adults gain the strength necessary to carry out everyday activities such as walking, climbing stairs, bathing or doing housework.

"Older adults seem to benefit from this type of exercise even at the age of 80, and even with some type of health condition. The data support the idea that muscle strength is largely improved after the training, and the impact on older adults' daily activities can be significant. Simply having enough strength to do things such as carrying groceries would make a difference for seniors" says lead researcher Chiung-ju Liu of the Department of Occupational Therapy at the Indiana University at Indianapolis in the US.

The 121 trials reviewed in the study involved 6,700 people over the age of 60, who trained two to three times a week. Training produced a large improvement in muscle strength, a moderate to large improvement in

doing simple activities such as getting up from a chair or climbing stairs and a small but statistically significant improvement in doing complex daily activities, such as bathing or preparing a meal.

Severe adverse events were rare and most reported events were muscle soreness and pain.

"We recommend older adults work with a health professional or an exercise professional to do progressive resistance strength training" says Liu. Because the long-term effect was not assessed in most trials, the Cochrane Researchers did not know how long the effects could last.

Blood pressure targets: Aiming lower offers no benefit

Aiming for lower than standard blood pressure targets offers no known clinical benefit, according to a Cochrane Review. In a systematic review of the evidence, researchers found that using antihypertensive drugs to reduce blood pressure below the 140/90 mm Hg standard was not associated with any reduction in death rates or serious morbidity.

"At present there is no evidence from randomized trials to support aiming for a blood pressure target lower than 140/90, in the general population of patients with elevated blood pressure," says lead researcher Jose Arguedas of the Faculty of Medicine at the University of Costa Rica in Costa Rica.

The findings do not support guidelines in a number of publications that recommend aiming for lower targets, based on the assumption that "lower is better" when it comes to blood pressure. The researchers were unable to determine whether it is safe to aim for lower targets because relevant data was missing from most of the trials.

The review is based on the results of seven trials, which together involved 22,089 people. Whilst patients aiming for targets below 135/85 mmHg did succeed in achieving greater reductions in blood pressure than those in the standard target group, there was no difference between the two groups in terms of the number of patients dying or suffering heart attacks, strokes, heart failure or kidney failure.

"Our research included patients with diabetes or chronic renal disease, and the evidence was slightly less robust for those subgroups of patients. We intend to carry out separate systematic reviews for those subgroups, especially because guidelines recommend even lower blood pressure targets for them", says Arguedas.

Operation for aneurysm yields nearly normal longevity

Preventive operations are being used more and more often to treat abdominal aortic aneurysms. Even though the operation is now being offered to ever older and sicker patients, the long-term survival of those who have had the operation has improved over the last two decades. This is shown in a major Swedish study in which researchers from Uppsala University examined 12,000 patients. The findings are published in Circulation: Journal of the American Heart Association.

Each year between 700 and 1,000 Swedes die as a result of rupture of abdominal aortic aneurysms. The number of preventive operations is on the rise throughout the Western world, for one thing because the population is growing older and also because with new methods it is possible today to treat older and sicker patients. How patients' long-term survival following the operation has been affected by the fact that older and sicker patients are being operated on has been unclear until now. Long-term survival is not only of great importance to the patient, but also to society, since the operation is a major and costly intervention.

The research team has previously reported that fewer and fewer patients are dying in connection with the operation. In the new study, which is based on the Swedish vascular registry (Swedvasc), the researchers have studied the long-term survival of more than 12,000 patients who underwent operations for abdominal aortic aneurysm in Sweden between 1987 and 2005.

The study shows that on average patients live nine years after the operation, which is only marginally shorter than the normal longevity of Swedes of the same age and sex. Men and patients over the age of 80 had better so-called relative survival than women and patients under 80. The fact that the women did not live as long as the men following the operation is believed be due to the circumstance that women with aortic aneurysm often also have more pronounced atherosclerosis.

"Patients who undergo operations for abdominal aortic aneurysm can look forward to nearly normal longevity," says Kevin Mani, a researcher at the Division of Vascular Surgery at Uppsala University and physician at Uppsala University Hospital. He is the lead author of the study.

"Patients are being treated more and more effectively after the operation, which has improved both the short- and long-term results. This is also good news in terms of the cost of health care: the longer patients survive after the intervention, the more cost-effective the operations are," says Kevin Mani.

Dieting Monkeys Offer Hope for Living Longer

By NICHOLAS WADE

A long-awaited study of aging in rhesus monkeys suggests, with some reservations, that people could in principle fend off the usual diseases of old age and considerably extend their life span by following a special diet.

Known as caloric restriction, the diet has all the normal healthy ingredients but contains 30 percent fewer calories than usual. Mice kept on such a diet from birth have long been known to live up to 40 percent longer than comparison mice fed normally.

Canto, left, a 27-year-old rhesus monkey, is on a restricted diet, while Owen, 29, is not. The two monkeys are part of a study of the links between diet and aging. **Jeff Miller/University of Wisconsin-Madison**

Would the same be true in people? More than 20 years ago, two studies of rhesus monkeys were begun to see if primates responded to caloric restriction the same way that rodents did. Since rhesus monkeys live an average of 27 years and a maximum of 40, these are experiments that require patience.

The results from one of the two studies, conducted by a team led by Ricki J. Colman and Richard Weindruch at the University of Wisconsin, were reported Thursday in Science. The researchers say that now, 20 years after the experiment began, the monkeys are showing many beneficial signs of caloric resistance, including significantly less diabetes, cancer, and heart and brain disease. “These data demonstrate that caloric restriction slows aging in a primate species,” they conclude.

Some critics say this conclusion is premature. But in an interview, Dr. Weindruch called it “very good news.”

“It says much of the biology of caloric restriction is translatable into primates,” he said, “which makes it more likely it would apply to humans.”

In terms of deaths, 37 percent of the comparison monkeys have so far died in ways judged to be due to old age, compared with 13 percent of the dieting group.

Dr. Weindruch and his statistician, David Allison of the University of Alabama, Birmingham, said the dieting monkeys were expected to enjoy a life span extension of 10 percent to 20 percent, based on equivalent studies started in mice at the same age.

Few people can keep to a diet with 30 percent fewer calories than usual. So biologists have been looking for drugs that might mimic the effects of caloric restriction, conferring the gain without the pain. One of these drugs is resveratrol, a substance found in red wine, though in quantities too small to have any effect.

Dr. Weindruch said the study data offered “very encouraging” signs that resveratrol could duplicate in people some of the effects of caloric restriction.

Critics, however, are not yet ready to accept that the rhesus study proves caloric restriction works in primates.

If caloric restriction can delay aging, then there should have been significantly fewer deaths in the dieting group of monkeys than in the normally fed comparison group. But this is not the case. Though a smaller number of dieting monkeys have died, the difference is not statistically significant, the Wisconsin team reports.

The Wisconsin researchers say that some of the monkey deaths were not related to age and can properly be excluded. Some monkeys died under the anesthesia given while taking blood samples. Some died from gastric bloat, a disease that can strike at any age, others from endometriosis. When the deaths judged not due to aging are excluded, the dieting monkeys lived significantly longer.

Some biologists think it is reasonable to exclude these deaths, but others do not. Steven Austad, an expert on aging at the University of Texas Health Science Center, said some deaths could have been due to caloric restriction, even if they did not seem to be related to aging. “Ultimately the results seem pretty inconclusive at this point,” Dr. Austad said. “I don’t know why they didn’t wait longer to publish.”

Leonard Guarente, a biologist who studies aging at the Massachusetts Institute of Technology, also had reservations about the findings. “The survival data needs to be fleshed out a little bit more before we can say that caloric restriction extends life in primates,” Dr. Guarente said. In mouse studies, people just count the number of dead animals without asking which deaths might be unrelated to aging, he said.

The second rhesus monkey study, being conducted by the National Institute on Aging, is not as advanced as the Wisconsin study. The researchers have not yet reported on the number of deaths in the dieting and normal monkey groups. But there are signs that the immune system is holding up better in the dieting group, said Julie Mattison, the leader of the institute’s study.

The outcome of the rhesus monkey studies bears strongly on the prospects of finding drugs that might postpone the aging process in people. Although people are similar to mice in many ways, they differ in other ways, notably in how many cancer treatments are effective in mice but do not work in people.

Even if caloric restriction extends longevity in people as well as in mice, the extent of the effect remains unclear, though Dr. Weindruch believes the effects will be in the same general range. His monkeys were not started on the diet until 6 to 14 years of age, and seemed to be doing as well as mice that were started at equivalent ages. The most striking extensions of life span occur when the mice are put on the diet from birth.

Dietary restriction seems to set off an ancient strategy written into all animal genomes, that when food is scarce resources should be switched to tissue maintenance from breeding. In recent years biologists have had considerable success in identifying the mechanisms by which cells detect the level of nutrients available to the body. The goal is to find drugs that trick these mechanisms into thinking that famine is at hand. People could then literally have their cake and eat it, too, enjoying the health benefits of caloric restriction without the pain of forgoing rich foods.

Sirtris, a company based in Cambridge, Mass., is conducting clinical trials of resveratrol. It has developed several chemicals that mimic resveratrol and can be given in much smaller doses. On Wednesday, another such compound, the drug rapamycin, was reported to extend life span significantly in elderly mice, though it is not yet clear whether rapamycin sets off the same circuits as those that increase longevity in caloric restriction.

Dr. Weindruch joined the rhesus monkey experiment in 1990. He said he was used to being introduced as a man of incredible patience by biologists who study aging in laboratory roundworms, which live about three weeks. Dr. Weindruch will need the patience: he says he has another 15 years to go before the last monkey is expected to die.

Material World

As Unbreakable as ... Glass?

By HENRY FOUNTAIN

CHICAGO — To truly appreciate how glass can be used structurally, make your way to 233 South Wacker Drive in downtown Chicago. More precisely, make your way 1,353 feet above South Wacker, to the 103rd floor of the Sears Tower. Once there, take a few steps over to the west wall, where the facade has been cut away. Then take one more step, over the edge.

You'll find yourself on a floor of glass, suspended over the sidewalk a quarter-mile below. If you can't bear looking straight down past your feet, shift your gaze out or up — the walls are glass, too, as is the ceiling. You've stepped into a transparent box, one of four that jut four and a half feet from the tower, hanging from cantilevered steel beams above your head. The glass walls are connected to the beams, and to the glass floor, with stainless-steel bolts. But what's really saving you from oblivion is the glass itself.

The boxes, which opened last week as part of an extensive renovation of the tower's observation deck, are among the most recent, and more outlandish, projects that use glass as load-bearing elements. But all glass structures have at least a bit of daring about them, as if they are giving a defiant answer to the question: You can't do that with glass, can you?

You can. Engineers, architects and fabricators, aided by materials scientists and software designers, are building soaring facades, arching canopies and delicate cubes, footbridges and staircases, almost entirely of glass. They're laminating glass with polymers to make beams and other components stronger and safer — each of the Sears Tower sheets is a five-layer sandwich — and analyzing every square inch of a design to make sure the stresses are within precise limits. And they are experimenting with new materials and methods that could someday lead to glass structures that are unmarked by metal or other materials.

"Ultimately what we're all striving for is an all-glass structure," said James O'Callaghan of Eckersley O'Callaghan Structural Design, who has designed what are perhaps the world's best-known glass projects, the staircases that are a prominent feature of some Apple Stores.

Through it all, they've realized one thing. "Glass is just another material," said John Kooymans of the engineering firm Halcrow Yolles, which designed the Sears Tower boxes.

It's a material that has been around for millennia. Although glass can be made in countless ways to have any number of specific uses — to conduct light as fibers, say, or serve as a backing for electronic circuitry, as in a laptop screen — structural projects almost exclusively use soda-lime glass, made, as it has always been, largely from sodium carbonate, limestone and silica.

"For years, the basic composition of soda-lime glass has not changed much," said Harrie J. Stevens, director of the Center for Glass Research at Alfred University. It's the same glass, more or less, that is used for the windows in your home and the jar of jam in your fridge — and that old elixir bottle you bought at an antique store.

It's basic stuff, but far from simple. "Of course, glass is an unusual material," said James Carpenter of James Carpenter Design Associates, who has designed glass facades and other structures and was a consultant for the glassmaker Corning in the 1970s. "Since we don't really know what it is."

Although there has long been debate as to whether glass is a solid or liquid, it is now usually described as an amorphous solid (there is no evidence that it flows, extremely slowly, over time as a liquid). The noncrystalline structure is achieved by relatively rapid cooling below what is referred to as the glass transition temperature, around 1,000 degrees Fahrenheit for the soda-lime variety.

Cooled further and cut, pristine glass is very strong. But like a new car that plummets in value the moment it is driven off the lot, glass starts to lose its strength the instant it's made. Tiny cracks begin to form through contact with other surfaces, or even with water vapor and carbon dioxide.

"If you take the freshly made surface and blow on it with your breath, you've reduced the strength of glass by a factor of two," said Suresh Gulati, a mechanical engineer and self-described "strength man" who retired in 2000 after 33 years at Corning but still works for the company as a consultant.

Even one gas molecule can break a silicon-oxygen bond in glass, generating a defect, said Carlo G. Pantano, a professor of materials science at Pennsylvania State University. While glass is very strong in compression, tensile stresses will make these tiny fissures start to grow, bond by bond. "That's what makes glass break," Dr. Pantano said. "And if it doesn't break, it weakens it."

Protective coatings are one way to avoid new cracks, although they can affect transparency, which is the main reason for using glass in the first place. Changing the glass recipe can also make it harder for cracks to form and propagate. "There is some evidence that you can modify the composition to make it innately stronger," Dr. Stevens said, although that risks altering other properties or making the glass too costly. (And glass projects are not cheap to start with; the glass in the Sears Tower project cost more than $40,000 per box.)

The manufacturing process can be modified, too, to keep the surfaces of the glass as pristine as possible. In one technique, used for laptop glass, molten glass is pumped into a V-shaped trough, spills over on both sides and flows down the outside of the V, joining together at the bottom into a sheet that continues to move downward as it cools. This way, each side of the sheet is a "melt surface," exposed only to the air and not touched by any part of the equipment.

For structural purposes, glass is often strengthened the old-fashioned way — by tempering. This puts the surface under compression, so that even more tensile force is needed for cracks to grow.

For flat glass, heat tempering is most often used. William LaCourse, a professor at Alfred, said the process took advantage of one property of glass — that when it cools slowly it becomes denser. By rapidly cooling the exterior of a sheet (usually with air), the surface stays less dense. "Inside it's still hot, and tries to cool to a more dense structure," Dr. LaCourse said. "This pulls the surface into compression."

In chemical tempering, sodium ions in the surface are replaced with potassium ions, which are about 30 percent larger. It's like taking a suitcase full of summer-weight clothes and replacing the top layer with winter-weight items; the suitcase will bulge at the seams when you try to close it. Glass cannot bulge at the seams, so the surface becomes compressed.

Tempered glass may take longer to crack, but it can still break. Because surface compression must be balanced by interior tension, when tempered glass does break it forms many more smaller pieces than untempered glass, as more fracture lines release more energy. "The more it is strengthened the more pieces it will fly into," Dr. Gulati said. An extreme example of this is a Prince Rupert's drop, a small glass ball with a long tail formed by dropping molten glass into water. You can pound on the ball end with a hammer and it will not break, but snip off the tail and the ball will explode into tiny pieces as the tensile forces are released.

In structural applications, breaking into smaller pieces is often preferred, because these have less chance of causing injury. But tempering alone is usually not enough.

A primary concern when building with glass is what happens if and when a component breaks — what engineers call "post-failure behavior." Unlike steel or other materials, glass does not deform or otherwise give advance warning of failure. If breakage occurs, maintaining the integrity of the structure is paramount so that people on or below it are safe.

That's where lamination comes in. In a typical project, glass sheets (one-half-inch thick in the Sears Tower project) are bonded with thin polymer interlayers. The interlayers add strength and, should one of the glass layers break, keep the structure together, and the pieces from falling.

But lamination makes fabricating glass for structural uses very difficult. Since cutting into tempered glass causes it to break, each sheet must be polished and drilled for the connecting fittings before it is tempered. Tolerances are extremely small, to avoid potentially destructive stresses in the assembled structure.

"It's doable," said Lou Cerny of MTH Industries, who managed the installation at the Sears Tower, where the tolerances were one-sixteenth of an inch. "There's just not a lot of people who want to get involved in it."

No wonder, then, that those who build with glass look forward to a day when their structures will be unencumbered by metal or other materials.

"My goal has always been to reduce the amount of fittings in glass," said Mr. O'Callaghan, whose Apple staircases use stainless steel and, occasionally, titanium to join the glass components.

Already, some engineers are using different glass shapes to reduce the dependence on metal. Rob Nijsse, a professor at the Delft University of Technology in the Netherlands and a structural engineer with the firm ABT Belgium, has used large sheets of corrugated glass, mounted vertically, for window walls in a concert hall in Porto, Portugal, and a museum being built in Antwerp, Belgium. The shape helps stiffen the glass against wind loads.

Other designers think about using different kinds of glass. "There are so many amazing types of glass available," Mr. Carpenter said. "There's an enormous potential to transfer some of their characteristics into architectural uses."

Using a glass that does not expand much when heated, for example, would enable components to be welded together, forming, in effect, a continuous piece of glass. Conventional soda-lime glass expands too much, so welding introduces stresses that can lead to failure.

Researchers at Delft have experimented with welding glass components. But low-expansion glass is much costlier than soda-lime glass.

Other engineers are starting to use adhesives to join glass directly to glass. Lucio Blandini, an engineer with Werner Sobek Engineering and Design in Stuttgart, Germany, used adhesives to create a thin glass dome, 28 feet across, for his doctoral thesis in a clearing in Stuttgart. "I think adhesives are the most promising connection device," Dr. Blandini said. "It allows glass to keep its aesthetic qualities." His firm is using adhesives in parts of structures being built at the University of Chicago and in Dubai.

But the long-term strength and reliability of adhesives has not been proved, so most people who work in glass think an all-glued structure is a long way off.

"We have way too many lawyers in this country," said Mr. Cerny, the installer at the Sears Tower. "It'll be awhile before we see that."

This article has been revised to reflect the following correction:

***Correction**: July 11, 2009*

An article on Tuesday about new structural uses of glass referred incorrectly to glass staircases that are a feature of Apple Stores. While many high-profile Apple Stores have such a staircase, there is not one in every store. And a graphic with the article misidentified a substance used as a layer between some joints in the glass observation boxes at the Sears Tower. It is silicone, a rubberlike compound containing silicon — not silicon itself, a nonmetallic chemical element. A corrected version of the graphic can be found at nytimes.com/science.

Remote-control closed system invented for inserting radio-active atoms inside fullerenes

The new material will increase control of radiation therapy

Blacksburg, Va. – Virginia Tech chemistry Professor Harry C. Dorn, Emory and Henry College chemistry Professor James Duchamp, and Panos Fatouros, professor and chair of the Division of Radiation Physics and Biology at the Virginia Commonwealth University School of Medicine have co-invented a hands-off process for filling fullerenes with radio-active material.

Fullerenes are hollow carbon molecules. Dorn has created new materials by filling them with atoms of various metals. An important example is a fullerene that encases a sensitive contrast agent (gadolinium) for MRI applications, including as a diagnostic and therapeutic agent for brain tumors. Dorn and Fatouros at VCU have funding from the National Institutes of Health's National Cancer Institute (NCI) to further develop, produce, and test fullerene nanoparticles that can identify brain tumor cells and selectively target them for radiation therapy.

What if the radioactive material could also be encased in a carbon cage? Dorn asked himself several years ago. With more funding from NCI and Virginia's Commonwealth Technology Research Fund (CTRF), he set out to do it.

Now Dorn and Duchamp have invented a generator that makes the new material by remote control. "The new materials come out the bottom like a beer product," Dorn said. The golden liquid is not dispensed into an open cup, of course.

Basically, rods about three times the size of a pencil lead that are made up of graphite and lutetium (Lu) are inserted into big jar through a tube on one side and moved slowly toward a source of electricity on the other side. The jolted rod burns dramatically and the inside of the jar is coated with ash. A nozzle kind of like a

miniature carwash wand is lowered from the top to rinse the soot to the bottom and out through a filter. The soot is trapped and the resulting beer-colored solution contains Lu atoms bound to nitrogen inside of fullerenes. This radiolabeled nanomaterial is then further purified by passage through a column that traps the empty-cage fullerenes. The resulting liquid is evaporated and hydroxyl atoms are attached to the molecules so they will be soluble in biofluids. All of the steps of the process are managed remotely and the purified product is decanted into a shielded container.

Dorn and Duchamp have used non-radioactive Lu to produce the trimetallic nitride endohedral metallofullerenes (Lu3N@C80) – in other words, three atoms of Lu attached to a nitrogen atom inside an 80-atom carbon molecule cage. Once the apparatus is at VCU, Fatouros will use isotope 177Lu, which is used to treat cancer. Although other details need to be worked out, Dorn is confident the generator will work just as well with the radiolabeled product and will produce (177Lu3N@C80).

It all takes less than a day, which is important because 177Lu has a half life of six and one-half days. "So we can't take 30 days to make the product," said Duchamp.

It will be the first time that 177Lu has been encapsulated in a fullerene and the first time any radioactive metal has been encapsulated under remote control with direct purification to a pure product.

"The advantage of the metal cage is we can control where it goes biologically," Dorn said.

"We believe it will mean fewer side effects with better targeted localization, but that remains to be tested," said Fatouros.

"Another advantage is we can deliver other materials inside the fullerene with the 177Lu – such as a targeting agent (interleukin-13) and an MRI contrast agent," said Dorn.

Creation of such a multi-modality material for use on brain tumors is a specific goal of Fatouros and Dorn's NCI-funded research project, "Metallofullerene imaging and targeting of glioma." "The MRI agent lets you see where you are going and the 177Lu lets you treat an exact region," said Dorn. "The imaging ability also lets you see if the tumor is shrinking or getting larger."

An earlier stage of the research was presented at the NCI Alliance for Nanotechnology in Cancer Investigators Meeting in September 2008 and a patent application has been filed.

Dorn points out that the new device will also allow the production of other kinds of radio-labeled fullerenes that can be used for environmental studies, such as to track fullerene nanomaterials.

Read more about Fatouros and Dorn's National Institutes for Health funded research: www.vtnews.vt.edu/story.php?relyear=2005&itemno=1062

How the turtle's shell developed

By Victoria Gill Science reporter, BBC News

The turtle's shell is an "evolutionary novelty"

Scientists have revealed a spectacular insight into turtle evolution - how the unique animals get their shells. A Japanese team studied the development of turtle embryos to find out why their ribs grow outward and fuse together to form a tough, external carapace.

Reporting in the journal Science, the researchers compared turtle embryos with those of chicks and mice. They found that, as turtles developed, part of their body wall folded in on itself forcing the ribs outward.

The team of researchers from the Riken Center for Developmental Biology in Kobe, Japan, described the turtle shell as an "evolutionary novelty". It represents such a leap from the soft-bodied ancestors that turtles share with mammals and birds, that scientists have long puzzled over how exactly it came about.

"Other groups have looked into why the shoulder blade in turtles is encased inside the rib cage," said Olivier Rieppel from Field Museum in Chicago, an expert in reptile evolution who was not involved in this study.

"That makes them unique."

Body map

This study identified the key event in the development of a turtle embryo that changes its fundamental "body plan" - when the upper part of the its body wall folds in on itself. This fold produces what scientists refer to as the carapacial disc - a thickening of the deep layer of the turtle's skin that maps out the position of its shell.

"Once you have this body plan, you have the carapacial disc and all the rest of it follows," said Dr Rieppel.

In the early embryo, the muscles and skeleton are in similar positions to those of the chicken and mouse, explained Shigeru Kuratani, one of the authors of the study.

As the embryo develops, this folding essentially "re-maps" the turtle's body - mechanically preventing the ribs from growing inward and holding the shoulder blades in place.

Dr Kuratani explained that some of the connections between developing bones and muscles were the same as in birds and mammals, but there were some, including the pectoral muscles, that "showed entirely unique (types of) connectivity in turtles".

The discovery helps define a position in evolutionary history for a 220-million-year-old turtle fossil discovered last year in China, which had an incomplete shell that only covered its underside. "The developmental stage of the modern turtle, when the ribs have not encapsulated the shoulder blade yet, resembles the (body) of this fossil species," said Dr Kuratani.

Dr Rieppel, who examined the Chinese fossil when it was discovered late in 2008, said this study illustrated that the ancient turtle was "basically an intermediate step in the animals' evolution".

The scientists do not yet know what causes the folding. "That belongs to a future project," said Dr Kuratani.

Stressing the importance of developmental research to evolutionary biology, Dr Kuratani said: "Developmental changes in evolution give rise to an enormous diversity of animal forms." "No matter how exquisite it may seem, as if it were some sort of magic, evolution is at most a good trick... and there is a way to make it work.

The turtle's shell is an "evolutionary novelty"

"In case of turtle evolution, a major part of the trick was found to be (this) embryonic folding."

Easter Island compound extends lifespan of old mice

UT Health Science Center at San Antonio, other centers reach same result: 28-38 percent longer life

SAN ANTONIO, Texas, U.S.A. — The giant monoliths of Easter Island are worn, but they have endured for centuries. New research suggests that a compound first discovered in the soil of the South Pacific island might help us stand the test of time, too.

Wednesday, July 8, in the journal Nature, The University of Texas Health Science Center at San Antonio and two collaborating centers reported that the Easter Island compound – called "rapamycin" after the island's Polynesian name, Rapa Nui – extended the expected lifespan of middle-aged mice by 28 percent to 38 percent. In human terms, this would be greater than the predicted increase in extra years of life if cancer and heart disease were both cured and prevented.

The rapamycin was given to the mice at an age equivalent to 60 years old in humans.

The studies are part of the National Institute on Aging (NIA) Interventions Testing Program, which seeks compounds that might help people remain active and disease-free throughout their lives. The other two centers involved are the University of Michigan at Ann Arbor and Jackson Laboratory in Bar Harbor, Maine.

The Texas study was led by scientists at two institutes at the UT Health Science Center: the Institute of Biotechnology (IBT) and the Barshop Institute for Longevity and Aging Studies.

"I've been in aging research for 35 years and there have been many so-called 'anti-aging' interventions over those years that were never successful," said Arlan G. Richardson, Ph.D., director of the Barshop Institute. "I never thought we would find an anti-aging pill for people in my lifetime; however, rapamycin shows a great deal of promise to do just that."

Versatile compound

Discovered in the 1970s, rapamycin was first noted for its anti-fungal properties and later was used to prevent organ rejection in transplant patients. It also is used in stents, which are implanted in patients during angioplasty to keep coronary arteries open. It is in clinical trials for the treatment of cancer.

The new aging experiments found that adding rapamycin to the diet of older mice increased their lifespan. The results were the same in Texas, Michigan and Maine.

"We believe this is the first convincing evidence that the aging process can be slowed and lifespan can be extended by a drug therapy starting at an advanced age," said Randy Strong, Ph.D., who directs the NIA-funded Aging Interventions Testing Center in San Antonio. He is a professor of pharmacology at the UT Health Science Center and a senior research career scientist with the South Texas Veterans Health Care System.

The findings have "interesting implications for our understanding of the aging process," said Z. Dave Sharp, Ph.D., director of the Institute of Biotechnology and professor and chairman of the Health Science Center's Department of Molecular Medicine.

"In addition," Dr. Sharp said, "the findings have immediate implications for preventive medicine and human health, in that rapamycin is already in clinical usage."

Molecular pathway

Aging researchers currently acknowledge only two life-extending interventions in mammals: calorie restriction and genetic manipulation. Rapamycin appears to partially shut down the same molecular pathway as restricting food intake or reducing growth factors. It does so through a cellular protein called mTOR (mammalian target of rapamycin), which controls many processes in cell metabolism and responses to stress.

A decade ago, Dr. Sharp proposed to his colleagues that mTOR might be involved in calorie restriction. "It seemed like an off-the-wall idea at that time," Dr. Richardson said.

In 2004, a year after the launch of the NIA Interventions Testing Program, Dr. Sharp submitted a proposal that rapamycin be studied for anti-aging effects. The proposal was approved, and testing centers in San Antonio and elsewhere began to include rapamycin in the diets of mice.

The male and female mice were cross-bred from four different strains of mice to more closely mimic the genetic diversity and disease susceptibility of the human population.

Dr. Strong soon recognized a problem: Rapamycin was not stable enough in food or in the digestive tract to register in the animals' blood level. He worked with the Southwest Research Institute in San Antonio to improve the bioavailability of the compound through a process called microencapsulation. The reformulated drug was stable in the diet fed to the mice and bypassed the stomach to release in the intestine, where it could more reliably enter the bloodstream.

Older mice

The original goal was to begin feeding the mice at 4 months of age, but because of the delay caused by developing the new formulation, the mice were not started until they were 20 months old – the equivalent of 60 years of age in humans. The teams decided to try the rapamycin intervention anyway.

"I did not think that it would work because the mice were too old when the treatment was started," Dr. Richardson said. "Most reports indicate that calorie restriction doesn't work when implemented in old animals. The fact that rapamycin increases lifespan in relatively old mice was totally unexpected."

Added Dr. Strong: "This study has clearly identified a potential therapeutic target for the development of drugs aimed at preventing age-related diseases and extending healthy lifespan. If rapamycin, or drugs like rapamycin, works as envisioned, the potential reduction in overall health cost for the U.S. and the world will be enormous."

Fruit and vegetable intake in pregnant women reduces risk of upper respiratory tract infection

(Boston) – Boston University School of Medicine researchers (BUSM) have observed in a study of pregnant women that consumption of at least seven servings per day of fruits and vegetables moderately reduced the risk of developing an upper respiratory tract infection (URTI). The BUSM study appears online in the journal Public Health Nutrition.

URTIs include the common cold and sinus infections, which can lead to lower respiratory problems, such as asthma or pneumonia. Even though the majority of URTIs are uncomplicated colds, identifying ways to prevent their occurrence is important because colds are the most common reason for school and work absences. Eating nutritious foods, especially fruits and vegetables, improves immunity but hadn't previously been associated with reducing the risk of URTIs in pregnant women.

BUSM researchers studied more than 1,000 pregnant women and found those who ate the most fruits and vegetables were 26 percent less likely to have URTI relative to those who ate the least amount. Neither fruit nor vegetable intake alone was found to be associated with the five-month risk of URTI. The patterns observed for total fruit and vegetable intake and either fruit or vegetable intake alone in relation to the three-month risk of URTI were consistent with those when assessing the five-month risk of URTI. Women in the highest quartile of fruit and vegetable intake had a stronger reduced three-month risk than the five-month risk of URTI. Moreover, there was a significant decreasing linear trend for the three-month risk of URTI with consumption of fruits and vegetables.

Pregnant women have been recommended to consume at least five servings of fruits and vegetables per day. This study showed that intake of higher levels, 6.71 servings per day, was associated with a moderate risk reduction for URTI.

"Pregnant women may require more fruits and vegetables than usual because of the extra demands on the body," said senior author Martha M. Werler, M.P.H., Sc.D., professor at Slone Epidemiology Center at Boston University.

This study was supported by the National Institute of Dental and Craniofacial Research. The Institute had no role in the design and conduct of the study, the collection, management, analysis and interpretation of the data, or the preparation, review and approval of the manuscript.

Health Clinic Conditions May Be To Blame For Decrease In Primary Care Physicians

New Study Evaluates Role of Clinic Environment on Physician Job Satisfaction

Maywood – Adverse work conditions may be to blame for the decline in the number of primary care physicians nationwide, according to a study published in the latest issue of the Annals of Internal Medicine.

"Unfavorable work conditions are associated with stress, burnout and intent to leave for primary care physicians," said Dr. Anita Varkey, study author and assistant professor in the department of medicine, Loyola University Chicago Stritch School of Medicine. "These factors contribute to poor job satisfaction, which is among the reasons we are seeing a decrease in the number of primary care physicians."

The Association of American Medical Colleges estimates that the overall shortage of doctors may grow to 124,400 by 2025.

"There are not enough primary care physicians to meet current needs," said Varkey, who also is medical director of the general medicine clinic at Loyola Outpatient Center, Loyola University Health System. "These findings suggest that a chaotic clinic environment may further exacerbate this problem and potentially lead to lower quality of patient care due to physician turnover and lack of continuity in care."

Data for this study were collected from 422 family practitioners and general internists and 1,795 of their adult patients with diabetes, hypertension or heart failure at 119 clinics in New York and the Midwest. Study participants were asked about perception of clinic workflow (time pressure and pace), work control, organizational culture, physician satisfaction, stress, burnout and intent to leave practice.

More than half of the physicians (53.1 percent) reported time pressure during office visits, 48.1 percent said their work pace was chaotic, 78.4 percent noted low control over their work and 26.5 percent reported burnout. Adverse workflow (time pressure and chaotic environments), low work control and unfavorable organizational culture were strongly associated with low physician satisfaction, high stress, burnout and intent to leave. Some work conditions also were associated with lower quality of patient care and more errors, but findings were inconsistent across work conditions and medical diagnoses.

The authors indicated that interventions in primary care clinics should target measures to reduce physician burnout, clinic chaos and work control measures. A healthier workplace for physicians may result in better recruitment and retention of primary care physicians, which may then translate to higher quality patient care.

"While further research is needed, health care reform strategies should consider the role that work environment plays in physician job satisfaction and quality of patient care," Varkey added.

Varkey is an internist who specializes in primary care, preventive medicine and women's health. She sees patients at Loyola Outpatient Center.

Co-authors of the Archives study include Linda Baier Manwell, M.S.; James A. Bobula, Ph.D.; Dr. Mark Linzer, Roger L. Brown, Ph.D., all of the University of Wisconsin-Madison; Dr. Ann Maguire of Medical College of Wisconsin; Dr. Bernice Man of Rush Medical College; Dr. Julia McMurry of William S. Middleton Memorial Veterans Hospital; Eric S. Williams, Ph.D., of the University of Alabama; Dr. Barbara A. Horner-Ibler, of the University of Wisconsin-Milwaukee; and Dr. Mark D. Schwartz of Veterans Affairs New York Harbor Healthcare

Monkeys have a memory for grammar

* 00:01 08 July 2009 **by Catherine Brahic**

Primates can intuitively recognise some rules of grammar, according to a study of cotton-topped tamarin monkeys (Saguinus oedipus).

The findings do not mean primates can communicate using language, but they do suggest that some of the skills required to use language may be linked to very basic memory functions.

One grammatical structure that is found across many languages is affixation: the addition of syllables, either at the beginning or at the end of a word, to modify its meaning.

For instance, in English, the suffix "–ed" is added to verbs to make the past tense. In German, the same effect is achieved by adding the prefix "ge–" to the front of verb stems.

Ansgar Endress and colleagues at Harvard University thought that, because this structure is found in so many languages, it might be linked to basic memory functions that are independent of language. If they could prove this was true, it would suggest ways that children might be learning grammatical structures.

He may not be conjugating Latin verbs, but this cotton-topped tamarin can remember some simple grammar **(Image: Gary Ramage / Newspix / Rex Features)**

Nonsense words

To test this, Endress and colleagues studied 14 cotton-top tamarins, which, like all other non-human primates, do not use language to communicate.

They first played a sequence of nonsensical "words" to the monkeys that all had the same prefix, like "shoybi", "shoyka", and "shoyna".

The following morning, the animals were played a different set of entirely new words. This second set had completely different stems – brain, brest, and wasp instead of bi, ka, and na – but were preceded by the same prefix. Mixed in to the new batch of words were a few that violated the familiar prefix pattern by having a suffix instead of a prefix ("brainshoy" instead of "shoybrain").

The researchers hypothesised that, if the monkeys were able to recognise the prefix pattern they had heard the day before, they would be more likely to look at the loudspeakers when they heard a word that violated the grammatical pattern.

"This is exactly what they did," says Endress. The team found the same result if they familiarised the monkeys with words that had suffixes, then mixed in a few prefixes.

No food

The fact that the tamarins appeared to understand the prefix and suffix patterns, without being trained with food rewards, does not prove that they have language and grammar, says Endress. But it does suggest that their memory is able to recognise certain linguistic patterns.

Memory organisation in humans means we find it easiest to track what occurs in the first and the last position of sequences. "This is a basic and well-known fact about the organisation of memory for sequences," says Endress.

"If you try to remember the sequence NBGHQPZRXV, it is easier to remember that N was in the first position, and V in the last position," than it is to remember that the H was in the fourth position.

The results suggest that grammar may have evolved from this basic memory structure. It could also explain how rules like the English past-tense are learned.

Endress explains: "Our results suggest a fairly pedestrian mechanism: human infants, like monkeys, might be particularly prone to track what occurs in the first and the last position of words and other linguistic units. They might use these mechanisms of memory organization for learning affixation rules."

Kate Arnold of the University of St. Andrews, UK, says the finding that some primates are able to differentiate a valid sequence from an invalid one may relate to some very unusual behaviour she has seen in wild monkeys. Last year, Arnold showed that putty-nosed monkeys in Nigeria are able to combine two different calls into a sequence that causes other monkeys in the area to move to a different area. This is the closest anyone has ever come to observing animals using syntax. *Journal reference: Biology Letters, DOI: 10.1098/rsbl.2009.0445 (in press)*

Explosive growth of life on Earth fueled by early greening of planet

TEMPE, Ariz. – Earth's 4.5-billion-year history is filled with several turning points when temperatures changed dramatically, asteroids bombarded the planet and life forms came and disappeared. But one of the biggest moments in Earth's lifetime is the Cambrian explosion of life, roughly 540 million years ago, when complex, multi-cellular life burst out all over the planet.

While scientists can pinpoint this pivotal period as leading to life as we know it today, it is not completely understood what caused the Cambrian explosion of life. Now, researchers led by Arizona State University geologist L. Paul Knauth believe they have found the trigger for the Cambrian explosion.

This is a late Precambrian carbonate outcropping at south end of Death Valley, California. Carbon isotopes in these layers bear evidence of the first extensive greening of the Earth. **Credit: L.P. Knauth, Arizona State University**

It was a massive greening of the planet by non-vascular plants, or primitive ground huggers, as Knauth calls them. This period, roughly 700 million years ago virtually set the table for the later explosion of life through the development of early soil that sequestered carbon, led to the build up of oxygen and allowed higher life forms to evolve.

Knauth and co-author Martin Kennedy, of the University of California, Riverside, report their findings in the July 8 advanced on-line version of Nature (www.nature.com). Their paper, "The Precambrian greening of Earth," presents an alternative view of published data on thousands of analyses of carbon isotopes found in limestone that formed in the Neoproterozoic period, the time interval just prior to the Cambrian explosion.

"An explosive and previously unrecognized greening of the Earth occurred toward the end of the Precambrian and was an important trigger for the Cambrian explosion of life," said Knauth, a professor in

Arizona State's School of Earth and Space Exploration.

"During this period, Earth became extensively occupied by photosynthesizing organisms," he added. "The greening was a key element in transforming the Precambrian world – which featured low oxygen levels and simple, bacteria dominant life forms – into the kind of world we have today with abundant oxygen and higher forms of plant and animal life."

Knauth calls the work "isotope geology of carbonates 101."

In order to understand what happened on Earth such a long time ago, researchers have studied the isotopic composition of limestone that formed during that period. Researchers have long studied these rocks, but Knauth said many focused only on the carbon isotopes of Neoproterozoic limestones.

Knauth and Kennedy's study looked at a bigger picture.

"There are three atoms of oxygen for every atom of carbon in limestone," Knauth says. "We looked at the oxygen isotopes as well, which allowed us to see that the peculiar carbon isotope signature previously interpreted in terms of catastrophes was always associated with intrusions of coastal ground waters during the burial transformation of initial limestone muds into rock. It's the same as we see in limestones forming today."

Brave new world

By gathering all of these published measurements and carefully plotting carbon isotopic data against oxygen isotopic data, a process Knauth said took three years, the researchers began to formulate a very different type of scenario for what led to complex life on Earth. Rather than a world subject to periods of life-altering catastrophes, they began to see a world that first greened up with primitive plants.

"The greening of Earth made soils which sequestered carbon and allowed oxygen to rise and get dissolved into sea water," Knauth explained. "Early animals would have loved breathing it as they expanded throughout the ocean of this new world."

A key element to this scenario is not so much what the researchers saw in the data, but what was missing. When they plotted the data for various areas from which it was derived they kept noticing an area on the plots that contained little or no data. They dubbed it the "forbidden zone."

"If previous interpretations of carbon isotope data were correct, there would be no forbidden zone on these cross plots," Knauth said. "The forbidden zone would be full of Neoproterozoic data."

"These zones show that the isotopic fingerprints in limestone we see today started in the late Precambrian and must have involved the simultaneous influx of rain water that fell on vegetated areas, infiltrated into coastal ground waters and mixed with marine pore fluids. During sea level drops, these coastal mixing zones are dragged over vast geographic regions of the flooded continents of the Neoproterozoic," Knauth said. "Vast areas of limestone can form in these mixed pore fluids."

All of which points to an environmental trigger of the Cambrian explosion of life.

Carbonate layers hold carbon isotope evidence of the late Precambrian greening of the Earth. These are located in the Old Dad Mountains in California. **Credit: L.P. Knauth, Arizona State University**

"Our work presents a simple, alternative view of the thousands of carbon isotope measurements that had been taken as evidence of geochemical catastrophes in the ocean," Knauth explained. "It requires that there was an explosive greening of Earth's land surfaces with pioneer vegetation several hundred million years prior to the evolution of vascular plants, but it explains how a massive increase in Earth's oxygen could happen, which has been long postulated as necessary for animals to evolve big time."

"The isotopes are screaming that this happened in the Neoproterozoic," he added.

NASA and the U.S. National Science Foundation funded this work.

Inflammation may trigger Alzheimer's disease, Saint Louis University findings suggest

Pair of studies give clues to how disease develops and may be treated

ST. LOUIS -- The anti-inflammatory drug indomethacin could hold promise as a treatment for Alzheimer's disease, says a Saint Louis University doctor and researcher.

Two research studies published by William A. Banks, M.D., professor of geriatrics and pharmacological and physiological science at Saint Louis University School of Medicine, support this conclusion and offer what he calls a "one-two punch" in giving clues on how Alzheimer's disease develops and could be treated.

His study in the July edition of the Journal of Alzheimer's Disease supports the idea that toxic levels of amyloid beta protein, the substance scientists believe is responsible for Alzheimer's disease, accumulate in the brain because a pump that pushes it into the blood and past the blood-brain barrier malfunctions.

The blood-brain barrier is a system of cells that regulates the exchange of substances between the brain and the blood. The blood-brain barrier transporter known as LRP is the pump that removes amyloid beta protein from the brain and into the bloodstream.

"LRP malfunctions like a stop light stuck on red, and keeps amyloid beta protein trapped in the brain," said Banks, who also is a staff physician at Veterans Affairs Medical Center in St. Louis.

He tested the hypothesis by giving mice an antisense, which is a molecular compound that blocked the production of LRP. Amyloid beta protein accumulated in the brain and the mice showed memory loss and learning impairment.

The finding raises the question of what causes LRP to malfunction. Banks' study in the May issue of Brain Behavior and Immunity suggests inflammation as the culprit and supports using indomethacin, an anti-inflammatory medication, as a buffer to protect LRP from being turned off.

Inflammation, which is part of the body's natural immune response, occurs when the body activates white blood cells and produces chemicals to fight infection and invading foreign substances.

"We induced inflammation in mice and found that it turned off the LRP pump that lets amyloid beta protein exit the brain into the bloodstream. It also revved up an entrance pump that transports amyloid beta into the brain. Both of these actions would increase the amount of amyloid beta protein in the brain."

Banks then gave mice indomethacin, which prevented inflammation from turning off the LRP (exit pump).

His findings help to explain what doctors who are studying the use of indomethacin to treat people with Alzheimer's disease are seeing in their clinical practice.

"Nonsteroidal anti-inflammatory drugs, especially indomethacin, have been associated with protection against Alzheimer's disease. Our work could influence that debate and thinking at the patient-care level," Banks said.

Link between migraines and reduced breast cancer risk confirmed in follow-up study

SEATTLE – The relationship between migraine headaches in women and a significant reduction in breast cancer risk has been confirmed in a follow-on study to landmark research published last year and conducted by scientists at Fred Hutchinson Cancer Research Center. The new study found a 26 percent reduced risk of breast cancer among both premenopausal and postmenopausal women with a clinical diagnosis of migraines.

The study appears in the July 2009 issue of Cancer Epidemiology, Biomarkers and Prevention, a journal of the American Association for Cancer Research. It was led by Christopher I. Li, M.D., Ph.D., a breast-cancer epidemiologist and associate member of the Hutchinson Center's Public Health Sciences Division. Li led the first-of-its-kind study linking migraines with breast cancer risk reduction that was published in the same journal last November.

This time researchers found that the risk reduction remained statistically similar regardless of a woman's menopausal status, her age at migraine diagnosis, use of prescription migraine medications or whether she avoided known migraine "triggers" such as alcohol consumption, smoking and taking hormone replacements. These triggers are also well-established breast cancer risk factors.

Some key differences between this study and the initial one that discovered the link include:

* The sample size was more than four times larger this time – more than 4,500 cases and controls versus about 1,000 each in the first study – and was more diverse geographically, drawing women from five metropolitan areas instead of only one. "From an epidemiological perspective, having a larger and more diverse study in its underlying population helps in replicating the finding," Li said.

* The age range of women studied was wider this time, 34-64 years of age versus 55-74 years old. "We were able to look at whether this association was seen among both pre-menopausal and post menopausal women," Li said. "In breast cancer this is relevant because there are certain risk factors that are different between older and younger women. In this study we saw the same reduction in breast cancer risk associated with a migraine history regardless of age."

* Researchers were able to ascertain whether women in the study had lifestyle behaviors that are known migraine triggers – alcohol consumption, smoking and taking hormone replacement therapy. Researchers posited that perhaps women who had migraines drank and smoked less and didn't take hormone replacements. "But in this study we looked at women who never drank, never smoked and who also didn't use hormones and found the same association within each of those groups, suggesting that the association between migraine and reduced breast cancer risk may be independent of those other factors and may stand alone as a protective factor," he said.

What remains unknown is how migraine confers its apparent protection against breast cancer. "We know that migraine is definitely related to hormones and that's why we started looking at this in the first place," Li

said. "We have different ideas about what may be going on but it's unclear exactly what the biological mechanisms are."

In the meantime, research on migraines and breast cancer continues. Li and his colleagues are conducting a follow-up investigation among the women in the first study to determine the types, timing, intensity and severity of their migraines in hopes that the data may elicit additional clues.

And, the research group has submitted a third study for publication that found that the association between migraine and reduced breast cancer risk holds up independent of whether women with migraine took non-steroidal anti-inflammatory drugs such as aspirin and ibuprofen. Earlier studies linked these medications to reduced breast cancer risk as well.

New oral agents may prevent injury after radiation exposure

(Boston) – Researchers from Boston University School of Medicine (BUSM) and collaborators have discovered and analyzed several new compounds, collectively called the "EUK-400 series," which could someday be used to prevent radiation-induced injuries to kidneys, lungs, skin, intestinal tract and brains of radiological terrorism victims. The findings, which appear in the June issue of the Journal of Biological Inorganic Chemistry, describe new agents which can be given orally in pill form, which would more expedient in an emergency situation.

These agents are novel synthetic "antioxidants" that protect tissues against the kind of damage caused by agents such as "free radicals." Free radicals, and similar toxic byproducts formed in the body, are implicated in many different types of tissue injury, including those caused by radiation exposure. Often, this kind of injury occurs months to years after radiation exposure. The BUSM researchers and their colleagues are developing agents that prevent injury even when given after the radiation exposure.

This paper describes a newer class of compounds, the "EUK-400 series," that are designed to be given as a pill. According to the researchers, experiments described in their paper prove that these agents are orally active. They also show that the new agents have several desirable "antioxidant" activities, and protect cells in a "cell death" model.

These same BUSM researchers and collaborators had previously discovered novel synthetic antioxidants that effectively mitigate radiation injuries, but had to be given by injection. "We have developed some of these agents and have studied them for over 15 years beginning with our work at the local biotechnology company Eukarion," said senior author Susan Doctrow, PhD, a research associate professor of medicine at BUSM's Pulmonary Center. "These injectible antioxidants are very effective, but there has also been a desire to have agents that can be given orally. A pill would be more feasible than an injection to treat large numbers of people in an emergency scenario," she adds.

Future studies will focus on the EUK-400 compounds' effects in various experimental models for radiation injury. Data showing their benefits in models for radiation injury in blood vessel cells have been presented at two major scientific conferences and will be the topic of future publication. More broadly, beyond the potential for treating victims of radiological terrorism, these compounds could also be useful drugs against a variety of diseases where an effective antioxidant has potential benefits, for example, various neurological, pulmonary, cardiovascular, and autoimmune disorders. Previously, Doctrow's lab and others have published studies showing that the injectible versions of these compounds are beneficial in models for several such diseases.

Funding for this study was provided by the U.S. Centers for Medical Countermeasures Against Radiation (CMCR) program, administered by National Institute of Allergy and Infectious Diseases. The study was initiated with CMCR "Pilot Grant" funding awarded to Dr. Rosalind Rosenthal, first author of the paper and currently a research associate at BUSM. Doctrow's laboratory at BUSM is a member of a five-institution CMCR program, based at the Medical College of Wisconsin in Milwaukee.

Losing sight of people in a crowd can spell disaster, warns new report

Focusing on technology instead of people is a key factor in events going wrong, according to a major series of reports into crowd behaviour and management, published this week.

Compiled for the Cabinet Office by researchers from two centres within Leeds University Business School (COSLAC and CSTSD), the reports also claim that over-reliance on technical and IT solutions means we fail to learn the lessons from past disasters.

The Understanding Crowd Behaviours reports are the first to bring together sociological and psychological research on events and crowd behaviour, reviewing over 550 academic papers and drawing on in-depth interviews with 27 specialists in the field (police, emergency planners and event managers) to produce detailed guidelines for event organisers. The findings will be of use to all those managing events involving large numbers of people and are particularly timely in the run up to 2012.

The reports are available on the Cabinet Office UK Resilience website (http://www.cabinetoffice.gov.uk/ukresilience/news/crowd-behaviour.aspx).

The researchers cite the recent debacle at the opening of Heathrow's Terminal Five as a prime example of a situation where faith in the power of new software and other technology meant that the importance of people – in this case, training and familiarisation in the new building and systems and involving those on the front line in decision making – was overlooked.

Researcher in Organisational Psychology, Rose Challenger, and colleagues Professor Chris Clegg and Mark Robinson, believe that an approach which treats technical and sociological/ psychological considerations in parallel – known in organisational psychology as a 'systems approach' – is the best preparation for a crowd event. It would also, they believe, help us learn lessons from previous mistakes.

"A systems approach is widely seen as best practice in organisational management, particularly in managing change – and is clearly applicable in crowd and event management as well," says Challenger, who led the research. "Technical solutions will give you the engineering calculations to determine the ideal width of exits but you need to tie that in with understanding how people will behave and use those exits in given situations and how you will communicate with people in an emergency to ensure best use of them.

"Believing new technology can be the answer to all problems means we are more likely to overlook basic lessons from past events. For example, what happened at the Kings Cross Underground fire is unsurprising given all that is known about human psychology and behaviour from existing research."

In the reports, the team highlights gaps in knowledge and areas where further research is needed, including more detailed analysis of the different types of crowd and their behaviour and better simulation models which take the complexity of behaviour into account.

Also identified is a need for more sophisticated risk assessment tools, which can ensure a full range of 'what if' scenarios are taken into account. The reports highlight how the chaos at Terminal Five was caused not because of one major failure, but when lots of smaller and otherwise manageable problems had a cumulative effect.

"There can be a tendency when planning events to prepare for the big dramatic 'what ifs' but ignore the smaller, less visible although more likely ones which collectively can cause serious problems," says Challenger. "It's important to ensure your risk assessment isn't blinkered. For example, at Hillsborough there was an over emphasis on hooliganism as that was the big issue of the day, but other more generic safety issues were overlooked. Today, we may tend to focus on the risk of a terrorist attack and ignore more banal risks such as power or transport failures or a gas leak."