Social amoeba seek kin association

HOUSTON –Starving "social amoebae" called Dictyostelium discoideum seek the support of "kin" when they form multi-cellular organisms made up of dead stalks and living spores, said researchers from Baylor College of Medicine and Rice University in Houston in a report that appears online today in the open-access journal Public Library of Science Biology.

"In fact, these single cells aggregate based on genetic similarity, not true kinship," said Dr. Gad Shaulsky, professor of molecular and human genetics at BCM. However, it demonstrates a discrimination between "self" and "non-self" that is similar to that seen in the immune systems of higher organisms, he said.

Dictyostelium discoideum begins as a single-celled organism. As long as these single cells have sufficient food and a pleasant environment, they are happy to remain that way. However, when food supplies run low, they first move toward one another to form an aggregate. Eventually the aggregate forms a multi-cellular organism made up of spores that can survive and reproduce, and dead cells that form a stalk. The stalk to spore ratio is about one to four.

"Cooperation is one of the success stories of the evolution of life," said Dr. Joan Strassmann, professor and chair of ecology and evolutionary biology at Rice, "Part of that success involves allowing cooperation in a way that controls conflict. One of the best ways to control conflict is cooperating with genetically similar individuals."

This kind of work is important in understanding biofilms, colonies of bacteria or fungi that can harm humans and other mammals, she said. For example, people with cystic fibrosis are vulnerable to the formation of biofilms that can damage the lungs.

In previous work, the collaborators found that Dictyostelium cells sometimes "cheat" by avoiding the deadly stalk pathway, thereby increasing the chances that their genes will be reproduced in future generations.

In this work, they determined that while cheating is still a possibility, the aggregation by genetic similarity reduces the likelihood that the stalk cells will "die" for a genetically distant individual.

"It's not exclusive," said Shaulsky, "but it's a preference. In that context, what are the benefits of cooperating versus the risks? By segregating, they minimize the risk that cells of their genetic similarity will die.'

In the laboratory, the scientists mixed cells from genetically distinct strains and found that they segregate into clusters of genetically similar "kin" after they have aggregated into the multi-cellular form.

"It's as much a self, non-self mechanism as anything," said Strassmann. "The more distant you are genetically, the more able you are to trigger the non-self recognition."

Dr. Elizabeth Ostrowski, a post-doctoral researcher in the Strassmann/(Dr. David) Queller laboratory at Rice and first author on the report, said, "We knew that Dictyostelium was unusual in that it brings different genotypes together in the multi-cellular organism. These results suggest that these organisms also have mechanisms to limit the levels of genetic diversity in the multi-cellular organism." A human's cells, for example, have the same genome everywhere in the body because humans begin development as a single cell.

This kind of work shows the strength of Dictyostelium as a model for understanding other multi-cellular organisms, she said. "What role does this discrimination for genetic similarity play in the ability of organisms to become multi-cellular?" she said.

"The big thing we found is that Dictyostelium discoideum have social behavior," said Dr. Mariko Katoh, an instructor in molecular and human genetics at BCM and the other first author on the report. "We didn't really know if they could discriminate when the genetic differences were small. That was the surprising part."

In the future, the scientists plan to determine the molecular mechanisms behind the aggregation phenomenon.

Queller also took part in this research. Funding for this research came from the National Science Foundation.
http://biology.plosjournals.org/perlserv/?request=index-html&issn=1545-7885

14 drugs identified as most urgently needing study for off-label use, Stanford professor says

STANFORD, Calif. — Physicians and policy-makers know that drugs are frequently prescribed to treat certain diseases despite a lack of FDA approval — a practice known as off-label prescribing. Yet they say the problem is so big they don't know how to begin tackling it.

But a potential game plan now exists. In a paper to be published in the December issue of Pharmacotherapy, a group of researchers has developed a list of 14 widely prescribed medications most urgently in need of additional study to determine how effective and safe they are for their off-label uses. Antidepressants and antipsychotics are the most prominent classes of drugs on the list, which specifically targets drugs that have high levels of off-label use without good scientific backing.

"Off-label prescribing means that we're venturing into uncharted territory where we lack the usual level of evidence presented to the FDA that tells us these drugs are safe and effective," said Randall Stafford, MD, PhD,

associate professor of medicine at the Stanford Prevention Research Center, who is the senior author of the study. "This list of priority drugs might be a start for confronting the problem of off-label use with limited evidence."

Stafford collaborated on the research with lead author Surrey Walton, PhD, assistant professor of pharmacy administration at the University of Illinois-Chicago, and other researchers at UIC and the University of Chicago.

At the top of the list was quetiapine (brand name Seroquel), an antipsychotic approved by the U.S. Food and Drug Administration in 1997 for treating schizophrenia. Not only did this drug lead all others in its high rate of off-label uses with limited evidence (76 percent of all uses of the drug), it also had features that raised additional concerns, including its high cost at $207 per prescription, heavy marketing and the presence of a "black-box" warning from the FDA, Stafford said.

Rounding out the top five were warfarin, escitalopram, risperidone and montelukast.

The most common off-label use for six of the 14 drugs on the list was for bipolar disorder. "Many of the drugs and the conditions on the list represent situations where inadequate response to treatment is common and where drug side-effects are frequent," Stafford said. "Not only are these areas where patients and physicians are naturally interested in trying off-label therapies, but areas targeted for expansion by the makers of these drugs.

"When the volume of off-label use of any drug reaches the magnitude that we're documenting, it suggests a role of the pharmaceutical industry in facilitating these types of uses," he added.

Although companies are largely prohibited from marketing off-label uses to physicians and consumers, they make use of exceptions or may market drugs illegally, Stafford said. Companies are allowed to share with physicians any published research that supports off-label uses. Several recent lawsuits have identified systematic plans on the part of some companies to market their products for off-label uses, he noted.

Previous studies have demonstrated the breadth of off-label prescribing. A 1985 study found that of the 100 most common uses of marketed drugs, 31 of those uses did not have approval from the FDA. And a study that Stafford led in 2006 showed that of the estimated 21 percent of off-label drug uses in 2001, 73 percent did not have strong scientific support.

To get a drug approved by the FDA, a pharmaceutical company must complete three rounds of testing in human subjects to demonstrate its safety and effectiveness in treating a specific condition. Once a drug is approved and on the market, though, physicians may choose to prescribe it for any condition. But this carries unknown risks because often the drug hasn't been rigorously tested on patients with that condition.

"Many patients and physicians assume that the FDA has scrutinized all of the different ways a drug can be used, but they've only examined those uses that have gone through the approval process," Stafford said.

And pharmaceutical companies aren't often interested in spending money to investigate additional conditions that the drug might treat. Stafford said the companies may consider it risky to invest in additional testing that could show undesired results, especially when a drug is already widely used off-label.

To come up with a plan for determining which drugs were most in need of additional research for off-label use, Stafford and his colleagues convened a panel of nine experts from the FDA, the health-insurance industry, the pharmaceutical industry and academia. Based on the panel's input, the researchers identified three factors to help them prioritize the drugs that should appear on the list, including:

* The volume of off-label drug use with inadequate evidence supporting that use (based on a large, ongoing national survey of physician prescribing patterns conducted by IMS Health, a private market-research company).
* The safety of the drug (based on any safety warnings issued by the FDA).
* A composite of the drug's cost, how long it had been on the market and the amount spent marketing the drug.

After collecting the information, the researchers computed the drug rankings in each category and then came up with an overall list of the 14 drugs most in need of additional study. "Despite examining the data in a variety of ways by providing more or less emphasis on certain factors, we still came up with a very consistent list of drugs," Stafford said.

He said that in addition to prompting the FDA and other government agencies to study the priority drugs on the list, he hopes the research spurs patients to ask their doctors why they are prescribing a particular drug. "A dialogue needs to occur more frequently between physicians and patients regarding the level of evidence that supports a particular use of a drug."

Stafford also noted the societal costs associated with off-label drug use. With the prescription drug benefit now available through Medicare, taxpayers are getting the bill for costly drugs that may not be proven for the conditions they're prescribed to treat.

A link to the study can be found at the URL below:http://www.eurekalert.org/images/release_graphics/pdf/off-label-chart.pdf
The study was funded by the U.S. Agency for Healthcare Research and Quality.

ACTs may achieve malaria transmission reductions comparable to insecticide treated nets

In low-transmission areas, if widely used, artemisinin combination therapy (ACT) may reduce malaria transmission as effectively as the widespread use of insecticide-treated bed nets, says a new study published in next week's PLoS Medicine. The study also finds that the use of longer-acting anti-malarial regimens with or without artemisinin components may be an effective way to reduce transmission in high-transmission areas, provided the development of parasite resistance can be avoided. Lucy Okell and colleagues from the London School of Hygiene & Tropical Medicine present a mathematical model that predicts the impact on Plasmodium falciparum malaria transmission of the introduction of ACT and alternative first-line treatments for malaria in six regions of Tanzania with different levels of malaria transmission.

Using data from a survey of 5700 residents in Tanzania prior to the introduction of ACT, the model predicts that the relative reduction in malaria prevalence and incidence associated with a 100% switch to a short-acting ACT would be greater in areas with low initial transmission rates than in areas with high transmission rates. For example, in the area with the lowest initial transmission rates, the model predicted that the prevalence of infection would drop by 53%, but in the area with the highest initial transmission rate, the drop would be only 11%. However, because more people get malaria in high-transmission areas, the total number of malaria illness episodes prevented would be ten times higher in the area with highest transmission than in the area with lowest transmission. Using a long-acting ACT is predicted to have more effect on transmission than using a short-acting ACT, particularly in the high transmission areas. For example, the drop in the prevalence of infection in the area with highest initial transmission rates is estimated to be 36% with a long-acting ACT.

The authors say that with the renewed interest in minimizing transmission and moving toward malaria elimination, "it is increasingly important to evaluate the ability of antimalarial treatments not only to cure disease, but also to reduce transmission," as well as to maximize available resources. Their findings suggest that best public health control measures should take the properties of anti-malarial drugs into account together with the levels of transmission in the area when designing treatment policies in order to achieve the highest impact on malaria transmission.

In a related Perspective article, Maciej Boni from Oxford University and colleagues (not involved in the research) describe the importance of mathematical modeling for long-term planning of malaria control and elimination, but caution that future predictive models must take account of the potential for drug resistance. "If we can secure sustained adequate funding, and overcome all the political and operational obstacles," the authors say, "then the evolution of mosquito resistance to current insecticides and parasite resistance to current ACTs are the greatest dangers we face in our current attempts to control malaria. Mathematical modeling is an important tool for developing strategies to contain the threat of resistance."

Citation: Okell LC, Drakeley CJ, Bousema T, Whitty CJM, Ghani AC (2008) Modelling the impact of artemisinin and long-acting therapies on malaria transmission intensity. PLoS Med 5(11): e226. doi:10.1371/journal.pmed.0050226
http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050226

New study finds publication bias among trials submitted to FDA

A quarter of drug trials submitted in support of new drug applications to the US Food and Drug Administration (FDA) remain unpublished five years after the fact, says new research published in the open access journal PLoS Medicine. Among those trials published, unexplained discrepancies between the FDA submissions and their corresponding publications—the addition or deletion of outcomes, changes in the statistical significance of reported outcomes, and changes in overall trial conclusions—tended to lead to more favorable presentations of the drugs in the medical literature available to health care professionals.

Lisa Bero and colleagues from the University of California San Francisco reviewed the publication status of all 164 efficacy trials carried out in support of the 33 new drug applications (NDA) for new molecular entities approved by the FDA in 2001, and compared information from the FDA reviews with published journal articles. Seventy-eight percent of the trials were published. Trials with favorable outcomes for the drugs were more likely to be published as those without favorable outcomes. Of a total of 179 primary outcomes included in the NDAs, 41 were omitted from the papers. The papers included 138 outcomes that were also in the NDAs (77%), plus 15 additional outcomes that favored the test drug, and two other neutral or unknown additional outcomes. Thus, the papers included more outcomes favoring the test drug than did the NDAs, report the authors.

The research also found additional discrepancies between the FDA reviews and the published papers. Of the 43 primary outcomes reported in the NDAs that showed no statistically significant benefit for the test drug, only half were included in the papers; for five of the reported primary outcomes, the statistical significance differed between the NDA and the paper and generally favored the test drug in the papers. Nine out of 99 conclusions differed between the NDAs and the papers; each time, the published conclusion favored the test drug. The

authors did not investigate why the discrepancies existed, nor whether the changes were prompted by the drug sponsor, authors, or journals.

Because of their findings of publication bias and selective reporting, the authors conclude that "the information that is readily available in the scientific literature to health care professionals is incomplete and potentially biased."

In a commentary on the research, An-Wen Chan from the Mayo Clinic in Rochester (uninvolved in the study) says this new research makes an important contribution to the growing body of evidence that the trial literature is skewed towards reporting favorable results. "Biased reporting of results from NDA trials is particularly concerning because these journal articles are the only peer reviewed source of information on recently approved drugs for health care providers, who will have had limited clinical experience with these new treatments," Dr Chan says. "There are also substantial cost implications if the efficacy is overestimated and the drugs overused."

Before a new drug is approved for the treatment of a specific disease in the United States and becomes available for doctors to prescribe, the drug's sponsors must submit a "New Drug Application" (NDA) to the FDA, which provides details of the drug's development from laboratory and animal studies through to clinical trials. FDA reviewers use this evidence to decide whether to approve a drug.

Citation: Rising K, Bacchetti P, Bero L (2008) Reporting bias in drug trials submitted to the Food and Drug Administration: A review of publication and presentation. PLoS Med 5(10): e217. doi:10.1371/journal.pmed.0050217
http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050217

Mammograms may detect some cancers that would have otherwise regressed

Breast cancer rates increased significantly in four Norwegian counties after women there began undergoing mammography every two years, according to a report in the November 24 issue of Archives of Internal Medicine, one of the JAMA/Archives journals. Rates among regularly screened women remained higher than rates among women of the same age who were screened only once after six years, suggesting that some of the cancers detected by mammography may have spontaneously regressed had they not been discovered and treated.

Throughout Europe, the start of screening mammography programs has been associated with increased incidence of breast cancer, according to background information in the article. "If all of these newly detected cancers were destined to progress and become clinically evident as women age, a fall in incidence among older women should soon follow," the authors write. "The fact that this decrease is not evident raises the question: What is the natural history of these additional screen-detected cancers?"

Per-Henrik Zahl, M.D., Ph.D., of the Norwegian Institute of Public Health, Oslo, and colleagues examined breast cancer rates among 119,472 women age 50 to 64 who were all invited to participate in three rounds of screening mammograms between 1996 and 2001 as part of the Norwegian Breast Cancer Screening Program. They compared these to rates among a control group of 109,784 women age 50 to 64 in 1992, who would have been invited for screening if the program had existed at that time. Cancers were tracked for six years using a national registry, and at the end of that time all participants were invited to undergo a one-time screening to assess breast cancer prevalence.

As anticipated, breast cancer rates were higher among screened women than among the control group before the final prevalence screening. "Even after prevalence screening in controls, however, the cumulative incidence of invasive breast cancer remained 22 percent higher in the screened group," the authors write. Of every 100,000 screened women, 1,909 had breast cancer during the six-year period, compared with 1,564 of every 100,000 in the control group. Screened women were more likely to have breast cancer at every age.

"Because the cumulative incidence among controls never reached that of the screened group, it appears that some breast cancers detected by repeated mammographic screening would not persist to be detectable by a single mammogram at the end of six years," the authors write. "This raises the possibility that the natural course of some screen-detected invasive breast cancers is to spontaneously regress."

"Although many clinicians may be skeptical of the idea, the excess incidence associated with repeated mammography demands that spontaneous regression be considered carefully," they continue. "Spontaneous regression of invasive breast cancer has been reported, with a recent literature review identifying 32 reported cases. This is a relatively small number given such a common disease. However, as some observers have pointed out, the fact that documented observations are rare does not mean that regression rarely occurs. It may instead reflect the fact that these cancers are rarely allowed to follow their natural course."

The findings do not answer the question of whether mammograms prevent deaths from breast cancer, the authors note. "Instead, our findings simply provide new insight on what is arguably the major harm associated with mammographic screening, namely, the detection and treatment of cancers that would otherwise regress," they conclude.

Editorial: Results Emphasize Our Lack of Knowledge Regarding Cancer's Natural History

"Despite the appeal of early detection of breast cancer, uncertainty about the value of mammography continues," write Robert M. Kaplan, Ph.D., of the University of California, Los Angeles, and Franz Porzsolt, M.D., Ph.D., of Clinical Economics University of Ulm, Germany, in an accompanying editorial. "In this issue of the Archives, Zahl et al use a clever study design in an attempt to estimate the value of screening."

"Perhaps the most important concern raised by the study by Zahl et al is that it highlights how surprisingly little we know about what happens to untreated patients with breast cancer," Drs. Kaplan and Porzsolt continue. "In addition to not knowing the natural history of breast cancer for younger women, we also know very little about the natural history for older women. We know from autopsy studies that a significant number of women die without knowing that they had breast cancer (including ductal carcinoma in situ). The observation of a historical trend toward improved survival does not necessarily support the benefit of treatment."

"If the spontaneous remission hypothesis is credible, it should cause a major re-evaluation in the approach to breast cancer research and treatment. Certainly it is worthy of further evaluation," they conclude.

(Arch Intern Med. 2008;168[21]:2311-2316. Available pre-embargo to the media at www.jamamedia.org.)

Editor's Note: *This study was supported in part by a Research Enhancement Award from the Department of Veterans Affairs. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, funding and support, etc.(Arch Intern Med. 2008;168[21]:2302-2303. Available pre-embargo to the media at www.jamamedia.org.)*

Bacterial biofilms as fossil makers

BLOOMINGTON, Ind. -- Bacterial decay was once viewed as fossilization's mortal enemy but new research suggests bacterial biofilms may have actually helped preserve the fossil record's most vulnerable stuff -- animal embryos and soft tissues.

A team of 13 scientists led by Indiana University Bloomington biologists Rudolf and Elizabeth Raff found that the invasion of dying embryo cells by bacteria -- and the subsequent formation of densely packed bacterial biofilms inside the embryo cells -- can completely replace embryo cell structure, generating a faithful replica of the embryo. The scientists call this formation a "pseudomorph," a model of the embryo made of bacteria. Their report will appear online via the Proceedings of the National Academy of Sciences "Early Edition" as early as Nov. 24.

This early-stage embryo is protected by a fertilization envelope, seen here as a white line encircling the embryo cells.
E.C. Raff and R.A. Raff

"The bacteria consume and replace all the cytoplasm in the cells, generating a little sculpture of the embryo," said Elizabeth Raff, the report's lead author. "We did find, however, that certain conditions must be met if the bacteria are going to aid the preservation process."

Among those conditions, Raff said that at the time of its death, the embryo must exist in a low-oxygen or reducing environment, such as the bottom of a deep ocean or buried in anoxic lakeside mud. If significant oxygen is available, the embryo will undergo "autolysis," or self-destruction, as digestive enzymes get free and wreak havoc. Without oxygen, autolytic enzymes remain stuck inside their organelle prisons.

"The next step, we believe, is that bacteria able to survive in low-oxygen conditions must then infest the cells of the dying embryo," Raff said.

The bacteria form biofilms, crowded assemblies of bacterial cells held together by sticky fibers made of proteins and sugars. As the biofilms fill the embryo cells, the tiny bacteria insinuate themselves between and among the organelles, forming a faithful representation of the cell's innards.

Lastly, the bacteria must leave a permanent record. In the case of finely preserved fossil embryos, the bacteria likely excrete tiny crystals of calcium phosphate ($CaPO_4$), which eventually replace the bacterial sculptures. It is these crystals, Raff says, that provide the support for embryo and soft tissue fossilization.

"That's a crucial step," said Rudolf Raff. "Calcium deposits can show us even minute details of structure and shape, not only of the bacteria laying down the minerals, but also of the embryo cell structures all around them. In our experiments, we observed bacteria depositing calcium carbonate ($CaCO_3$), but not calcium phosphate. We'll need to simulate different conditions to fully replicate this step."

High resolution imaging of a trove of half-a-billion-year-old animal embryo fossils from Doushantuo, China, provided scientists with tantalizing evidence that bacteria may have been involved in the preservation of the delicate cells. Scanning electron microscopy shows oblong concavities on the surface of the embryo fossils, suggesting the cells had been infested with bacteria or bacterial biofilms.

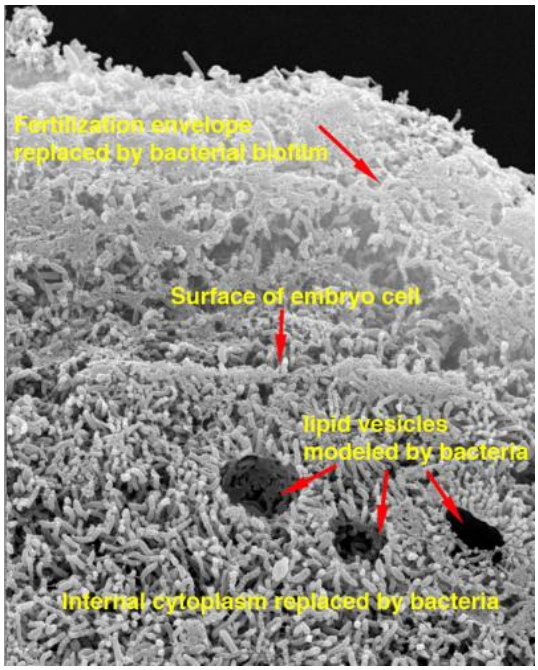
The research presented in the PNAS paper reveals how bacteria-aided fossilization could happen.

The Raffs studied early-stage embryos of two Australian sea urchin species, Heliocidaris erythrogramma and Heliocidaris tuberculata. The experimental results with modern embryos were compared to the high resolution images of fossil embryos prepared by colleagues from China, England, Sweden, and Switzerland.

The scientists examined embryos in the presence of high and low oxygen, with or without inoculums of oxygen-poor marine mud, and in the presence or absence of bacteria-killing antibiotics. In the experiments that produced embryo-infesting biofilms, the scientists used DNA sequence comparisons to identify the bacterial species present.

The researchers learned low-oxygen conditions block autolysis, and that embryos prevented from autolyzing are quickly colonized by marine bacteria. Once inside, the bacteria form biofilms that fill the embryo cells. Sturdy cell membranes and the embryo's fertilization envelope provide the exterior cast. These biofilms formed detailed replicas of the embryos they had replaced.

Species of the common marine bacterium Pseudoalteromonas provided the majority of the bacterial flora present inside the embryo cells under aerobic conditions. Under oxygen-poor conditions, a much greater diversity of bacterial species was present, not detectable under aerobic conditions.



The invasion of dying Heliocidaris erythrogramma cells by bacteria can create a faithful replica. Scientists believe embryo fossils are actually a bacterial "sculpture" -- a vestige of the embryos' destruction **F.R. Turner, E.C. Raff, and R.A. Raff**

The scientists also examined oxygen-starved embryos exposed to inoculums of oxygen-poor marine mud, and again found a high diversity of bacterial flora present in embryo replica biofilms, with species of the Bacteroidetes phylum being most common.

Although it is impossible to know whether bacteria aided the preservation of 550-million-year-old embryo fossils from Doushantuo and elsewhere, the Raffs argue the evidence they gathered strongly favors the view that bacteria are a fundamental force in fossil formation, as rapid biological processes must be available to convert highly delicate cells into a stable form and catalyse mineralization.

"This work is important because it helps us understand fossilization as a biological as well as geological process," Elizabeth Raff said. "It gives us a window onto the evolution of the embryos of the earth's first animals."

Kaila Schollaert, David Nelson, F. Rudolf Turner, Barry Stein (Indiana University Bloomington), Philip Donoghue, Ceri-Wyn Thomas (University of Bristol), Xiping Dong (Peking University), Stefan Bengtson (Swedish Museum of Natural History), Therese Huldtgren (Swedish Museum of Natural History and Stockholm University), Marco Stampanoni (Paul Scherrer Institute and Institute for Biomedical Engineering), and Yin Chongyu (Chinese Academy of Geological Scientists) also contributed to this report. The Raffs' research was supported largely by Indiana University.

Gasping helps cardiac arrest victims survive

Gasping should not be mistaken for breathing and CPR should be initiated

People who witness an individual collapse suddenly and unexpectedly should perform uninterrupted chest compressions even if the patient gasps or breathes in a funny way, research from the Resuscitation Research Group at The University of Arizona Sarver Heart Center shows. The study is set to publish in the Nov. 24 online issue of Circulation, the official journal of the American Heart Association, http://circ.ahajournals.org. When an individual breathes abnormally or gasps after collapsing from sudden cardiac arrest there is a greater chance of surviving, the researchers report. Gasping can be thought of as a survival reflex triggered by the brain. Each day, about 500 Americans collapse because their hearts suddenly stop beating. Data collected by Sarver Heart Center researchers show that in more than half of witnessed cardiac arrest cases, the patient gasped.

"Gasping is an indication that the brain is still alive, and it tells you that if you start and continue uninterrupted chest compressions, the person has a high chance of surviving," said Gordon A. Ewy, MD, corresponding author of the study, professor and chief of cardiology at the UA and director of its Sarver Heart Center. "We need people to promptly recognize sudden cardiac arrest, to call 9-1-1 and to start chest compressions right away."

Gasping has been described as snoring, gurgling, moaning, snorting or agonal or labored breathing. However, bystanders often misinterpret gasping and other unusual vocal sounds as normal breathing and don't call 9-1-1 or begin lifesaving chest compressions quickly enough, Dr. Ewy said.

The authors hope their findings lead to greater willingness of untrained bystanders to jump in and perform continuous chest compressions. Bystander-initiated CPR has been shown to be a cardiac arrest victim's only chance of survival until an automated external defibrillator or the paramedics get to the scene.

Many bystanders are hesitant to perform mouth-to-mouth ventilation, and in a case of a witnessed (seen or heard) collapse, so-called rescue breathing is not necessary and may be harmful, Dr. Ewy said. "When the patient gasps, there is a negative pressure in the chest, which not only sucks air into the lungs but also draws blood back to the heart. In contrast, mouth-to-mouth breathing creates overpressure in the chest and actually inhibits blood flow back to the heart. Gasping during cardiac arrest is much better than mouth-to-mouth breathing."

But what about choking? "That's very different," Dr. Ewy said. "Someone who is choking will be seen to grasp their throat and struggle to breathe, which means they're responsive. These individuals need the Heimlich maneuver." A primary cardiac arrest is the witnessed unexpected collapse of an individual who is not responsive, Dr. Ewy said. "Cardiac arrest will cause the stricken individual to pass out and collapse to the ground within seconds."

The Arizona researchers examined data from two sources. Transcripts from the Phoenix Fire Department Regional Dispatch Center included information on gasping in patients found by bystanders, whether their collapse was witnessed or not. The department's first-care reports on 1,218 witnessed patients provided the incidence of gasping upon or after the arrival of emergency medical service (EMS) personnel. Among the 481 patients who received bystander CPR, 39 percent of gaspers survived, but only 9.4 percent of those who didn't gasp survived.

Performing uninterrupted chest compressions (a technique developed at the UA Sarver Heart Center and endorsed by the American Heart Association as "Hands-Only CPR" for lay individuals) may cause a person who has stopped gasping to resume gasping. "This scares many people and they stop pressing on the chest," Dr. Ewy said, "This is bad because gasping is an indication that you're doing a good job."

The authors of the study are: Bentley J. Bobrow, MD; Mathias Zuercher, MD; Gordon A. Ewy, MD; Lani Clark, BS; Vatsal Chikani, MPH,; Dan Donahue BS, NREMT-P, Arthur B. Sanders, MD; Ronald W. Hilwig, DVM; Robert A. Berg, MD; and Karl B. Kern, MD.

The study was funded in part by a grant from the Arizona Department of Health Services Bureau of Emergency Medical Services.

Important note: Experts continue to promote a combination of rescue breathing and chest compressions for victims of cardiac arrest due to non-cardiac causes, like near drowning or electrocution, and all victims of pediatric cardiac arrest.

Los Alamos Observatory Fingers Cosmic Ray 'Hot Spots'

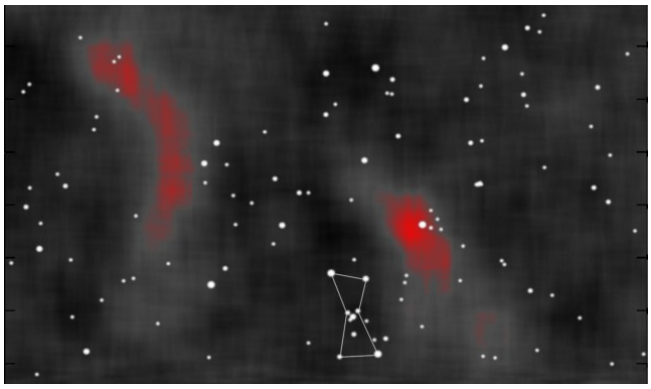
Milagro Observatory unveils something never before seen from Earth

Contact: James E. Rickman, elvis@lanl.gov, (505) 665-9203 (04-391)

LOS ALAMOS, N.M., November 24, 2008 — A Los Alamos National Laboratory cosmic-ray observatory has seen for the first time two distinct hot spots that appear to be bombarding Earth with an excess of cosmic rays. The research calls into question nearly a century of understanding about galactic magnetic fields near our solar system.

Joining an international team of collaborators, Los Alamos researchers Brenda Dingus, Gus Sinnis, Gary Walker, Petra Hüntemeyer and John Pretz published the findings today in Physical Review Letters.

"The source of cosmic rays has been a 100-year-old problem for astrophysicists," Pretz said. "With the Milagro observatory, we identified two distinct regions with an excess of cosmic rays. These regions are relatively tiny bumps on the background of cosmic rays, which is why they were missed for so long. This discovery calls into question our understanding of cosmic rays and raises the possibility that an unknown source or magnetic effect near our solar system is responsible for these observations."



Cosmic rays are high-energy particles that move through our Galaxy from sources far away. No one knows exactly where cosmic rays come from, but scientists theorize they might originate from supernovae - massive stars that explode - from quasars or perhaps from other exotic, less-understood or yet-to-be-discovered sources within the universe.

An international team of researchers, using Los Alamos National Laboratory's Milagro observatory, has seen for the first time two distinct hot spots that appear to be bombarding Earth with an excess of cosmic rays. The hot spots were identified in the two red-colored regions near the constellation Orion. **Credit: courtesy John Pretz, P-23**

Researchers used Los Alamos' Milagro cosmic-ray observatory to peer into the sky above the northern hemisphere for nearly seven years starting in July 2000. The observatory is unique in that it monitors the entire sky above the northern hemisphere. Because of its design and field of view, Milagro was able to record over 200 billion cosmic-ray collisions with the Earth's atmosphere.

"Our observatory is unique in that we can detect events of low enough energies that we were able to record enough cosmic-ray encounters to see a statistically significant fractional excess coming from two distinct regions of the sky," Dingus said.

Because cosmic rays are charged particles, magnetic fields from the Milky Way and our solar system change the flight paths of the particles so much that researchers had not been able to pinpoint their exact origin. Consequently, traditional wisdom has held that cosmic-ray events appear uniformly throughout the sky.

But because Milagro was able to record so many cosmic-ray events, researchers for the first time were able to see statistical peaks in the number of cosmic-ray events originating from specific regions of the sky near the constellation Orion. The region with the highest hot spot of cosmic rays is a concentrated bulls eye above and to the right visually of Orion, near the constellation Taurus. The other hot spot is a comma-shaped region visually occurring near the constellation Gemini.

The researchers created a graphic depiction of the hot spots that makes them appear as a pair of red cosmic rashes in a field of stars.

Milagro scientists are currently working with researchers in Mexico to build a second-generation observatory known as the High-Altitude Water Cherenkov (HAWC) experiment. If built, the HAWC observatory could help researchers solve the mystery of cosmic-ray origin.

In addition to the Los Alamos Milagro team, collaborators include nearly three dozen researchers from the following institutions: Naval Research Laboratory; University of California-Santa Cruz; University of Maryland; University of California-Irvine; George Mason University; New York University; Instituto de Astronomia, Universidad Nacionál Autonoma de Mexico; Michigan State University; NASA Goddard Space Flight Center; University of New Hampshire.
Funding for the research came from the U.S. Department of Energy's Office of High-Energy Physics and Office of Nuclear Physics; Los Alamos National Laboratory's Laboratory-Directed Research and Development fund and the Laboratory's Institute for Geophysics and Planetary Physics; and the National Science Foundation.

A scientific breakthrough on the control of the bad cholesterol

Montréal, November 24, 2008 – A study performed by the team of Dr. Nabil G. Seidah, Director of the Biochemical Neuroendocrinology Research Unit at the IRCM, shows for the very first time that the degradation by PCSK9 of the LDLR receptor, which is responsible for removing the bad cholesterol (LDL-cholesterol) from the bloodstream, may be inhibited by a third protein, annexin A2. This major discovery co-authored by Gaétan Mayer, a postdoctoral fellow, Steve Poirier, a doctoral student, and Dr. Seidah was published on November 14 in the Journal of Biological Chemistry (JBC).

Genetic studies on humans have clearly shown that PCSK9 is a prime therapeutic target for the prevention and treatment of cardiovascular diseases. PCSK9 proprotein convertase promotes the degradation of the receptor responsible for eliminating LDL-cholesterol particles. Thus, the presence of PCSK9 leads to a surplus of bad cholesterol in the bloodstream and contributes to plaque formation, leading to blockage of blood vessels and arteries. This phenomenon is a major risk factor that can lead to cardiovascular diseases, such as heart attack, atherosclerosis and stroke. Mutations of human genes have demonstrated that a rise in PCSK9 activity results in a major increase in LDL-cholesterol and familial hypercholesterolemia. Conversely, in people with a non-functional mutation in the gene coding for PCSK9, a decrease in its activity brings down the LDL-cholesterol concentration levels in the bloodstream and diminishes by up to 88% the risks of developing cardiovascular diseases.

"By performing a series of biochemical experiments, we discovered that annexin A2 binds strongly to PCSK9 and inhibits its function," remarks Gaétan Mayer, the article's first author. This discovery should pave the way toward the development of a new drug that would lower blood cholesterol to recommended levels. Currently, cholesterol lowering drugs known as "statins" are used by more than 25 million people worldwide. Statins decrease cholesterol synthesis and increase the number of LDL-receptors, thus efficiently decreasing plasma cholesterol levels; however, they also increase the amount of PCSK9, which degrades those receptors, thus reducing the effect of statins. A drug that would block PCSK9 could either be used alone or jointly with statins and would be highly beneficial to patients in whom statins do not work or are unable to take this drug.

This work was supported by the Canadian Institutes of Health Research (CIHR) and by a Canada Research Chair.
Reference: Mayer G, Poirier S, and Seidah NG. (2008) Annexin A2 is a C-terminal PCSK9-binding protein that regulates endogenous low density lipoprotein receptor levels. J Biol Chem, November 14; 283(46): 31791-801.
The on-line version of this article is available at: www.jbc.org/content/vol283/issue46/index.shtml.

Adult brain neurons can remodel connections

Could lead to creating growth in cells and regions normally unable to repair themselves

By Deborah Halber, Picower Institute

CAMBRIDGE, Mass. — Overturning a century of prevailing thought, scientists are finding that neurons in the adult brain can remodel their connections. In work reported in the Nov. 24 online edition of the Proceedings of the National Academy of Sciences (PNAS), Elly Nedivi, associate professor of neurobiology at the Picower Institute for Learning and Memory, and colleagues found that a type of neuron implicated in autism spectrum disorders remodels itself in a strip of brain tissue only as thick as four sheets of tissue paper at the upper border of cortical layer 2.

"This work is particularly exciting because it sheds new light on the potential flexibility of cerebral cortex circuitry and architecture in higher-level brain regions that contribute to perception and cognition," said Nedivi, who is also affiliated with MIT's departments of brain and cognitive sciences and biology. "Our goal is to extract clues regarding the contribution of structural remodeling to long-term adult brain plasticity — the brain's ability to change in response to input from the environment — and what allows or limits this plasticity."

In a previous study, Nedivi and Peter T. So, professor of mechanical engineering and biological engineering at MIT, saw relatively large-scale changes in the length of dendrites — branched projections of nerve cells that conduct electrical stimulation to the cell body. Even more surprising was their finding that this growth was limited to specific type of cell. The majority of cortical neurons were stable, while the small fraction of locally connecting cells called interneurons underwent dynamic rearrangement.

In the current study, they show that the capacity of interneurons to remodel is not predetermined by genetic lineage, but imposed by the circuitry within the layers of the cortex itself. "Our findings suggest that the location of cells within the circuit and not pre-programming by genes determines their ability to remodel in the adult brain," Nedivi said. "If we can identify what aspect of this location allows growth in an otherwise stable brain, we can perhaps use it to coax growth in cells and regions that are normally unable to repair or adjust to a changing environment.

"Knowing that neurons are able to grow in the adult brain gives us a chance to enhance the process and explore under what conditions we can make it happen," Nedivi said. "In particular, we need to pay more attention to the unique interneuron population that retains special growth features into adulthood."

In addition to Nedivi and So, authors are Brain and Cognitive Sciences graduate student Wei-Chung Allen Lee; *Biology graduate students Jennifer H. Leslie and Jerry L. Chen; MIT research affiliate Hayden Huang; and Yael Amitai of Ben-Gurion University in Israel. This work is supported by the National Eye Institute.*

Researchers identify new leprosy bacterium

M. D. Anderson scientists use genetic fingerprint to nail 'killing organism'

HOUSTON - A new species of bacterium that causes leprosy has been identified through intensive genetic analysis of a pair of lethal infections, a research team reports in the December issue of the American Journal of Clinical Pathology.

All cases of leprosy, an ancient disease that still maims and kills in the developing world, previously had been thought to be caused by a single species of bacterium, said lead author Xiang-Yang Han, M.D., Ph.D., associate professor in Laboratory Medicine at The University of Texas M. D. Anderson Cancer Center.

"We have identified a second species of leprosy mycobacterium, and in identifying this killing organism we've better defined the disease that it causes, diffuse lepromatous leprosy (DLL)." Han said. DLL occurs mainly in Mexico and the Caribbean.

There are hundreds of thousands of new cases of leprosy worldwide each year, but the disease is rare in the United States, with 100-200 new cases annually, mostly among immigrants. Leprosy initially attacks skin and nerve cells. It can be successfully treated with antibiotics in its early and intermediate stages.

R. Geetha Nair, M.D., a physician with Maricopa Integrated Health System in Phoenix, contacted Han in 2007 for help confirming a possible leprosy diagnosis in a patient who died that February.

The patient, a 53-year-old man originally from Mexico, was admitted that month for treatment of extensive leg wounds. While undergoing antibiotic treatment and additional diagnostic testing the next day, he was stricken with high fever and shock. He died after 10 days in intensive care.

Analysis of autopsied tissue at the Phoenix hospital suggested a diagnosis of diffuse lepromatous leprosy, a form first described in Mexico in 1852. Han said DLL uniquely attacks a patient's skin vasculature, blocking or impeding blood flow. This leads to extensive skin death at late stage and may cause secondary infection and fatal shock. The DLL bacterium had never been studied.

The research team also analyzed samples from a similar lethal case of a 31-year-old man in 2002 with so much skin damage that he was first admitted to a hospital burn unit.

Telltale fingerprint points to new species

Han and M. D. Anderson colleagues diagnose infections in cancer patients. Han developed in 2002 a way to identify unusual bacteria by analyzing small but significant differences in the 16S ribosomal RNA gene. "This is like a fingerprint analysis to solve crimes," Han said. He has discovered and named several new bacterial species that cause unusual infections.

Across a group of bacteria called mycobacteria, the 16S rRNA gene is 93 to 100 percent identical. There are 110 species of mycobacteria, with those causing tuberculosis and leprosy the best known. Sequencing the 16S rRNA gene is a fast and accurate way to identify mycobacteria, which usually grow slowly, Han noted. Accurate identification improves patient care decisions.

Han and colleagues compared the lethal bacterium's 16S rRNA gene and five other genes to other mycobacteria. They found that the bacterium had the most in common with Mycobacterium leprae, previously thought to be the sole cause of leprosy.

Yet there were also significant differences with M. leprae. The lethal bacterium's 16S rRNA gene sequence differed by 2.1 percent. "That may sound like a small difference, but to anyone familiar with mycobacteria, it's huge," Han said. In all previously studied M. leprae strains, no variation in the 16S rRNA gene had been noted at all.

Analysis of the other five genes turned up more differences. The researchers named the new species Mycobacterium lepromatosis. They have since confirmed M. lepromatosis as the cause of two lethal cases of DLL in Singapore.

What's next for M. lepromatosis

The team is working to better understand the bacterium and how it causes DLL. They are attempting to sequence the entire M. lepromatosis genome and looking for ways to grow the organism in the lab. Neither leprosy mycobacteria can be cultured because over millions of years they lost genes necessary to survive outside their hosts, a process called reductive evolution.

One of the puzzles of leprosy is that M leprae strains collected worldwide are virtually identical, while the clinical features of the disease and its severity vary greatly both geographically and from person to person. Evidence suggests that individual host immune factors play the key role in determining how the disease progresses.

The authors conclude that the new species M lepromatosis could account for some of this geographical and individual variation.

Funding for the project came from private philanthropy at M. D. Anderson Cancer Center, a National Cancer Institute grant to M. D. Anderson's DNA Core Facility, a National Institute of Allergy and Infectious Disease grant to Colorado State University and a College Research Council Award from Colorado State University.

Co-authors with Han and Nair are Yiel-Hea Seo, M.D., Ph.D., Kurt Sizer, M.D., Taylor Schoberle, M.S., and Gregory May, Ph.D., all of M. D. Anderson's Department of Laboratory Medicine; and John Spencer, Ph.D., and Wei Li, Ph.D., of the Mycobacterial Research Laboratories, Department of Microbiology, Immunology and Pathology at Colorado State University.

Old flies can become young moms

A fly can have it all: Frequent breeding and long life, new study by USC biologists finds

Female flies can turn back the biological clock and extend their lifespan at the same time, University of Southern California biologists report. Their study, published online this month in Molecular Genetics and Genomics, casts doubt on the old notion of a tradeoff between reproduction and longevity.

Popular wisdom and scientific opinion have held that "the more you reproduce, the shorter you're going to live," said senior author John Tower, associate professor of biological sciences at USC College. While that may be true in some cases, Tower added, recent research has hinted at exceptions to the rule.

The latest study is a striking example.

Tower and graduate student Yishi Li screened 8,000 genes in search of ones that could make older flies lay more eggs. They found two. When older female flies were altered to over-express either of these two genes, they lived 5 to 30 percent longer and produced more offspring.

Tower speculated that the genes are boosting activity of stem cells in the flies' reproductive system. Stem cell activity declines with age, and reproduction in older flies could not happen without a return of stem cells to peak form. "This would appear to be stimulating the stem cells to divide more in the old fly and therefore produce more offspring," Tower said.

Next, Tower and Li plan to see if stem cells in other parts of the fly's body also returned to their youthful prime. If they did, over-expression of the two genes would seem to act as a fountain of youth for the entire organism. The implications for mammals are not clear, Tower said, though one of the genes has a human equivalent that helps cells to grow and blood vessels to form.

But Tower's method at least provides a proof of concept. "It both makes females lay more eggs and live longer, so it really argues against any kind of obligatory tradeoff between reproduction and lifespan," Tower said.

Research for this study was supported by the Ellison Medical Foundation and the Department of Health and Human Services.

Ocean growing more acidic faster than once thought

Increasing acidity threatens sea life

University of Chicago scientists have documented that the ocean is growing more acidic faster than previously thought. In addition, they have found that the increasing acidity correlates with increasing levels of atmospheric carbon dioxide, according to a paper published online by the Proceedings of the National Academy of Sciences on Nov. 24.

"Of the variables the study examined that are linked to changes in ocean acidity, only atmospheric carbon dioxide exhibited a corresponding steady change," said J. Timothy Wootton, the lead author of the study and Professor of Ecology and Evolution at the University of Chicago.

The increasingly acidic water harms certain sea animals and could reduce the ocean's ability to absorb carbon dioxide, the authors said. Scientists have long predicted that higher levels of atmospheric carbon dioxide would make the ocean more acidic. Nevertheless, empirical evidence of growing acidity has been limited.

The new study is based on 24,519 measurements of ocean pH spanning eight years, which represents the first detailed dataset on variations of coastal pH at a temperate latitude—where the world's most productive fisheries live.

"The acidity increased more than 10 times faster than had been predicted by climate change models and other studies," Wootton said. "This increase will have a severe impact on marine food webs and suggests that ocean acidification may be a more urgent issue than previously thought, at least in some areas of the ocean."

The ocean plays a significant role in global carbon cycles. When atmospheric carbon dioxide dissolves in water it forms carbonic acid, increasing the acidity of the ocean. During the day, carbon dioxide levels in the ocean fall because photosynthesis takes it out of the water, but at night, levels increase again. The study documented this daily pattern, as well as a steady increase in acidity over time.

"Many sea creatures have shells or skeletons made of calcium carbonate, which the acid can dissolve," said Catherine Pfister, Associate Professor of Ecology and Evolution at the University of Chicago and a co-author of the study. "Therefore, the increased acidity of the ocean could interfere with many critical ocean processes such as coral reef building or shellfish harvesting."

Conducted at Tatoosh Island in the Pacific Ocean off the coast of Washington, the study documented that the number of mussels and stalked barnacles fell as acidity increased. At the same time, populations of smaller, shelled species and noncalcareous algae increased.

"Models revealed strong links between the dynamics of species living on the shore and variation in ocean pH," Wootton said. "The models project substantial shifts in the species dominating the habitat as a consequence of both the direct effects of reduced calcification and indirect effects arising from the web of species interactions."

The study, "Dynamical Patterns and Ecological Impacts of Declining Ocean pH in a High-Resolution Multi-Year Dataset," will be published in the Dec. 2 issue of PNAS. The third co-author, James Forester, was at the University of Chicago's Department of Ecology and Evolution but is currently at Harvard University.

"To date there is a lack of information about how the ocean carbon cycle has changed in recent years," Pfister said. "Atmospheric carbon dioxide concentrations will continue to increase, and our work points to the urgent need to better understand the ocean pH changes that this is likely to drive as well as how these changes will affect marine life."

Sealing off portion of intestinal lining treats obesity, resolves diabetes in animal model

Non-invasive device mimics effects of gastric bypass, alters complex gastrointestinal signals

Lining the upper portion of the small intestine with an impermeable sleeve led to both weight loss and restoration of normal glucose metabolism in an animal model of obesity-induced diabetes. Investigators from the Massachusetts General Hospital (MGH) Weight Center and Gastrointestinal Unit report in the journal Obesity that the procedure reproducing several aspects of gastric bypass surgery led to a significant reduction in the animals' food intake and a resolution of diabetes symptoms. The study, which has received early online release, is the first controlled test of a new procedural approach to treating obesity.

"This is a clear proof of principle that the human version of this device may be an effective treatment for obesity and diabetes. The clinical device would be placed endoscopically, making it far less invasive than surgical therapies," says Lee Kaplan, MD, PhD, director of the MGH Weight Center, who led the study. "The next step will be to complete large-scale controlled trials of this procedure in human patients. We also need to learn more about how this device affects the complex interplay between receptors that line the stomach and

intestine – which are stimulated by ingested food – and the brain, pancreas, liver and other organs involved in metabolism and in eating behavior."

Several surgical procedures have been developed to treat obesity and its complications, such as type 2 diabetes. The most common operation – Roux-en-Y gastric bypass – has five key components: isolation and reduction in size of the upper portion of the stomach, exclusion of the rest of the stomach from the flow of ingested food, exclusion of the upper portion of the small intestine (the duodenum and upper jejunum) from the flow of food, delivery of undigested nutrients to the middle portion of the small intestine, and partial severing of the vagus nerve, a key conduit between the gastrointestinal system and the brain in the control of appetite, digestion and glucose metabolism.

The device used in the current study – a 10-cm-long impermeable sleeve secured at the outlet of the stomach and lining the duodenum and upper jejunum of rats – prevents the sensing and absorption of nutrients in that area and also delivers relatively undigested nutrients to the lower jejunum. The researchers implanted the device, called an endoluminal sleeve, in eight rats that had been brought up on a high-fat diet, resulting in obesity and mild diabetes. Another eight rats underwent a similar procedure without implantation of the endoluminal sleeve. After a one-week recovery period, both groups were given access to the same high-fat diet.

During subsequent weeks, animals receiving the device took in almost 30 percent fewer calories than did those receiving the sham procedure. The treated rats weighed 20 percent less than the control group by the seventh week after the procedure and maintained that weight loss during the 16-week study period. Their fasting blood glucose levels, insulin levels and oral glucose tolerance all returned to normal levels.

To test whether the endoluminal sleeve could prevent obesity, the investigators implanted the device in rats genetically prone to rapid weight gain but lean since they had been brought up on a low-fat diet. The treated rats and a control group that had the sham procedure were then given access to a high-fat diet. While both groups gained weight during the postsurgical period, most of the rats receiving the endoluminal sleeve ate less than the control rats and weighed 12 percent less four weeks after the procedure. Examination of the treated animals that gained as much as the controls revealed that the sleeves had become detached and were eventually excreted.

"A key finding of this study is that the device induced a decrease in food intake as part of its effect and does not act by reducing absorption of nutrients," Kaplan says. "Like gastric bypass, it appears to change the way that neural and endocrine signals stimulated by nutrients act on their target organs. We still don't know much about the mechanisms underlying these effects, but we and several other groups are working hard to improve our understanding." Kaplan is an associate professor of Medicine at Harvard Medical School.

Vincent Aguirre, MD, PhD, of the MGH Gastrointestinal Unit is the lead author of the Obesity article. Additional co-authors are Nicholas Stylopoulos, MD, and Ronit Grinbaum, MD, MGH Weight Center. The study was supported by grants from the National Institutes of Health and from GI Dynamics, a medical device company developing a version of the endoluminal sleeve for human patients.

Mammals can be stimulated to regrow damaged inner retina nerve cells

First-time evidence of retina cell regrowth in mice holds promise for treating retinal damage

Researchers at the University of Washington (UW) have reported for the first time that mammals can be stimulated to regrow inner nerve cells in their damaged retinas. Located in the back of the eye, the retina's role in vision is to convert light into nerve impulses to the brain.

The findings on retina self-repair in mammals will be published this week in the Early Edition of the Proceedings of the National Academy of Sciences. Other scientists have shown before that certain retina nerve cells from mice can proliferate in a laboratory dish. Today's report gives evidence that retina cells can be encouraged to regenerate in living mice.

The UW researchers in the laboratory of Dr. Tom Reh, professor of biological structure, studied a particular retinal cell called the Müller glia. "This type of cell exists in all the retinas of all vertebrates," Reh said, "so the cellular source for regeneration is present in the human retina." He added that further studies of the potential of these cells to regenerate and of methods to re-generate them may lead to new treatments for vision loss from retina-damaging diseases, like macular degeneration.

The researchers pointed out the remarkable ability of cold-blooded vertebrates like fish to regenerate their retinas after damage. Birds, which are warm-blooded, have some limited ability to regenerate retinal nerve cells after exposure to nerve toxins. Fish can generate all types of retinal nerve cells, the researcher said, but chicks produce only a few types of retinal nerve cell replacements, and few, if any, receptors for detecting light.

Müller glia cells generally stop dividing after a baby's eyes pass a certain developmental stage. In both fish and birds, the researchers explained, damage to retinal cells prompts the specialized Müller glia cells to start

dividing again and to increase their options by becoming a more general type of cell called a progenitor cell. These progenitor cells can then turn into any of several types of specialized nerve cells.

Compared to birds, the scientist said, mammals have an even more limited Müller glia cell response to injury. In an injured mouse or rat retina, the cells may react and become larger, but few start dividing again.

Because the Müller glia cells appeared to have the potential to regrow but won't do so spontaneously after an injury, several groups of researchers have tried to stimulate them to grow in lab dishes and in lab animals by injecting cell growth factors or factors that re-activate certain genes that were silenced after embryonic development. These studies showed that the Müller glia cells could be artificially stimulated to start dividing again, and some began to show light-detecting receptors. However, these studies, the researchers noted, weren't able to detect any regenerated inner retina nerve cells, except when the Müller glia cells were genetically modified with genes that specifically promote the formation of amacrine cells, which act as intermediaries in transmitting nerve signals.

"This was puzzling," Reh said, "because in chicks amacrine cells are the primary retinal cells that are regenerated after injury." To resolve the discrepancy between what was detected in chicks and not detected in rodents, the Reh laboratory conducted a systematic analysis of the response to injury in the mouse retina, and the effects of specific growth factor stimulation on the proliferation of Müller glia cells.

The researchers injected a substance into the retina to eliminate ganglion cells (a type of nerve cell found near the surface of the retina) and amacrine cells. Then by injecting the eye with epidermal growth factor (EGF), fibroblast growth factor 1 (FGF1) or a combination of FGF1 and insulin, they were able to stimulate the Müller glia cells to re-start their dividing engines and begin to proliferate across the retina.

The proliferating Müller glia cells first transformed into unspecialized cells. The researchers were able to detect this transformation by checking for chemical markers that indicate progenitor cells. Soon some of these general cells changed into amacrine cells. The researchers detected their presence by checking for chemicals produced only by amacrine cells.

Many of the progenitor cells arising from the dividing Müller glia cells, the researchers observed, died within the first week after their production. However, those that managed to turn into amacrine cells survived for at least 30 days. "It's not clear why this occurs," the researchers wrote, "but some speculate that nerve cells have to make stable connections with other cells to survive."

In addition to Reh, the authors of the research findings, "Stimulation of Neural Regeneration in the Mouse Retina," were Mike O. Karl, Susan Hayes, Branden Nelson, Kristine Tan, and Brian Buckingham, all of the UW Department of Biological Structure. The research was supported by postdoctoral fellowships from the German Research Foundation, ProRetina Travel Grants, National Research Service Awards, and a National Eye Institute grant from the National Institutes of Health.

Video: Astronaut's tool bag seen from Earth

Sandrine Ceurstemont, online video producer

An astronaut's lost tool bag is probably not what you would expect to see when you look up at the night sky. But that's just what a man in Brockville, Ontario, Canada, captured on videotape from his backyard observatory last Saturday.

On November 18, shuttle Endeavour astronaut Heidemarie Stefanyshyn-Piper set off on a spacewalk from the International Space Station. Midway through the outing, she noticed that grease gun she was carrying to lubricate joints on the station had leaked in her tool bag. As she tried to clean it out, the bag slipped away and drifted off into space - all under the watchful eye of NASA's video cameras.

The toolbox is the dark spot in the lower left (negative image)

There will be further opportunities to spot the bag in the coming weeks. SpaceWeather.com's Satellite Tracker is monitoring the toolbag as it orbits the Earth. Enter your postcode (US and Canada only) and it will tell you if and when you can see it for yourself.

Use of inhaled corticosteroids for COPD does not appear to improve survival

An analysis of randomized trials indicates that use of inhaled corticosteroids for the treatment of chronic obstructive pulmonary disease (COPD) does not improve the rate of survival after one year, but is associated with an increased risk of pneumonia, according to an article in the November 26 issue of JAMA.

COPD, a lung disease characterized by recurrent episodes of coughing and breathlessness, represents a substantial public health burden, affecting 10-15 million persons in the United States. COPD is currently the fourth leading cause of death in the United States, accounting for 120,000 deaths annually, and is expected to be the third leading cause of death by 2020, according to background information in the article. No

pharmacotherapy and few interventions, other than smoking cessation and supplemental oxygen, have been shown to improve the rate of death in patients with COPD. Recent studies regarding the use of inhaled corticosteroid (ICS) therapy for managing stable COPD have yielded conflicting results regarding survival and risk of adverse events.

M. Bradley Drummond, M.D., M.H.S., of Johns Hopkins University, Baltimore, and colleagues conducted a review and meta-analysis of 11 randomized controlled trials (14,426 participants) to determine associations of ICS use of 6 or more months' duration with all-cause death and risk of pneumonia in patients with stable COPD.

All-cause mortality at 1-year follow-up was reported in five studies (9,233 patients), and analysis indicated that ICS therapy was not associated with a decreased risk of death after one year. There were 128 deaths among 4,636 individuals in the treatment group, and 148 deaths among 4,597 individuals in the control group.

Seven studies (10,776 patients) reported pneumonia outcomes, and indicated that patients receiving ICS had a 34 percent higher incidence of pneumonia. These studies included 777 events among 5,405 individuals in the treatment group and 561 events among 5,371 individuals in the control group.

"The association of ICS therapy with increased rates of pneumonia reported in our meta-analysis should be considered by clinicians and guideline developers when evaluating the role of ICS therapy in the management of stable COPD. This finding must be balanced with those of other reports describing beneficial effects of ICS therapy," the authors write.

Subgroup analyses indicated an increased risk of pneumonia in the following groups: highest ICS dose, shorter duration of ICS use, lowest baseline forced expiratory volume in the first second of expiration (a measure of lung function) and combined ICS and bronchodilator therapy.

"Recognizing the adverse events associated with ICS use is especially important, since clinicians may increase ICS therapy from moderate to high doses in patients who are not responding. Our data suggest that increasing to higher ICS doses may place patients at greater risk for pneumonia. While the results of our subgroup analysis suggest the existence of subpopulations of patients with COPD who might be at higher risk for pneumonia, our evidence is not conclusive and is only hypothesis-generating. Analysis of existing observational studies and future clinical trials may help physicians determine an optimal ICS dose that balances the potential risks and benefits of this therapy. Until studies can confirm an unequivocal benefit of ICS therapy in a group of patients with COPD, patients should receive the lowest effective ICS dose to minimize potential adverse effects," the authors write. *(JAMA. 2008;300[20]:2407-2416. Available pre-embargo to the media at www.jamamedia.org)*

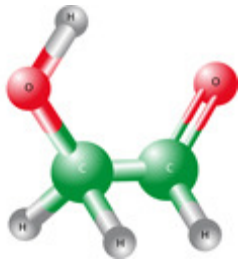
Sweet molecule could lead us to alien life

Plateau de Bure Interferometer **Rebus**

Scientists have detected an organic sugar molecule that is directly linked to the origin of life, in a region of our galaxy where habitable planets could exist. The discovery, part funded by the UK's Science and Technology Facilities Council (STFC), is published today (25th November) on the Astro-ph website.

The international team of researchers, including a researcher at University College London (UCL), used the IRAM radio telescope in France to detect the molecule in a massive star forming region of space, some 26000 light years from Earth.

Dr Serena Viti, one of the paper's authors from University College London, said, "This is an important discovery as it is the first time glycolaldehyde, a basic sugar, has been detected towards a star-forming region where planets that could potentially harbour life may exist."



Model of the glycolaldehyde molecule **:IRAM**

The molecule - glycolaldehyde - has previously only been detected towards the centre of our galaxy where conditions are extreme compared to the rest of the galaxy. This new discovery, in an area far from the galactic centre, also suggests that the production of this key ingredient for life could be common throughout the galaxy. This is good news in our search for alien life, as a wide spread of the molecule improves the chances of it existing along side other molecules vital to life and in regions where Earth-like planets may exist.

The team were able to detect glycolaldehyde by using the telescope to observe the region with high-angular resolution and at different wavelengths. The observations confirmed the presence of three lines of glycolaldegyde towards the most central part of the core of the region.

Glycolaldehyde, the simplest of the monosaccharide sugars, can react with the substance propenal to form ribose, a central constituent of Ribonucleic acid (RNA), thought to be the central molecule in the origin of life.

Professor Keith Mason, Chief Executive of the Science and Technology Facilities Council (STFC), said, "The discovery of an organic sugar molecule in a star forming region of space is very exciting and will provide

incredibly useful information in our search for alien life. Research like this, combined with the vast array of other astronomical projects involving UK researchers, is continually expanding our knowledge of the Universe and keeping the UK at the forefront of astronomy."

The massive star forming region where the sugar molecules were detected is known as G31.41+0.31
The paper will also be published in the Astrophysical Journal Letters publication.

The international team of scientists are from:

** The Universitat de Barcelona-CSIC, Barcelona*
** INAF-Istituto di Radioastronomia and INAF-Osservatorio Astrofisico di Arcetri in Florence*
** University College London*
** Institute de Radiastronomie Millimétrique, Grenoble*

Solar-powered sea slug harnesses stolen plant genes

*** 17:24 24 November 2008 by Catherine Brahic**

It's the ultimate form of solar power: eat a plant, become photosynthetic. Now researchers have found how one animal does just that.

Elysia chlorotica is a lurid green sea slug, with a gelatinous leaf-shaped body, that lives along the Atlantic seaboard of the US. What sets it apart from most other sea slugs is its ability to run on solar power.

Mary Rumpho of the University of Maine, is an expert on E. chlorotica and has now discovered how the sea slug gets this ability: it photosynthesises with genes "stolen" from the algae it eats.

She has known for some time that E. chlorotica acquires chloroplasts - the green cellular objects that allow plant cells to convert sunlight into energy - from the algae it eats, and stores them in the cells that line its gut.

***Elysia chlorotica, the solar-powered sea slug, is about 3 cm long* (Image: PNAS)**

Video: Watch a sea slug eat algae to nab some of its chloroplasts, and the genes that keep them functioning

Young E. chlorotica fed with algae for two weeks, could survive for the rest of their year-long lives without eating, Rumpho found in earlier work. But a mystery remained. Chloroplasts only contain enough DNA to encode about 10% of the proteins needed to keep themselves running. The other necessary genes are found in the algae's nuclear DNA. "So the question has always been, how do they continue to function in an animal cell missing all of these proteins," says Rumpho.

Gene 'theft'

In their latest experiments, Rumpho and colleagues sequenced the chloroplast genes of Vaucheria litorea, the alga that is the sea slug's favourite snack. They confirmed that if the sea slug used the algal chloroplasts alone, it would not have all the genes needed to photosynthesise. They then turned their attention to the sea slug's own DNA and found one of the vital algal genes was present. Its sequence was identical to the algal version, indicating that the slug had probably stolen the gene from its food.

"We do not know how this is possible and can only postulate on it," says Rumpho, who says that the phenomenon of stealing is known as kleptoplasty.

One possibility is that, as the algae are processed in the sea slug's gut, the gene is taken into its cells as along with the chloroplasts. The genes are then incorporated into the sea slug's own DNA, allowing the animal to produce the necessary proteins for the stolen chloroplasts to continue working.

Another explanation is that a virus found in the sea slug carries the DNA from the algal cells to the sea slug's cells. However, Rumpho says her team does not have any evidence for this yet.

In another surprising development, the researchers found the algal gene in E. chlorotica's sex cells, meaning the ability to maintain functional chloroplasts could be passed to the next generation.

The researchers believe many more photosynthesis genes are acquired by E. chlorotica from their food, but still need to understand how the plant genes are activated inside sea-slug cells.

Human photosynthesis?

Greg Hurst of Liverpool University in the UK says that DNA jumping from one species to another is not unheard of but that normally the DNA does not appear to function in the new species. "Here we have something going across and working in an entirely different context, which is altogether more interesting," he told New Scientist. "There was an example recently of a whole bacterial genome that ended up in a fruit fly species, but no-one knows if it functions," he says. "What is really unique here is the fact that the gene is transferred and appears to function."

Other animals are able to harness sunlight after eating plants, says Rumpho, but this is only because they acquire entire plant cells, which is very different to transforming an animal cell into a solar-powered plant-animal hybrid.

It is unlikely humans could become photosynthetic in this way. "Our digestive tract just chews all that stuff up - the chloroplasts and the DNA," she adds.

Journal reference: Proceedings of the National Academy of Sciences (DOI: 10.1073/pnas.0804968105)

Study: Want to be happier? Be more grateful

Want to quickly improve your happiness and satisfaction with life? Research done at Kent State University shows the pen may be a mighty weapon

Want to quickly improve your happiness and satisfaction with life? Then the pen may be a mighty weapon, according to research done by Kent State University's Dr. Steven Toepfer.

Toepfer, an assistant professor of family and consumer studies at university's Salem Campus, says that expressive writing is something that has been available to mankind since ink first appeared in Egypt more than 4,000 years ago.

"Everyone is pursuing the American dream. We are wealthier than previous generations, consuming more and experiencing more, but yet so many of us are so unhappy," Toepfer says. "The question of 'is there something simple we can do to be happier?' is one that I have been thinking about for many years and one that has interested people for much longer."

With that question in mind, Toepfer enlisted students from six courses to explore the effects of writing letters of gratitude to people who had positively impacted the students' lives. Over the course of a six-week period, students wrote one letter every two weeks with the simple ground rules that it had to be positively expressive, required some insight and reflection, were nontrivial and contained a high level of appreciation or gratitude.

After each letter, students completed a survey to gauge their moods, satisfaction with life and feelings of gratitude and happiness.

"I saw their happiness increase after each letter, meaning the more they wrote, the better they felt," says Toepfer, who also witnessed improvement in participants' life satisfaction and gratitude throughout the study. "The most powerful thing in our lives is our social network. It doesn't have to be large, and you don't always need to be the life of the party, but just having one or two significant connections in your life has shown to have terrific psychological and physical benefits."

In all, 75 percent of the students said they planned to continue to write letters of gratitude even when the course was over.

Studies demonstrate, according to Toepfer, that practicing expressive writing is often associated with fewer health problems, decreased depression, an improved immune system and improved grades.

"We are all walking around with an amazing resource: gratitude," says Toepfer. "It helps us express and enjoy, appreciate, be thankful and satisfied with a little effort. We all have it, and we need to use it to improve our quality of life."

Life is a highway: Study confirms cars have personality

TALLAHASSEE, Fla. -- No one needs to tell Disney, which brought the likes of Herbie the Love Bug and Lightning McQueen to the big screen, that cars have personality.

Now a study co-authored by a Florida State University researcher has confirmed through a complex statistical analysis that many people see human facial features in the front end of automobiles and ascribe various personality traits to cars -- a modern experience driven by our prehistoric psyches. Researchers, product designers and, of course, filmmakers have long toyed with the idea that cars have faces, but this study is the first to investigate the phenomenon systematically. The study will be published in the December issue of the journal Human Nature.

"The study confirmed with some rigor what many people have already felt -- that cars seem to have consistent personality traits associated with them, and that this is similar to the way people perceive facial expressions," said Dennis Slice, an associate professor in Florida State's Department of Scientific Computing. "The most unique aspect of the study was that we were able to quantitatively link the perception of cars to aspects of their physical structure in a way that allows us to generate a car that would project, say, aggression, anger or masculinity or the opposite traits."

As a guest professor at the University of Vienna, Slice collaborated with doctoral student Sonja Windhager, the study's lead author, and several colleagues to explore the link between perception and the geometry of a car front and its parts. The researchers asked 40 people to view high-resolution, 3-D computer reconstructions and printed images of 38 actual 2004-06 car models, representing 26 manufacturers from Ford to Mercedes.

One-third (32.5 percent) of those participating in the experiment associated a human or an animal face with at least 90 percent of the cars. Generally, the headlights were marked as eyes; the nose tended to be the grill or emblem; the additional air intake slots, the mouth. Each participant in the experiment also was asked to rate each model on 19 traits, including dominance, maturity, gender and friendliness, and if they liked the car.

"In our study, people generally agreed in their ratings," Slice said, noting that 96 percent agreed on whether a car was dominant or submissive. "Thus, there must be some kind of consistent message that is being perceived in car fronts."

For example, cars scoring high in the so-called power traits had horizontally elongated hoods, pronounced lower car bodies relative to the windshields and more angular headlights that seemed to suggest a frown. Conversely, cars on the other end of the power scale -- that is, those perceived as childlike, submissive, female and friendly -- had headlights with their upper edge relatively close to the midline and had an upward shift of the car's lateral-most points. ("In this way, the car gives us a big smile," Slice said.)

In a finding that suggests perhaps there is a hidden road warrior in all of us, study participants liked power vehicles best -- the most mature, masculine, arrogant and angry-looking ones. Although people do not necessarily buy the kind of car they say they like, Slice said the finding spurs some interesting questions for future studies about pedestrian and driver behavior. For example, do people extend the perception of the car to the person behind the wheel? And does that affect how drivers interact with other cars on the road?

In addition, the study provides a check into the rearview mirror of our prehistoric psyches, Slice said. The researchers theorized that, through biological evolution, our brains have been designed to infer a great deal of information about another person -- age, sex, attitudes, personality traits and emotions -- from just a glance at their face. The ability to "read" faces in order to identify people, detect possible kin relationships and assess potential danger has been so important to human development that people have adapted a hypersensitivity to detecting facial features even if they are presented in rather abstract ways. As a result, we are tempted to see faces everywhere, even in clouds, stones and, yes, cars.

"The fact that we can so easily see faces in inanimate objects may tell us something about the evolutionary environment in which this capacity arose," Slice said. "Seeing too many faces, even in mountains or toast, has little or no penalty, but missing or misinterpreting the face of a predator or attacker could be fatal."

The Evidence Gap

New Arena for Testing of Drugs: Real World

By GINA KOLATA

Sylvia Syvenky went for a routine dental appointment in early October, expecting to have two caps on her teeth replaced. But something went terribly wrong.

“I felt like I was choking,” Mrs. Syvenky said. “I couldn’t take a breath. All sorts of gurgly sounds were coming out of me.”

She was rushed by ambulance to University Hospital near her home in Edmonton, Alberta, where doctors placed a mask on her face and forced air into her lungs. They told her she had heart failure. After her condition improved, they asked her to sign up for a study of a new drug to help with breathing.

Mrs. Syvenky is like many with heart failure who arrive at hospitals, unable to breathe. Yet she is the last person who would normally be asked to join a research study. At age 70, she was much older than typical study participants and her symptoms were too complex.

But now there is a growing movement to gather a new kind of evidence, the kind that will fill some of the biggest gaps in medical science: What treatment is best for typical patients with complex symptoms, like Mrs. Syvenky? Many are elderly with several chronic conditions and taking several unrelated medications. And what are the long-term effects of a treatment — death rates, side effects, progression of the disease?

A group of advocates, including medical researchers, medical societies and insurers, is lobbying Congress to pay for an Institute for Comparative Effectiveness Research that would assess treatments and identify gaps in evidence. When there are gaps, the institute would initiate what are being called “real world,” or “pragmatic,” clinical research trials to gather the evidence.

Some leading researchers who used to defend the status quo say they have switched.

“There has been a 90-degree turn” in thinking, said Dr. Eugene Braunwald, an eminent cardiologist at Harvard Medical School. “I personally have swung around.”

Although thousands of medical studies are completed every year, most have relatively limited goals. They often carefully select patients who have few medical problems other than the one under study, making it easier to get one clear result. They may not look at effects over the long term, assuming that if a treatment helps initially, patients will be better off.

But while such studies can help a drug acquire approval or answer a restricted research question, they can leave patients and doctors in a lurch because they may not tell how the new drug or treatment will work once it is tried in real patients with complex problems. Such limited studies, while they can have value, may no longer be enough, particularly when care has become so expensive and real evidence more crucial.

"They are at the heart of why we have trouble making decisions," said Dr. Scott Ramsey, a professor of medicine at the University of Washington.

It is an issue that arises again and again. For example, it is one reason for the debate over the popular diabetes drug Avandia, or rosiglitazone. When the drug was tested, the main question was whether it lowered blood sugar, which it did. Then, after it was on the market, some researchers found hints of increased risks for heart attacks, the major killer in diabetes. But there was no way to know for sure from the studies that led to the drug's approval.

At the same time, a move to conduct many more pragmatic trials would involve nothing less than a rethinking of how medical research is financed and managed.

"There's this gulf between what questions researchers have found interesting to study and what questions industry and the N.I.H. have chosen to fund and what users of information most want to know," said Dr. Sean Tunis, director of the Center for Medical Technology Policy, a nonprofit group that studies ways to get better medical evidence.

"One starts from the head and the other starts from the tail and they don't meet in the middle."

Dr. Robert Califf, a cardiology professor at Duke University School of Medicine and principal investigator in the heart failure study, cites the study Mrs. Syvenky entered as a model of what is so urgently needed in medicine.

The study, the largest ever in heart failure, is 15 times larger than any previous study of nesiritide. Unlike those that led to the drug's approval, it is enrolling patients like those doctors see every day. Anyone showing up at one of 450 medical centers around the world, unable to breathe because of heart failure, is eligible. Participants are randomly assigned to get an infusion of nesiritide or a placebo, a saltwater infusion. And the study, comparing the treatments, asks two simple questions: Are patients still alive a month later? And were they readmitted to the hospital?

Dr. Califf knows the evidence problem all too well. He spent years working on committees that formulate medical guidelines for treating heart disease patients. And over and over again, he says, he and other committee members ran into a problem. The studies did not ask whether one treatment was better than another and they did not ask what happened over long periods in typical patients with their complicated medical problems.

"We looked at the A.C.C. and A.H.A. guidelines," Dr. Califf said, referring to the American College of Cardiology and the American Heart Association. "Fifteen percent of the guidelines were based on good clinical evidence. And cardiology is where we have the most evidence."

He added that he was not indicting studies that looked at a more limited group of patients and often studied a drug's effects for a shorter time.

"You have to figure out the right dose. Is there a chance it could work?" Dr. Califf said. But something more is needed.

The Food and Drug Administration does not have a hard and fast rule about what it takes to show that a drug is effective, said Dr. Robert Temple, director for medical policy at the F.D.A.'s Center for Drug Evaluation and Research. A lot depends on what is known about the drug's short-term effects and how well they predict long-term outcomes.

But, he added, there are practical concerns with large pragmatic trials because companies have to look at a wide range of possible effects when they test a drug. "If you do a large outcome study in 10,000 people in the same way you do short-term studies, you'll never finish," Dr. Temple said.

"There's no white hat, black hat here," said Dr. Kevin Weiss, president and chief executive of the American Board of Medical Examiners. "Pharmaceutical companies are trying to do what they are supposed to do. The F.D.A. is trying to do what it is supposed to do. But they are not fully connected to what the public needs."

That was part of the problem with nesiritide. At first, all was well. The drug dilates blood vessels, making it easier for the heart to pump blood into the rest of the body. Patients breathed better.

The F.D.A. approved the drug in 2001 based on studies that asked about breathing in the first few hours and excluded patients with symptoms as complex as Mrs. Syvenky's, even though she is typical of half of all people with heart failure. The patients in the original studies, mostly white men, had an average age of 60. Yet more

than 800,000 Americans aged 65 and older were hospitalized for heart failure in 2006, the most recent year for which statistics are available.

In 2005, questions arose. Researchers lumped together data from several nesiritide studies. One analysis reported damage to kidney functions and the other found increased death rates. Sales plummeted.

But no single study was large enough to determine if those risks were real, and merging smaller studies in a so-called meta-analysis can be misleading.

In fact, said Dr. Adrian Hernandez, a cardiologist at Duke University, meta-analyses have been a risky business. When their conclusions were tested in subsequent studies, they have been correct just 60 percent of the time. They are good for generating hypotheses or perhaps when clinical trials are impractical. But as evidence? They are about as accurate as tossing a coin.

With fears about the drug growing, Johnson & Johnson, the drug's maker, asked Dr. Braunwald to put together an expert panel to advise it.

The questions about nesiritide were so pressing, Dr. Braunwald's panel concluded, that the drug should be given to only the sickest patients in a hospital setting. In the meantime, the company needed to conduct a large pragmatic trial looking at clinical outcomes in typical patients.

"The data on which the drug was approved were very sketchy," Dr. Braunwald said in a recent interview. "And since the question had been raised by these two meta-analyses, which in themselves were controversial, the idea of a pragmatic, outcomes-based clinical trial was very natural."

Dr. Steven Goodman, an oncologist and biostatistician at Johns Hopkins University School of Medicine, wants to insert a reality check on large pragmatic clinical trials.

"When they are first described, they sound wonderful," he said. But, he added, there's a rub. "You often give up the 'why.' "

Pragmatic trials, he explains, are most feasible when they are as simple as possible, measuring important outcomes like hospitalizations or deaths but not things like how much medication is taken, how well a procedure is performed or how accurately an X-ray is read.

An operation, for example, may not work well in the real world because it takes more skill and training than is typically found outside a few medical centers. A pragmatic trial will show the surgery is not working but not why.

Scientists, Dr. Goodman added, do not like giving up on the why. And that leads to a question of who is going to pay for these studies. Medicare pays for medical care but does not sponsor studies. Insurance companies, said Dr. Goodman, who helps review evidence for Blue Cross Blue Shield, may be seen as having a conflict if they sponsor studies because they may have to pay for treatments that are shown to be effective.

Drug companies sometimes do pragmatic studies, said Alan Goldhammer, the vice president for regulatory affairs at Pharma, a trade group for drug companies. But usually that is when "there are issues relating to the drug and the ability to affect drug and marketplace."

At the National Institutes of Health, said Dr. Elizabeth Nabel, director of the National Heart, Lung and Blood Institute, "many of us would love to do many more of these studies." But, she added, "we have a limited budget and there is only so much that we can do."

The nesiritide study was a direct result of Dr. Braunwald's panel's recommendation. Johnson & Johnson is paying for it. But the study's overall conduct, design and analysis are coordinated at Duke University through an academic consortium and led by an independent academic executive and steering committee.

When the study began, some heart specialists said it could never enroll enough patients. Who would agree to be randomly assigned to a placebo or a drug to ease breathing?

So far, however, recruitment is ahead of schedule, Dr. Hernandez said, which he attributes to the researchers' enthusiasm. And, he adds, there are already more patients from North America in this study than in any acute heart failure study ever done.

A Whisper, Perhaps, From the Universe's Dark Side

By DENNIS OVERBYE

Is this the dark side speaking?

A concatenation of puzzling results from an alphabet soup of satellites and experiments has led a growing number of astronomers and physicists to suspect that they are getting signals from a shadow universe of dark matter that makes up a quarter of creation but has eluded direct detection until now.

Maybe.

"Nobody really knows what's going on," said Gordon Kane, a theorist at the University of Michigan. Physicists caution that there could still be a relatively simple astronomical explanation for the recent

observations. But the nature of this dark matter is one of the burning issues of science. Identifying it would point the way to a deeper understanding of the laws of nature and the Einsteinian dream of a unified theory of physics.

The last few weeks have seen a blizzard of papers trying to explain the observations in terms of things like "minimal dark matter" or "exciting dark matter," or "hidden valley" theory, and to suggest how to look for them in particle accelerators like the Large Hadron Collider, set to begin operation again outside Geneva next summer.

"It could be deliriously exciting, an incredibly cool story," said Nima Arkani-Hamed of the Institute for Advanced Study in Princeton, N.J., who has been churning out papers with his colleagues. "Anomalies in the sky tell you what to look for in the collider."

On Thursday, a team of astrophysicists working on one of the experiments reported in the journal Nature that a cosmic ray detector onboard a balloon flying around the South Pole had recorded an excess number of high-energy electrons and their antimatter opposites, positrons, sailing through local space.

The particles, they conceded, could have been created by a previously undiscovered pulsar, the magnetized spinning remnant of a supernova explosion, blasting nearby space with electric and magnetic fields. But, they say, a better and more enticing explanation for the excess is that the particles are being spit out of the fireballs created by dark matter particles colliding and annihilating one another in space.

"We cannot disprove that the signal could come from an astrophysical object. We also cannot eliminate a dark matter annihilation explanation based upon current data," said John P. Wefel of Louisiana State University, the leader of the team, adding, "Whichever way it goes, for us it is exciting."

The results came on the heels of a report earlier this fall from Pamela, a satellite built by Italian, German, Russian and Swedish scientists to study cosmic rays. Pamela scientists reported in talks and a paper posted on the Internet that the satellite had recorded an excess of high-energy positrons. This, they said, "may constitute the first indirect evidence of dark matter particle annihilations," or a nearby pulsar.

Antimatter is rare in the universe, and so looking for it is a good way of hunting for exotic phenomena like dark matter.

Another indication that something funny is happening on the dark side of the universe is evident in maps of the cosmic background radiation left over from the Big Bang. Those maps, produced most recently this year by the Wilkinson Microwave Anisotropy Probe satellite, show a haze of what seem to be charged particles hovering around the Milky Way galaxy, according to an analysis by Douglas Finkbeiner of the Harvard-Smithsonian Center for Astrophysics.

Adding to the mix and mystery, the European Space Agency's Integral satellite detected gamma rays emanating from the center of the Milky Way, suggesting the presence of positrons there, but with much lower energies than Pamela and Dr. Wefel's experiments have seen.

What all this adds up to, or indeed whether it all adds up to anything at all, depends on which observations you trust and your theoretical presumptions about particle physics and the nature of dark matter. Moreover, efforts to calculate the background level of high-energy particles in the galaxy are beset with messy uncertainties. "The dark matter signal is easy to calculate," Dr. Kane said. "The background is much harder."

Dark matter has teased and obsessed astronomers since the 1930s, when the Caltech astronomer Fritz Zwicky deduced that some invisible "missing mass" was required to supply the gravitational glue to hold clusters of galaxies together. The idea became respectable in the 1970s when Vera C. Rubin of the Carnegie Institution of Washington and her collaborators found from studying the motions of stars that most galaxies seemed to be surrounded by halos of dark matter.

The stakes for dark matter go beyond cosmology. The most favored candidates for its identity come from a theory called supersymmetry, which unifies three of the four known forces of nature mathematically and posits the existence of a realm of as-yet-undiscovered particles. They would be so-called wimps — weakly interacting massive particles — which feel gravity and little else, and could drift through the Earth like wind through a screen door. Such particles left over from the Big Bang could form a shadow universe clumping together into dark clouds that then attract ordinary matter.

The discovery of a supersymmetric particle would also be a boost for string theory, the controversial "theory of everything," and would explicate the nature of a quarter of the universe. But until now, the dark matter particles have mostly eluded direct detection in the laboratory, the exception being a controversial underground experiment called Dama/Libra, for Dark Matter/Large Sodium Iodide Bulk for Rare Processes, under the Italian Alps, where scientists claimed in April to have seen a seasonal effect of a "dark matter wind" as the Earth goes around its orbit.

The sky could be a different story. Dark matter particles floating in the halos around galaxies would occasionally collide and annihilate one another in tiny fireballs of radiation and lighter particles, theorists say.

Dr. Wefel and his colleagues have been chasing sparks in the sky since 2000, when they flew an instrument known as ATIC, for Advanced Thin Ionization Calorimeter, around Antarctica on a balloon at an altitude of 23 miles, looking for high-energy particles known as cosmic rays raining from space.

In all they have made three flights, requiring them to spend the winter at the National Science Foundation's McMurdo Station, which Dr. Wefel described as very pleasant. "It's not bad until a storm moves in. You put your hand out till you can't see it. Then you go out and start shoveling snow," he explained.

The Nature paper includes data from the first two balloon flights. It shows a bump, over theoretical calculations of cosmic ray intensities, at energies of 500 billion to 800 billion electron volts, a measure of both energy and mass in physics. One way to explain that energy bump would be by the disintegration or annihilation of a very massive dark particle. A proton by comparison is about one billion electron volts.

Dr. Wefel noted, however, that according to most models, a pulsar could generate particles with even more energy, up to trillions of volts, whereas the bump in the ATIC data seems to fall off at around 800 billion electron volts. The ATIC results, he said, dovetail nicely with those from Pamela, which recorded a rising number of positrons relative to electrons, but only up to energies of about 200 billion electron volts.

Reached in China, where he was attending a workshop, Neal Weiner of New York University, who is working with Dr. Arkani-Hamed on dark matter models, said he was plotting ATIC data gleaned from the Web and Pamela data on the same graph to see how they fit, which was apparently very well.

But Piergiorgio Picozza, a professor at the University of Rome and the Pamela spokesman, said in an e-mail message that it was too soon to say the experiments agreed. That will depend on more data now being analyzed to learn whether Pamela continues to see more positrons as the energy rises.

Moreover, as Dr. Kane pointed out, Pamela carries a magnet that allows it to distinguish electrons from positrons — being oppositely charged, they bend in opposite directions going through the magnetic field. But the ATIC instrument did not include a magnet and so cannot be sure that it was seeing any positrons at all: no antimatter, no exotic dark matter, at least at those high energies.

But if he is right, Dr. Wefel said that the ATIC data favored something even more exotic than supersymmetry, namely a particle that is lost in the fifth dimension. String theory predicts that there are at least six dimensions beyond our simple grasp, wrapped up so tightly we cannot see them or park in them. A particle in one of these dimensions would not appear to us directly.

You could think of it as a hamster running around on a wheel in its cage. We cannot see the hamster or the cage, but we can sort of feel the impact of the hamster running; according to Einsteinian relativity, its momentum in the extra dimension would register as mass in our own space-time. Such particles are called Kaluza-Klein particles, after Theodor Kaluza and Oscar Klein, theorists who suggested such an extra-dimensional framework in the 1920s to unify Einstein's general theory of relativity and electromagnetism.

Dr. Wefel's particle would have a mass of around 620 billion electron volts. "That's the one that seems to fit the best," he said in an interview. The emergence of a sharp edge in the data, he said, "would be a smoking gun" for such a strange particle.

But Dr. Arkani-Hamed said that Kaluza-Klein particles would not annihilate one another at a fast enough rate to explain the strength of the ATIC signal, nor other anomalies like the microwave haze. He and his colleagues, including Dr. Weiner, Dr. Finkbeiner and Tracy Slatyer, also of Harvard, drawing on work by Matthew Strassler of Rutgers, have tried to connect all the dots with a new brand of dark matter, in which there are not only dark particles but also a "dark force" between them.

That theory was called "a delightful castle in the sky" by Dr. Kane, who said he was glad it kept Dr. Arkani-Hamed and his colleagues busy and diverted them from competing with him. Dr. Kane and his colleagues favor a 200 billion-electron-volt supersymmetric particle known as a wino as the dark matter culprit, in which case the Pamela bump would not extend to higher energies.

Dr. Wefel said he had not kept up with all the theorizing. "I'm just waiting for one of these modelers to say here is the data, here is the model," he said. "Fit it out. I'm not sure I've seen it yet."

Dr. Picozza said that it was the job of theorists to come up with models and that they were proliferating."At the end of the story only one will be accepted from the scientific community, but now it is too early," he said in an e-mail message.

Sorting all this out will take time, but not forever.

Pamela is expected to come out with new results next year, and the first results from the Fermi Gamma-ray Space Telescope, launched last summer, should also be out soon. Not to mention the Large Hadron Collider, which will eventually smash together protons of seven trillion electron volts. It is supposed to be running next summer.

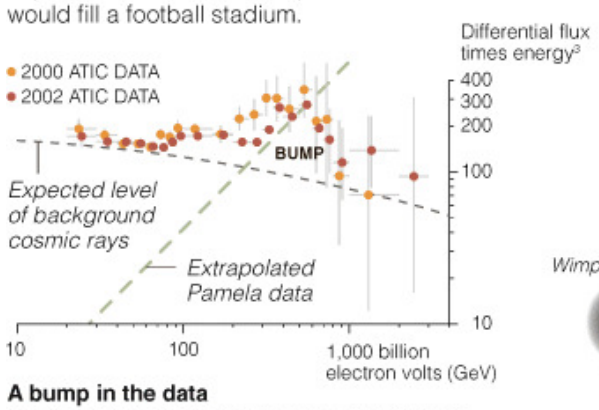
"With so many experiments, we will soon know so much more about all of this," Dr. Weiner said. "In a year or two, we'll either not be talking about this idea at all, or it will be all we're talking about."

This article has been revised to reflect the following correction:

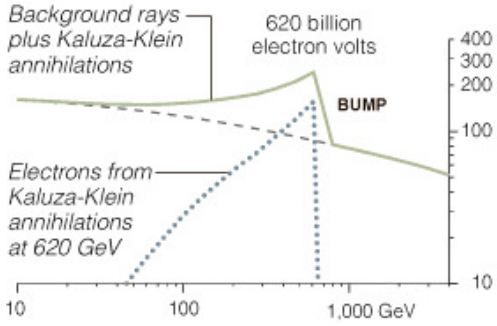
Searching for Dark Matter High Above the Antarctic

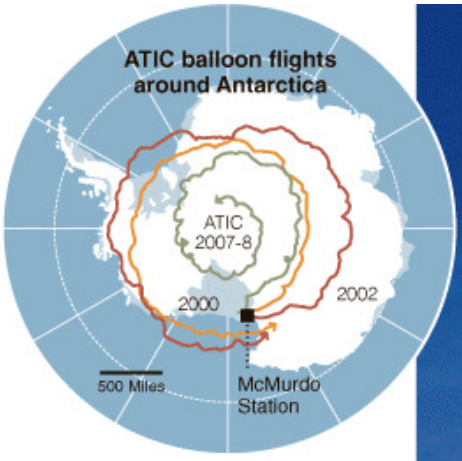
New experiments may be seeing signals of the elusive dark matter that is thought to permeate the universe.

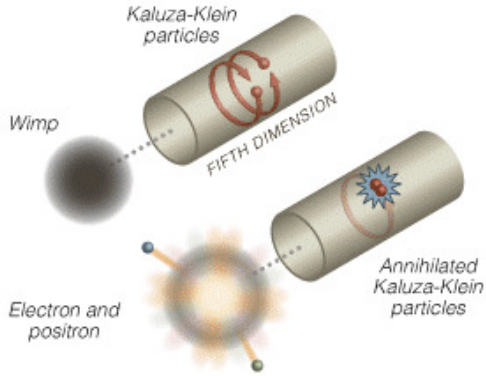
Advanced Thin Ionizing Calorimeter (ATIC)
The ATIC detector is designed to measure cosmic rays, high-energy particles from stars and other sources. The experiment has completed three flights around Antarctica at an altitude of about 23 miles, carried by an enormous helium balloon (at right, launching another experiment in 2007) that expands as it rises until it would fill a football stadium.



A bump in the data
Above, results from the first two ATIC flights show a greater than expected number of high energy electrons in a bump that peaks at about 620 billion electron volts. The bump of electrons also appears to line up with extrapolated data from another cosmic ray detector, the Pamela satellite.





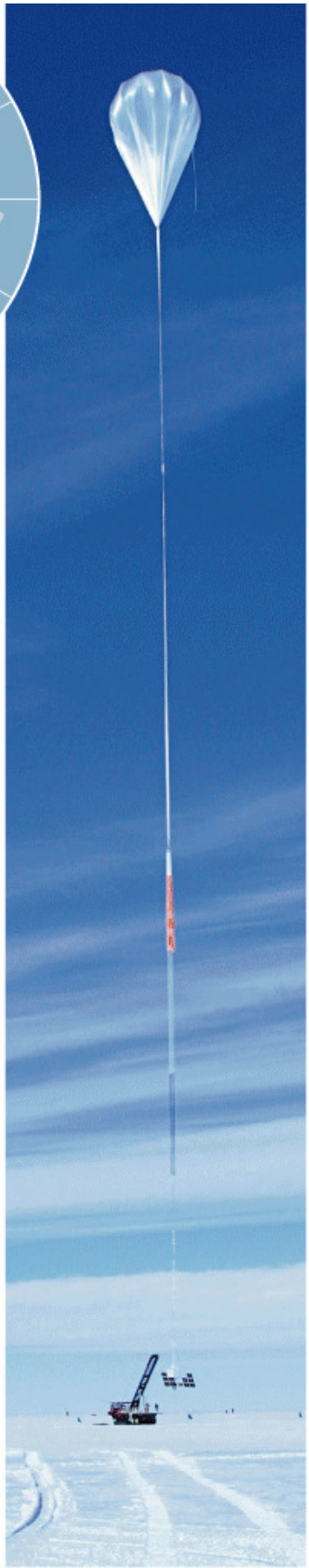


Particles from a fifth dimension?
The bump of high-energy electrons might be caused by theoretical particles called Kaluza-Klein particles, traveling in a fifth dimension that is curled up too small to observe. The momentum of these particles would appear in our dimensions as weakly interacting massive particles, or wimps, which are one candidate for dark matter. Wimps have not been detected directly, but the annihilation of Kaluza-Klein particles might be detectable as high-energy electrons and positrons (left).

The big picture
Below, measurements of the microwave sky taken by the Wilkinson Microwave Anisotropy Probe show a 'haze' of unexplained microwaves around the center of our galaxy, suggesting the presence of high-energy particles possibly associated with dark matter.

Other explanations
Anomalies measured by the ATIC detector could also be produced by more conventional sources, such as a previously undiscovered pulsar or micro-quasar. Other candidates for dark matter include a supersymmetrical particle known as a wino, and hidden particles experiencing "dark forces."

Physicists are eagerly awaiting more results from Pamela next year and the Fermi Gamma-ray Space Telescope launched this year. They also hope eventually to create dark matter particles in the Large Hadron Collider when it finally gets running at full energy.



Sources: Nature; Nima Arkani-Hamed; Douglas Finkbeiner; T. Gregory Guzik; Neal Weiner

JONATHAN CORUM/THE NEW YORK TIMES; WMAP HAZE IMAGE BY GREGORY DOBLER; PHOTOGRAPH BY T. GREGORY GUZIK

Correction: November 26, 2008
An article on Tuesday about dark matter in the cosmos misstated the energy of proton collisions at the Large Hadron Collider, a new particle accelerator at CERN, outside Geneva. When the machine is running at full strength, each colliding proton will have seven trillion electron volts of energy, not seven million.

Yale researchers enlist a new recruit in battle of the bulge

In the battle against obesity, Yale University researchers may have discovered a new weapon — a naturally occurring molecule secreted by the gut that makes rats and mice less hungry after fatty meals. The findings are published in the Nov. 26 issue of the journal Cell.

The report suggests the molecule may help regulate how much animals and people eat, according to the team headed by Gerald I. Shulman, Yale professor of medicine and cellular & molecular physiology and a Howard Hughes Medical Institute investigator.

Shulman's team studied a family of lipids called N-acylphosphatidylethanolamines, or NAPEs, which are synthesized and secreted into the blood by the small intestine after fatty foods are eaten. The team found that mice and rats injected regularly with NAPEs ate less food and lost weight. In addition, treatment with NAPEs appeared to reduce the activity of "hunger" neurons in the brain while stimulating activity in neurons that are believed to play a role in reducing appetite.

In the last two decades, scientists have made great inroads toward understanding how the body communicates with the brain to control food intake. So far, hormones such as leptin that act as regulators of this complex system have proved disappointing when tested as potential weight-loss treatments in humans.

The researchers are now planning to investigate how the findings in the Cell paper apply to humans. They will first study non-human primates to determine if NAPE concentrations increase in a similar fashion after fat ingestion. Then, says Shulman, "If chronic NAPE treatment is well tolerated and can cause weight loss by a reduction of food intake, we would have strong impetus to move forward with human NAPE trials."

Other Yale researchers involved in the study: Matthew P. Gillum, Dongyan Zhang, Xian-Man Zhang, Derek M. Erion, Rachel A. Jamison, Cheolsoo Choi, Jianying Dong, Marya Shanabrough, Hillary R. Duenas, David W. Frederick, Jennifer J. Hsiao, Tamas L. Horvath, Chun Min Lo, Pat Tso, and Gary W. Cline

The Howard Hughes Medical Institute funded the study.

Stanford/Packard study shows no benefit from drug widely used to prevent premature births

STANFORD, Calif. — When a pregnant woman goes into early labor, her obstetrician may give her drugs to quiet the woman's uterus and prevent premature birth.

New research shows, however, that one popular drug works no better than a placebo at maintaining pregnancy after the initial bout of preterm labor is halted, say scientists at the Stanford University School of Medicine, Lucile Packard Children's Hospital and Santa Clara Valley Medical Center. The new trial is the first-ever placebo-controlled test of nifedipine, a muscle relaxant originally developed to lower blood pressure, and its effect on premature delivery with prolonged treatment.

"Medication use should be minimized in pregnancy unless it's clearly indicated," said Deirdre Lyell, MD, assistant professor of obstetrics and gynecology at Stanford and the study's lead author. Serious side effects of nifedipine in pregnancy are rare, Lyell said, but even a low risk isn't worthwhile if the drug has no benefit. "We all want to prevent preterm birth, but prolonged treatment with nifedipine doesn't appear to be an answer."

The findings will appear in the December issue of the journal Obstetrics and Gynecology.

Preterm births, defined as deliveries before 37 weeks of pregnancy, are on the rise in the United States. Pregnancy normally lasts 40 weeks. A report released earlier in November by the March of Dimes gives the United States a "D" grade for its rate of preterm births, which increased between 1981 and 2005 from 9.4 to 12.7 percent of all births. Smoking, lack of insurance and early intervention by physicians were cited as major contributing factors.

"The scope of the problem is enormous," Lyell said.

In early life, preemies face health problems such as respiratory distress, bleeding on the brain and tissue-destroying intestinal infections. Long-term complications of prematurity include neurological disorders, chronic lung disease and vision and hearing problems. The earlier the delivery, the greater the risks. That means doctors are very motivated to help women in early labor stay pregnant as long as possible. A recent survey by the Society for Maternal-Fetal Medicine found 29 percent of obstetricians prescribed drugs to keep such patients from re-entering early labor. Of those, 79 percent said nifedipine was their first-choice therapy.

Lyell's team recruited 71 women who had been successfully treated for preterm labor between 24 and 34 weeks of pregnancy. The women were then randomly assigned to receive doses of nifedipine or placebo every six hours until 37 weeks of pregnancy or until delivery, whichever came first. The researchers hoped nifedipine

would prevent preterm labor from re-starting. They evaluated whether subjects' pregnancies lasted to 37 weeks and measured how long delivery was delayed. They also noted the babies' gestational age at delivery, birth weight and complications of prematurity.

The team saw no differences between nifedipine and placebo for any measurement. About 40 percent of women in both groups reached 37 weeks of pregnancy, with delivery delayed an average of a month. Babies' average health was the same in both groups, too.

Lyell cautioned that the study was designed to detect a 50 percent improvement in delayed deliveries. If nifedipine confers a smaller advantage, it would not have been spotted in this study, she said. Lyell thinks a larger study of nifedipine is warranted. "A small benefit would be especially significant at early gestational ages, and less so later on. But overall, there's no benefit to prematurity."

Based on the current lack of data to support this drug, Lyell believes obstetricians should proceed with caution. "All medications have side effects," she said. Though nifedipine has a fairly good safety record, a few case reports link it to dangerously low blood pressure in pregnant women.

"If something has not been shown to be of benefit, it shouldn't be used," Lyell concluded. "Every now and then, there will be a patient who has an unusual side effect.

"It's important to distinguish between acute treatment, which is given to a woman in preterm labor, and maintenance treatment, which is given to a woman following an episode of preterm labor that has ended," she added. "This study addresses maintenance treatment. We still use nifedipine for acute treatment of preterm labor."

Lyell collaborated with Stanford/Packard colleagues Yasser El-Sayed, MD, the study's senior author; Usha Chitkara, MD; Maurice Druzin, MD; and Kristin Pullen, MD. Other collaborators were Jana Mannan, MD, the study's lead investigator at Santa Clara Valley Medical Center, and Aaron Caughey, MD, PhD, of the University of California-San Francisco.
The study was funded by research funds from the Departments of Obstetrics and Gynecology at Stanford University and at Santa Clara Valley Medical Center.

Baffling chronic pain linked to rewiring of brain

Brain looks like inept cable guy changed the hookups

CHICAGO --- Scientists peered at the brains of people with a baffling chronic pain condition and discovered something surprising. Their brains looked like an inept cable guy had changed the hookups, rewiring the areas related to emotion, pain perception and the temperature of their skin.

The new finding by scientists at Northwestern University's Feinberg School of Medicine, begins to explain a mysterious condition that the medical community had doubted was real.

The people whose brains were examined have a chronic pain condition called complex region pain syndrome (CRPS.) It's a pernicious and nasty condition that usually begins with an injury causing significant damage to the hand or the foot. For the majority of people, the pain from the injury disappears once the limb is healed. But for 5 percent of the patients, the pain rages on long past the healing, sometimes for the rest of people's lives. About 200,00 people in the U.S. have this condition.

In a hand injury, for example, the pain may radiate from the initial injury site and spread to the whole arm or even the entire body. People also experience changes in skin color to blue or red as well as skin temperature (hotter at first, then becoming colder as the condition turns chronic.) Their immune system also shifts into overdrive, indicated by a hike in blood immune markers.

The changes in the brain take place in the network of tiny, white "cables" that dispatch messages between the neurons. This is called the brain's white matter. Several years ago, Northwestern researchers discovered chronic pain caused the regions in the brain that contain the neurons -- called gray matter because of it looks gray -- to atrophy.

This is the first study to link pain with changes in the brain's white matter. It will be published November 26 in the journal Neuron. "This is the first evidence of brain abnormality in these patients," said A. Vania Apkarian, professor of physiology at the Feinberg School and principal investigator of the study. " People didn't believe these patients. This is the first proof that there is a biological underpinning for the condition. Scientists have been trying to understand this baffling condition for a long time."

Apkarian said people with CRPS suffer intensely and have a high rate of suicide. "Physicians don't know what to do," he said. "We don't have the tools to take care of them."

The new findings provide anatomical targets for scientists, who can now look for potential pharmaceutical treatments to help these patients, Apkarian said. He doesn't know yet if chronic pain causes these changes in the brain or if CRPS patients' brains have pre-existing abnormalities that predispose them to this condition.

In the new study, the brains of 22 subjects with CRPS and 22 normal subjects were examined with an anatomical MRI and a diffusion tensor MRI, which enabled scientists to view the white matter. In addition to

changes in white matter, the CRPS patients' brains showed an atrophy of neurons or gray matter similar to what has been previously shown in other types of chronic pain patients.

Apkarian said the white matter changes in patients' brains is related to the duration and intensity of their pain and their anxiety. It is likely that white matter reorganizes in other chronic pain conditions as well, but that has not yet been studied, he noted.

Plate tectonics started over 4 billion years ago, geochemists report

Analysis of minerals in ancient magmas paints new picture of early Earth

A new picture of the early Earth is emerging, including the surprising finding that plate tectonics may have started more than 4 billion years ago — much earlier than scientists had believed, according to new research by UCLA geochemists reported Nov. 27 in the journal Nature.

"We are proposing that there was plate-tectonic activity in the first 500 million years of Earth's history," said geochemistry professor Mark Harrison, director of UCLA's Institute of Geophysics and Planetary Physics and co-author of the Nature paper. "We are reporting the first evidence of this phenomenon."

"Unlike the longstanding myth of a hellish, dry, desolate early Earth with no continents, it looks like as soon as the Earth formed, it fell into the same dynamic regime that continues today," Harrison said. "Plate tectonics was inevitable, life was inevitable. In the early Earth, there appear to have been oceans; there could have been life — completely contradictory to the cartoonish story we had been telling ourselves."

"We're revealing a new picture of what the early Earth might have looked like," said lead author Michelle Hopkins, a UCLA graduate student in Earth and space sciences. "In high school, we are taught to see the Earth as a red, hellish, molten-lava Earth. Now we're seeing a new picture, more like today, with continents, water, blue sky, blue ocean, much earlier than we thought."

The Earth is 4.5 billion years old. Some scientists think plate tectonics - the geological phenomenon involving the movement of huge crustal plates that make up the Earth's surface over the planet's molten interior - started 3.5 billion years ago, others that it began even more recently than that.

The research by Harrison, Hopkins and Craig Manning, a UCLA professor of geology and geochemistry, is based on their analysis of ancient mineral grains known as zircons found inside molten rocks, or magmas, from Western Australia that are about 3 billion years old. Zircons are heavy, durable minerals related to the synthetic cubic zirconium used for imitation diamonds and costume jewelry. The zircons studied in the Australian rocks are about twice the thickness of a human hair.

Hopkins analyzed the zircons with UCLA's high-resolution ion microprobe, an instrument that enables scientists to date and learn the exact composition of samples with enormous precision. The microprobe shoots a beam of ions, or charged atoms, at a sample, releasing from the sample its own ions, which are then analyzed in a mass spectrometer. Scientists can aim the beam of ions at specific microscopic areas of a sample and conduct a high-resolution isotope analysis of them without destroying the object.

"The microprobe is the perfect tool for determining the age of the zircons," Harrison said.
The analysis determined that some of the zircons found in the magmas were more than 4 billion years old. They were also found to have been formed in a region with heat flow far lower than the global average at that time.

"The global average heat flow in the Earth's first 500 million years was thought to be about 200 to 300 milliwatts per meter squared," Hopkins said. "Our zircons are indicating a heat flow of just 75 milliwatts per meter squared — the figure one would expect to find in subduction zones, where two plates converge, with one moving underneath the other."

"The data we are reporting are from zircons from between 4 billion and 4.2 billion years ago," Harrison said. "The evidence is indirect, but strong. We have assessed dozens of scenarios trying to imagine how to create magmas in a heat flow as low as we have found without plate tectonics, and nothing works; none of them explain the chemistry of the inclusions or the low melting temperature of the granites."

Evidence for water on Earth during the planet's first 500 million years is now overwhelming, according to Harrison. "You don't have plate tectonics on a dry planet," he said. Strong evidence for liquid water at or near the Earth's surface 4.3 billion years ago was presented by Harrison and colleagues in a Jan. 11, 2001, cover story in Nature.

"Five different lines of evidence now support that once radical hypothesis," Harrison said. "The inclusions we found tell us the zircons grew in water-saturated magmas. We now observe a surprisingly low geothermal gradient, a low rate at which temperature increases in the Earth. The only mechanism that we recognize that is consistent with everything we see is that the formation of these zircons was at a plate-tectonic boundary. In addition, the chemistry of the inclusions in the zircons is characteristic of the two kinds of magmas today that we see at place-tectonic boundaries."

"We developed the view that plate tectonics was impossible in the early Earth," Harrison added. "We have now made observations from the Hadean (the Earth's earliest geological eon) — these little grains contain a record about the conditions under which they formed — and the zircons are telling us that they formed in a region with anomalously low heat flow. Where in the modern Earth do you have heat flow that is one-third of the global average, which is what we found in the zircons? There is only one place where you have heat flow that low in which magmas are forming: convergent plate-tectonic boundaries."

Three years ago, Harrison and his colleagues applied a technique to determine the temperature of ancient zircons. "We discovered the temperature at which these zircons formed was constant and very low," Harrison said. "You can't make a magma at any lower temperature than what we're seeing in these zircons. You look at artists' conceptions of the early Earth, with flying objects from outer space making large craters; that should make zircons hundreds of degrees centigrade hotter than the ones we see. The only way you can make zircons at the low temperature we see is if the melt is water-saturated. There had to be abundant water. That's a big surprise because our longstanding conception of the early Earth is that it was dry."

Has universal ageing mechanism been found?

* 17:00 26 November 2008 **by Linda Geddes**

An overworked protein that causes yeast to age when it neglects one of its functions may trigger ageing in mice too. If the same effect is found in people, it may suggest new ways to halt or reverse age-related disease.

As we get older, genes can start to be expressed in the wrong body tissues - a process that is thought to contribute to diseases like diabetes and Alzheimer's. But while sunlight or chemicals are known to cause limited DNA damage, how more widespread changes in gene expression come about has been unclear.

To investigate, David Sinclair and colleagues at Harvard Medical School turned to yeast cells. These produce a dual-function protein called Sir2 that, while being involved in DNA repair, also helps keep certain genes switched off. As yeast cells age, the protein can't do both jobs and neglects its role as a gene suppressor.

'Unifying pathway'

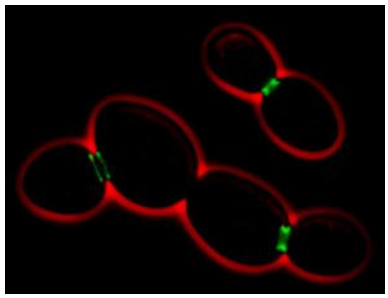
Now Sinclair's team has shown that SIRT1, the mammalian version of Sir2, also begins to neglect its gene-suppressor role in mice whose DNA is damaged, and that this may contribute to ageing. This raises the hope that, if gene-suppressing proteins become similarly overworked in ageing people, they could become prime targets for drugs to keep us young.

This possibility is boosted by the team's finding that mice engineered to over-express the gene for SIRT1 were better at repairing DNA, more resistant to cancer, and maintained a more youthful pattern of gene expression.

"The most exciting thing is that this work may unify in a single molecular pathway what we know about ageing in different organisms such as yeast and mammals," says Maria Blasco of the Spanish National Cancer Research Centre in Madrid, who works on mechanisms of cellular ageing.

"It opens up the possibility of restoring youth in the elderly by re-establishing a useful pattern of gene expression," adds Sinclair.

His team now hopes to study whether established changes in gene expression could be reversed by increasing production of SIRT1, perhaps using chemicals like resveratrol, which targets SIRT1 and has previously been associated with longevity.



The ageing-related protein Sir1 was first found in yeast, and has now been found to serve a similar role in mice. This fluorescent micrograph shows yeast (Saccharomyces cerevisiae), with some proteins tagged with Green Fluorescent Protein **(Image: Spitfire ch, Philippsen Lab, Biozentrum Basel)**

Cancer link?

Earlier this month two different groups of researchers showed that it might be possible to reverse cellular ageing by preventing the loss of telomeres - caps of repetitive DNA found at the ends of chromosomes that are thought to affect cell lifespan. "The [telomere] paper suggests that the rest of the genome also has issues that need to be addressed if we're going to slow down ageing," says Sinclair. Blasco adds that it would be interesting to find out how telomere shortening affects Sirt1-dependent ageing.

"This is another fascinating discovery from the lab that has done more than any other to characterise and manipulate the behaviour of one of the few bona-fide 'master control genes'," says Aubrey de Grey of the Methuselah Foundation, which promotes research into lifespan extension.

While yeast may use the mechanism to switch off reproduction in hard times, "in mammals it may mainly be important for preventing cancer", says de Grey. "This study further confirms the utility of discoveries in lower organisms for guiding us towards some of the therapies that may increase human healthy longevity."

Journal reference: Cell (DOI: 10.1016/j.cell.2008.10.025)

Pig organs: Ready for humans at last?

* 26 November 2008 **by Andy Coghlan**

IN THE not too distant future, a person in need of a heart transplant could be offered a pig's organ. That's the hope of a group that met in China last week to agree global guidelines for the first clinical trials of "xenotransplants". The meeting of clinicians, researchers and regulators in Changsha, Hunan province, which was organised by the World Health Organization, resulted in the so-called Changsha Communiqué - a document that should eventually guide global regulation of xenotransplants.

It sets out principles for research, recommends how the WHO and individual countries should monitor such research, and includes guidelines for trials (see "Trials and transplants"). Perhaps most importantly, with human organs in desperately short supply, it reflects how far research has come since a decade ago, when some of the problems associated with xenotransplants seemed insurmountable.

For example, one big concern related to porcine endogenous retroviruses (PERVs). These are dormant viral DNA present in the pig genome that researchers feared would reawaken in an organ transplanted into humans, who, unlike pigs, might not be able to keep the viruses dormant. Pigs have now been genetically engineered either to lack PERVs entirely or to carry RNA interference molecules primed to sabotage any that become active. "Most of us now agree the risk is quite manageable," says Megan Sykes of Massachusetts General Hospital in Boston, who attended the meeting.

The first pig tissue to find its way into humans probably won't be an organ, but insulin-producing islet cells from the pancreas, to treat people with diabetes. Two years ago, Bernard Hering's team at the University of Minnesota in Minneapolis reported injecting unaltered pig islet cells into the livers of diabetic monkeys, along with immunosuppressive drugs. The monkeys were able to go without insulin injections for the duration of the 100-day experiment (Nature Medicine, vol 12, p 301). Hering is now in discussions with the US Food and Drug Administration (FDA) about how to proceed with a human trial.

David White and his colleagues at the Robarts Institute in London, Ontario, Canada, are also talking to the FDA about a possible trial next year. To make islet cells less likely to be rejected, White mixes them with Sertoli cells from pig testes, which contain a molecule that seems to damp down attacks by human T-cells. White explains that Sertoli cells are equipped with the cellular machinery to protect sperm, which would otherwise be vulnerable to attack by the immune system because they have half the chromosomes of other cells.

Rafael Valdés-González of the Children's Hospital of Mexico in Mexico City, who first pioneered the Sertoli cell technique, has already tested it in a small number of people and claims that one patient is still insulin-independent as a result (Clinical Transplantation, DOI: 10.1111/j.1399-0012.2007.00648.x).

Also some grounds for optimism come from a handful of trials of pig islet cells in countries where regulation is less tight. In Russia, the New Zealand company LCT claims to have had some success treating five patients with pig islet cells, which they disguised from the immune system by encapsulating them in alginate, a substance from seaweed that allows nutrients and hormones to diffuse in and out but prevents contact with immune cells. Last month, LCT won authorisation to begin a trial in New Zealand.

Sykes hopes that success with initial islet trials will bring greater public acceptance of xenotransplantation, leading to the really exciting prospect of transplanting full organs. These naturally pose greater problems, though, mainly because they must be hooked up to a blood supply and so face the full force of the immune system.

In 2002, researchers at Revivicor, a company based in Blacksburg, Virginia, found a possible way around this. Their "knockout" pigs lacked the gene for the alpha-gal protein - the molecule that indicates the presence of foreign cells to the human immune system. Other Revivicor researchers have inserted "complement regulator" genes into pig organs, which prevented monkey antibodies from attacking them.

One problem that is proving more difficult to solve is clotting. "We think antibodies bind to blood vessels of the pig graft, and these activate coagulation factors," says David Cooper, a pioneer of xenotransplantation at the University of Pittsburgh Medical Center in Pennsylvania who collaborates with Revivicor.

To deal with this, two groups have produced pigs carrying human genes for anti-clotting substances. Revivicor has inserted a gene for a protein called tissue factor pathway inhibitor, which neutralises tissue factor, a key trigger of clot formation. And at the University of Melbourne in Australia, Anthony d'Apice and his colleagues have bred pigs that make human CD39, a protein that stops platelets from aggregating into clots. The hope is that these substances will only be produced locally, preventing clots in the transplanted organ but not disrupting vital clotting elsewhere (Transplant Immunology, DOI: 10.1016/j.trim.2008.10.003).

Even with these interventions, powerful immunosuppressant drugs would still be needed, weakening the body to other invaders, including cancer. To minimise this problem another idea is taking shape: engineer the

organ to make its own immunosuppressant. CTLA-4 Ig, for example, prevents T-cells being switched on, and is already used as an immunosuppressant for transplant patients.

One company is engineering pigs to produce an immunosuppressant in specific organs

Revivicor is now combining all these ideas in one animal by engineering pigs that make CTLA-4 Ig and an anticoagulant in specific organs, have the alpha-gal knockout and make the complement regulator throughout their bodies. D'Apice also claims to have created a pig with four added genes.

Because of the potential success of such experiments, guidelines are essential now. Peter Doyle, a delegate at the meeting and former secretary of the now-defunct UK Xenotransplantion Interim Regulatory Authority says: "Xenotransplantation has the potential to treat millions of people, but the threatened dangers are worrying unless it's properly regulated globally."

Trials and transplants

Global regulation of trials needed to monitor for dangers such as viruses

Trials banned in all countries incapable of effective regulation

All trials and recipients must be registered

Trial regulation must include scientific and ethical assessment, and "involve the public"

First recipients of xeno-organs must be carefully selected to ensure they and their families accept lifelong vigilance for any signs of novel disease

All source animals should be kept in closed colonies free from pathogens

"Compelling justification" needed for trials, including adequate evidence of safety and efficacy from animal studies

New approaches make retinal detachment highly treatable

New England Journal of Medicine study by NewYork-Presbyterian/Weill Cornell ophthalmologist and surgeon highlights advanced techniques used to save vision

NEW YORK (Nov. 26, 2008) -- Retinal detachment, a condition that afflicts about 10,000 Americans each year, puts an individual at risk for vision loss or blindness. In a new study in today's issue of the New England Journal of Medicine, a leading ophthalmologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center writes, however, that a high probability of reattachment and visual improvement is possible by using one of three currently available surgical techniques.

"Although no randomized trials have been conducted that show definitively that one procedure is best for every situation, improvements in these surgical techniques have led to effective treatments for most patients," says Dr. Donald J. D'Amico, ophthalmologist-in-chief at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, professor and chairman of ophthalmology at Weill Cornell Medical College, and an international leader in vitreoretinal surgery.

Although relatively rare, retinal detachment can occur when holes, tears or breaks appear in the light-sensitive retina as a result of trauma or pulling away of the gelatinous mass, known as the vitreous, that fills the back of the eye. Retinal tears occur most often in adults over age 60, but may occur much earlier, particularly in those with high myopia. The sudden onset of light flashes and "floaters" could be the warning signs of an impending retinal detachment, although these symptoms do not always mean that a retinal tear has occurred. Surgery is the only treatment for a retinal detachment.

In the article "Primary Retinal Detachment," Dr. D'Amico offers his recommendations for treating a 57-year-old man who experiences sudden flashes and floaters in one eye, progressive loss of vision and a retinal detachment.

The three surgical options currently in use to treat such a case are:

1. Scleral Buckling. A common way to treat a retinal detachment, scleral buckling surgery has been performed with success for several decades. In this procedure, a piece of silicone is sutured onto the outside wall of the eyeball and left in place permanently to create an indentation, or buckle, that restores contact with the detached retina. The individual tears are then closed by a localized scar that is induced with a freezing probe or laser. According to Dr. D'Amico, scleral buckling is a relatively involved procedure and requires the use of a hospital operating room. It is usually performed on an outpatient basis with local anesthesia with intravenous sedation, and the overall success rate for reattachment is about 90 percent.
2. Pneumatic Retinopexy. A newer and less invasive procedure than scleral buckling, pneumatic retinopexy is usually done in the retina specialist's office under local anesthesia. The procedure involves injecting a gas bubble into the vitreous cavity of the eye, then positioning the patient's head so that the bubble floats to the break in the detached retina. The bubble spans and closes the retinal break, and this allows the natural forces in the eye to reattach the retina. The break is permanently sealed by the application of a freezing probe or laser to create a scar around the break. The gas bubble then resolves over several days, and in successful cases, the

retina is left reattached without a trip to the operating room, and with no permanent buckling material applied to the eye. According to Dr. D'Amico, pneumatic retinopexy is not suitable for every patient and has a somewhat lower success rate with initial treatment than does scleral buckling or vitrectomy. Nevertheless, he says, because of its minimally invasive attributes, and the fact that an attempted pneumatic does not reduce the ultimate chance for success if additional surgery is required for recurrent detachment, patient and surgeons increasingly select pneumatic retinopexy for suitable primary retinal detachments after a careful discussion of the limitations.

3. Vitrectomy. In contrast to scleral buckling, vitrectomy is a surgery within the eye in which the vitreous gel is removed. Because vitreous traction is the typical cause of the retinal tears in a detachment, this approach has the advantage of directly attacking the underlying cause of the detachment. Vitrectomy surgery -- a few decades old -- is a newer surgery than scleral buckling, and it is continually improving due to innovations in instrumentation and technique. Recent studies have shown success rates comparable to those of scleral buckling. Dr. D'Amico notes that there is a very strong shift toward vitrectomy, and away from buckling, for retinal detachment, particularly by younger surgeons and for patients that have detachment after cataract surgery. Vitrectomy for detachment may be associated with a higher risk of postoperative cataract, and this appears to be its main disadvantage compared to buckling, which has lower risk of cataract but higher risk of other complications. In cases where bleeding in the vitreous gel is present with the detachment, a vitrectomy approach is clearly preferred to remove the vitreous hemorrhage in order to gain better visualization to find and repair tears or holes in the retina. Vitrectomy, like scleral buckling, is typically done on an outpatient basis with local anesthesia with intravenous sedation.

For the patient described in the vignette who went to his ophthalmologist with classic symptoms of primary retinal detachment, including flashing lights, floaters and progressive loss of vision, Dr. D'Amico's first recommendation would be to perform a pneumatic retinopexy. "I would select this option for this patient because this specific detachment is well-suited to pneumatic retinopexy by virtue of the retinal breaks being located close together in the superior retina, which is the easiest location to treat with an intraocular gas bubble. Furthermore, the procedure can be done immediately in the doctor's office at lower cost and with fewer risks of complications, compared to buckling or vitrectomy, and it also compares quite favorably with the other procedures with having a 75 percent chance of restoring vision to 20/50 or better after this minimally invasive procedure," Dr. D'Amico says.

As with any surgery, there are risks associated with each of these techniques. For example, vitrectomy can cause cataract or elevated pressure inside the eye, especially in people with glaucoma; scleral buckling can cause a change in the shape of the eye that may require alteration of the eyeglass prescription; and pneumatic retinopexy often requires more than one surgery to reattach the retina.

"The benefits of surgery, however, far outweigh the risks," says Dr. D'Amico, who performs all of these procedures. "No matter which procedure the surgeon chooses, there is a very good chance today that a patient's retina can be reattached and his or her vision preserved."

Route to obesity passes through tongue

Obesity gradually numbs the taste sensation of rats to sweet foods and drives them to consume larger and ever-sweeter meals, according to neuroscientists. Findings from the Penn State study could uncover a critical link between taste and body weight, and reveal how flab hooks the brain on sugary food.

"When you have a reduced sensitivity to palatable foods, you tend to consume it in higher amounts," said Andras Hajnal, associate professor of neural and behavioral sciences at Penn State College of Medicine. "It is a vicious circle."

Previous studies have suggested that obese persons are less sensitive to sweet taste and crave sweet foods more than lean people. However, little is known about the specific differences between obese and lean individuals in their sense of taste and the pleasure they derive from sweet foods.

Hajnal and his Penn State colleague Peter Kovacs, a post-doctoral fellow, investigated these differences by studying the taste responses of two strains -- OLETF and LETO rats.

Compared to the lean and healthy LETO rats, the taste responses in OLETF rats mirror those in obese humans. These rats have normal body weight at first, but they tend to chronically overeat due to a missing satiety signal, become obese and develop diabetes. The obese rats also show an increased preference for sweet foods and also are willing to work harder to obtain sweet solutions as a reward for their learning.

"When you have excess body weight, the brain is supposed to tell you not to eat more, or not choose high caloric meals" said Hajnal. "But this control apparently fails and thus the obesity epidemic is rising, and we want to find out how the sense of taste drives up food intake."

The researchers implanted electrodes in the rodents' brains to record the firing of nerve cells when the rats' tongues were exposed to various tastes -- salt, citric acid, plain water and six different concentrations of sucrose.

Hajnal and Kovacs specifically looked at differences in processing taste in the pontine parabrachial nucleus (PBN), a part of the brain that uses nerve cells to relay information from the surface of the tongue to the brain.

"We found that compared to the LETO rats, the OLETF rats had about 50 percent fewer neurons firing when their tongues were exposed to sucrose, suggesting that obese rats are overall less sensitive to sucrose," explained Hajnal, whose findings appeared in a recent issue of the Journal of Neurophysiology. The response to salt was the same for both strains.

However, when the obese rats were fed a stronger concentration of sucrose, their nerve cells fired more vigorously than in the lean rats. In other words, obese rats have a weaker response to weak concentrations and a stronger response to strong concentrations.

"These findings tell us that there is a difference in activation of neurons between lean and obese rats when they are exposed varying concentrations of sucrose," noted Hajnal. "If you sense sweetness less, you may be inclined to eat sweeter foods."

The Penn State researchers believe that the increased consumption of sweet foods over time could be influencing the brain's reward center by relaying progressively weaker nerve signals, which affects the perception of taste of the meals through the PBN.

In obese humans, an increase in the weight-height ratio is usually accompanied by a decrease in dopamine, which is a neurotransmitter associated with the brain's pleasure system.

"In these obese rats, like in humans, the dopamine system is suppressed and it is very possible that the obese rats are seeking a hedonistic experience or reward by eating larger meals and when they have a chance they also eat more sweets," Hajnal added.

The findings linking taste responses and obesity could hold an important message for a condition that affects more than 60 percent of adult Americans.

For instance, Hajnal points to an ever-increasing amount of fat and sugar in processed foods. The enhanced taste of these foods, he says, stimulates our taste and food reward neurons on a chronic basis, making them less sensitive over time. And what do we do when this happens?

"Instead of eating less, we seek out higher palatability," Hajnal explained. "We simply start putting an extra spoonful of sugar in our coffee."

Down's symptoms may be treatable in the womb

* 26 November 2008 **by Aria Pearson**

A PREGNANT woman who knows her unborn child has Down's syndrome might one day be able to prevent some symptoms before giving birth.

That at least is the hope raised by experiments in mice. When fetal mouse pups that had a syndrome similar to Down's were treated with nerve-protecting chemicals, some of the developmental delays that are part of the condition were removed.

Children with Down's have an extra copy of chromosome 21, while mice engineered to have a similar condition are given an extra copy of a segment of chromosome 16. In both species, the development of certain motor and sensory abilities is delayed. These "trisomic" individuals may also have learning difficulties and symptoms of Alzheimer's later in life.

Inhibiting the neurotransmitter GABA in trisomic mice can improve cognition and some have suggested this could be used in children. It would be even better, however, to treat Down's before a child is born and so improve cognitive potential.

Previous studies both of people with Down's and trisomic mice have also revealed malfunctions in glial cells - brain cells that regulate the development of neurons by releasing certain proteins. The aberrant cells produce less of these proteins than normal. And adding segments of some of these proteins - known as NAP and SAL - to cultured neurons from people with Down's, which would otherwise degenerate, seems to protect the neurons (Current Pharmaceutical Design, DOI: 10.2174/138161207780618957).

Armed with this knowledge, Catherine Spong and colleagues at the National Institutes of Health in Bethesda, Maryland, injected NAP and SAL into mice pregnant with trisomic pups in the middle of their pregnancy. When the pups were born, they reached developmental milestones such as grasping a rod, righting themselves and responding to tactile stimulation at the same time as normal mice (Obstetrics and Gynecology, vol 112, p 1242). "We were able to prevent a significant amount of the delay," says Spong.

When the pups were born, they reached developmental milestones at the same time as normal mice

The brains of the treated mice also showed normal levels of ADNP - one of the regulatory proteins underproduced by Down's-affected glial cells - and of another compound that is a marker for healthy glial cells. Both findings indicate that some effects of Down's had been removed.

Now Spong is watching to see if mice treated as fetuses also display less of a learning deficit as they mature. She hopes that the prenatal treatment might permanently increase the expression of the proteins in question.

What works in mice or cultured human cells doesn't always work in people, of course. Several compounds have shown promise in human cells for the treatment of Alzheimer's but disappointed when tested in people, warns Jorge Busciglio, a neurobiologist at the University of California, Irvine, who was one of the team that treated cultured human neurons with NAP and SAL. Nonetheless he is cautiously optimistic.

Charles Cantor of the company Sequenom in San Diego, California, which is developing a non-invasive prenatal blood-screening test for Down's (New Scientist, 11 October, p 10), is excited at the prospect of a prenatal treatment. "I'd love to see these early screening tests lead to therapy and not just termination," he says. "It would have a big impact, especially for families that are not willing to consider abortion as an option."

New acceptance for Down's syndrome

* 26 November 2008

ACCORDING to one dystopian vision of where advances in genetics are taking us, society will descend into a monoculture of super-smart people with gleaming white teeth.

The parents of children with Down's syndrome are at the sharp end of the debate about where to draw the line between selecting perfection, preventing disability and accepting diversity. With the rise of prenatal screening, they fear for their children's well-being in a world where there are fewer people like them. This unease could deepen with the realisation (see "Prenatal treatment for Down's works in mice") that some Down's symptoms could be treated in the womb.

Another vision emerges from a survey by the British Down's Syndrome Association, however. More babies with Down's are being born now than when screening was widely introduced. Though the statistics are complicated by the rise in the numbers of older mothers - who are more likely to have children with the syndrome - it suggests that when parents have the choice, they may well accept what some insurers call "elective disability". Our genetic future suddenly looks less eugenic and more interesting.

Experimental TB drug explodes bacteria from the inside out

Research advance may lead to new ways to attack latent TB and other bacteria

An international team of biochemists has discovered how an experimental drug unleashes its destructive force inside the bacteria that cause tuberculosis (TB). The finding could help scientists develop ways to treat dormant TB infections, and suggests a strategy for drug development against other bacteria as well.

A report describing the research, led by Clifton E. Barry, III, Ph.D., of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, is published in the Nov. 28 issue of Science. Dr. Barry's collaborators included scientists from NIAID and from the Novartis Institute for Tropical Diseases in Singapore.

One-third of the world's population is infected with Mycobacterium tuberculosis (M. tb), the bacteria that cause TB. "Currently, there are no drugs available that specifically target latent tuberculosis infections in which bacteria are present but are not actively dividing," notes NIAID Director Anthony S. Fauci, M.D. "Dr. Barry and his colleagues have now given us a detailed picture of how the candidate TB drug PA-824 is metabolized inside Mycobacterium tuberculosis. Their discovery is a promising step towards developing effective drugs against latent TB as well as other bacteria."

Previously, Dr. Barry and his collaborators found that M. tb mutants lacking a specific bacterial enzyme were resistant to PA-824, but at that time, they did not know the function of the enzyme.

"It took several years, but at last we were able to recreate in the test tube what happens inside mycobacterial cells when the bacterial enzyme, which we named Ddn, and a second bacterial component called a cofactor, interact with PA-824," says Dr. Barry. The key event in PA-824 metabolism, they found, is the production of nitric oxide (NO) gas. "This highly reactive molecule," he adds, "is akin to a bomb blast that kills the bacteria from within."

NO gas is produced naturally by certain immune system cells after they engulf M. tb or other bacteria. This is one way that people with healthy immune systems can contain M. tb infection. However, this natural immune response is not always enough to completely rid the body of TB bacteria. In essence, PA-824 performs similarly to the NO-producing immune cells--but the drug's effect is more specific and triggered only after it enters the bacteria.

The non-dividing M. tb bacteria characteristic of latent TB infections are walled off by immune cells that aggregate around the bacteria to form a body called a granuloma. Oxygen levels are low inside granulomas. In

their latest research, the scientists observed that NO-generation during PA-824 metabolism is greatest when oxygen levels are low. This observation suggests how PA-824 may work against non-dividing M. tb.

PA-824 was originally designed to work best under aerobic, or oxygenated, conditions. With this new understanding of how the bacterial enzyme and cofactor act on PA-824 under low-oxygen conditions, Dr. Barry says, scientists can design drugs with a chemical structure similar to PA-824 but optimize them from the start to behave best under low-oxygen conditions. This work is already proceeding in the laboratory at NIAID and in partnership with collaborators from the Novartis Institute for Tropical Diseases in Singapore as well as with scientists from the Genomics Institute of the Novartis Research Foundation in San Diego.

Because humans have neither the bacterial cofactor nor any enzymes equivalent to Ddn, PA-824 has no effect on human cells. Conversely, many bacteria have enzymes in the same family as Ddn. Thus, says Dr. Barry, it is possible to envision new kinds of NO-generating drugs designed to interact with enzymes associated with other disease-causing bacteria as well.

In addition to NIAID funding, this research received grant support through the Grand Challenges in Global Health Program, which is jointly funded by the Bill & Melinda Gates Foundation and the Wellcome Trust.

Background Information

In 2000, Dr. Barry and colleagues at NIAID collaborated with the Seattle-based firm PathoGenesis to publish the first description of PA-824 (http://www3.niaid.nih.gov/news/newsreleases/2000/pa824.htm).

PA-824 entered human clinical trials in 2005 (http://www3.niaid.nih.gov/news/newsreleases/2005/tb_pa_824.htm).

The M. tb enzyme now named Ddn was first described by Dr. Barry and his colleagues in 2005 *(http://www3.niaid.nih.gov/news/newsreleases/2005/tbdrug.htm).*

Reference: R Singh et al. Bicyclic nitroimidazoles are intracellular NO donors and kill non-replicating Mycobacterium tuberculosis. Science DOI: 10.1126/science.1164571 (2008).

CSHL scientists discover a new way in which epigenetic information is inherited

A class of small RNAs inherited from the mother determines offspring's fertility trait

Hereditary information flows from parents to offspring not just through DNA but also through the millions of proteins and other molecules that cling to it. These modifications of DNA, known as "epigenetic marks," act both as a switch and a dial – they can determine which genes should be turned on or off, and how much message an "on" gene should produce.

One way in which epigenetic information is known to be passed from parent to offspring is through the pattern of chemical "caps" added onto certain "letters" of the DNA sequence, ensuring the sequence is "silenced." How these DNA capping patterns, which are inherited, are precisely set is not yet known. But in some cases, enzymes that add these caps are guided to DNA by small RNA molecules. These guides themselves do not carry hereditary information, but they do mark the spots where DNA is to be modified.

A team of scientists at Cold Spring Harbor Laboratory (CSHL) led by Professor Gregory J. Hannon, Ph.D., has now discovered that a class of small RNAs does carry epigenetic information and in fact passes on the trait of fertility from mother to offspring in fruit flies.

A new mechanism of inheritance

In a paper to be published on Nov 27th in Science, the CSHL team reports that maternal small RNAs called Piwi-interacting RNAs (piRNAs) that are deposited into fruit fly embryos "silence" DNA sequences that induce sterility, thus ensuring the fertility of the progeny. "This is a whole new way in which heredity can be transmitted," says Professor Hannon, who is a pioneer in small RNA research. "With this finding we've effectively doubled the number of mechanisms by which epigenetic information is known to be inherited."

The piRNAs are found only in cells of sex organs and partner up with proteins called Piwi to suppress the activity of mobile DNA sequences called transposons. Discovered half a century ago by CSHL scientist and Nobel laureate Barbara McClintock, Ph.D., transposons jump around the genome, inserting themselves into genes and causing mutations. Such genetic havoc is thought to underlie many diseases, including cancer.

A high rate of mutations also disturbs gametogenesis – the process of creating viable sex cells – and can result in sterility. Piwi proteins and piRNAs form something akin to an immune system in sex cells that guards against transposon-inflicted genome damage.

Solving the fruit fly fertility puzzle

The CSHL team wondered whether piRNAs were also the key to a long-standing conundrum about fertility in fruit flies. When lab-bred female flies are bred with male flies caught in the wild, their progeny are sterile or unable to produce offspring -- a phenomenon called hybrid dysgenesis. But the genetically identical offspring of wild-caught female flies and lab-bred males are fertile. The genetic difference between the lab-bred and wild flies is a single transposon, which is absent in lab strains.

In hybrid dysgenesis, the transmission of the transposon by a parent induces sterility in the offspring unless the offspring also inherits a factor that suppresses the transposon and maintains fertility. Since the phenomenon

had only been seen when the transposon-transmitting parent was male, the suppressing factor was thought to be maternally transmitted. But it was never identified.

Hannon's team has now found that the stockpile of maternally derived proteins, RNA, and nourishing raw material in developing fruit fly oocytes, or egg cells, also includes piRNAs. And these maternally deposited piRNAs prove to be essential for mounting a silencing response against transposons.

Inheritance via small RNAs

Hannon likens this protection to that afforded by the adaptive immune system which protects against pathogens like bacteria and viruses. "We've evolved ways to transmit immunity from mother to child via the secretion of antibodies," he says, referring to the proteins that can cross the placenta and protect the fetus or get passed on to an infant via breast-milk. "We now have a way in which immunity (against sterility) is passed on from mother to child, in flies but possibly other organisms also, via small RNAs."

In contrast to short-lived adaptive immunity, however, this small RNA-driven immunity has a long reach. The team's experiments show that the effect on fertility doesn't just impact the child alone, but also the next generation. Because the trait – fertility – is controlled or encoded in the RNA, "you're passing on a trait that's essentially not only controlling an event that happens in the organism's adulthood, but is also propagated to the progeny of that organism," explains Hannon.

The impact of environment

The ability of the mother to transmit epigenetic information can be altered by the environment that she finds herself in. Other researchers have found that raising the temperature in which female flies are reared raises the proportion of fertile progeny.

To the CSHL team, this suggests that "the experience of the mother translates into a dominant effect on the progeny." The group's data suggest that one way that the mother's experience might get communicated to the child is through variations in the populations of small RNAs that get deposited in the oocytes.

Now that one trait has been discovered to be driven by maternally inherited piRNA, Hannon is eager to know if the spectrum of information that's transmitted in this way can be broadened to cover other cellular processes. And of course, it also remains to be seen whether this mechanism of epigenetic inheritance is found in organisms besides fruit flies. "Small RNAs are probably deposited in oocytes of every animal," he hypothesizes.

"An epigenetic role for maternally inherited piRNAs in transposon silencing" appears online on November 27th in Science. The full citation is: Julius Brennecke, Colin D. Malone, Alexei A. Aravin, Ravi Sachidanandam, Alexander Stark, Gregory J. Hannon. The paper will be available on www.science.com at 2pm on November 27th, 2008.

Did Neanderthal cells cook as the climate warmed?

* 15:49 27 November 2008 **by Ewen Callaway**

Neanderthals may have gone extinct because their cells couldn't cope with climate change, according to a new hypothesis presented at a genetics conference this month.

Metabolic adaptations to Ice Age Europe may have proved costly to Neanderthals after the continent's climate started to change, says Patrick Chinnery, a molecular biologist at Newcastle University, UK.

He and colleague Gavin Hudson identified potentially harmful mutations in the newly sequenced Neanderthal mitochondrial genome. In particular, the researchers found genes that are associated with neurodegenerative diseases and deafness. "If they were found in modern humans they would be bad news," Chinnery says.

The extinction of Neanderthals, close relatives of modern humans, some 25,000 years ago remains unexplained.

One theory holds that they were physically outcompeted by modern humans , another that they were economically eclipsed by us.. Yet another theory suggests that Neanderthals couldn't adapt to climate change.

This Neanderthal skeleton was found in 1856 in the Neander Valley in Mettmann **(Image: Action Press / Rex Features)**

Cooked cells?

The discovery of harmful mutations in the Neanderthal mitochondrial genome supports the climate-change idea, with a twist.

Chinnery and Hudson suggest that mutations in mitochondria helped Neanderthals cope with the cold weather, but that when the climate started fluctuating between warm and cold periods, they were at a disadvantage.

In all cells, from yeast to human, a mitochondrion's main job is to produce the energy that powers cells - this takes the form of a chemical called ATP. Our mitochondria do this quite efficiently under ideal conditions, making 36 ATP molecules with the energy stored in a single molecule of glucose sugar.

Mutations that sap this efficiency would generate heat instead - a potentially useful trick for Neanderthals who are known to have had adaptations to cold weather, Chinnery says. However, a warmer and less climatically stable habitat could have spelled trouble for Neanderthals with such mutations.

Perhaps the Neanderthals' mitochondrial DNA adapted them to the cold, and they couldn't cope when the climate started to change, he says.

Mum's mitochondria

However, with only a single Neanderthal DNA sequence decoded so far, that hypothesis remains provisional. "This 'n of 1' experiment raises a question which needs to be tested on a large number of cases," Chinnery says.

They might not have to wait long. "We hope to be able to provide [Neanderthal] subjects for doing that kind of analysis really soon," says Edward Green, a researcher at Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. Green and colleague Svante Pääbo published the first complete Neanderthal mitochondrial genome earlier this year.

However, Green cautions against reading too much into a Neanderthal's - or a human's - mitochondria.

Unlike DNA in the cell's nucleus, mitochondrial DNA does not reflect a healthy mix of maternal and paternal genes. We inherit all mitochondrial genes from our mothers, so a potentially advantageous gene has no way to spread through a population, without bringing along the rest of the genome.

Most scientists contend that changes to mitochondrial genes instead occur by chance, making them a good marker for human and Neanderthal ancestry.

Parents of new babies should be considered for a whooping cough booster, say experts

Lesson of the week: Rapidly fatal invasive pertussis in babies -- how can we change the outcome? BMJ Online

A booster vaccination for parents of new babies and other household members may be the most effective way of preventing the fatal form of whooping cough in young infants, say a group of paediatric intensive care doctors on bmj.com today.

Whooping cough (pertussis) is a distressing infectious disease which affects infants and young children. Vaccination is effective and is usually given to infants at two to four months of age, with a further booster after three years. But evidence is growing that the incidence of pertussis is rising in adolescents and adults.

Infectious adults within a family are the main source of infection for unimmunised infants.

Doctors at the Royal Hospital for Sick Children in Edinburgh report two fatal cases of invasive pertussis in unvaccinated young infants.

In the first case, a one-month old boy presented to hospital with a five-day history of cough, runny nose and difficulty feeding. Both parents, and an elder sibling, reported coughing spells with vomiting in the previous two weeks.

The sibling was fully vaccinated. There was no record of the parents' childhood vaccination status but the mother received a pertussis booster in 1986.

The child was transferred to intensive care, but despite maximum therapy, died within 24 hours.

In the second case, a six-week old girl presented to hospital with a five-day history of cough and breathlessness. Her mother had a persistent cough for more than two weeks. The mother had received all her childhood immunisations including pertussis, there was no record of the father's pertussis immunisation status.

The child died within 30 hours despite maximum therapy. The patient's mother subsequently tested positive for pertussis infection.

This report demonstrates the devastating course of invasive pertussis in young infants, say the authors.

Pre-vaccination infants now account for the majority of pertussis-related complications, hospitalisations and deaths and most infants catch the disease from affected household members, with parents accounting for more than half of the cases.

As a result, several countries, including the USA and Australia, have introduced booster doses for adolescents and adults. France and Germany also recommend a targeted booster for parents and healthcare workers in contact with young children.

Mortality remains high for young infants developing invasive pertussis despite modern paediatric intensive care, say the authors. The best solution is to prevent infection. The introduction of an adult booster or more targeted vaccination of household contacts of young infants should be considered, they conclude.

Perfect athlete's 100m sprint time calculated

* 13:32 28 November 2008 **by David Robson**

Usain Bolt and Michael Phelps slashed world records in this year's Olympics, but eventually athletes will reach the limits of the human body, making it much harder to trump previous performances.

The fastest possible time for the 100 metres will be 9.48 seconds, according to new research.

Mark Denny from Stanford University in Pacific Grove, California, examined performance records for greyhounds, racing horses, and human athletes from the 1920s to the present day. He found that for various greyhound and horse races, the top speeds reached a plateau between the 1940s and the 1970s.

This may be because fierce selective breeding helped the animals to reach an optimum body type for racing. Improved training methods have helped female sprinters to reach their optimum performances too, with increasingly fewer significant improvements since the 70s.

Male track athletes haven't yet reached a plateau in this way, but fitting the data to a mathematical model that matches the other results, Denny predicts future male sprinters will at best shave 0.21 seconds off Usain Bolt's current world record of 9.69 seconds for the 100 metres.

Female marathon runners seem even closer to reaching their plateau, with the projected future world record just 2 minutes 44 seconds shorter than Paula Radcliffe's current record.

Abbe Brady, a sports scientist from the University of Gloucestershire in the UK, points out that while it's possible that human performances will reach a plateau in this way, we are still changing the way we train and select athletes, so the predicted values may be conservative. *Journal reference: Journal of Experimental Biology*

Researchers find oldest-ever stash of marijuana

OTTAWA — Researchers say they have located the world's oldest stash of marijuana, in a tomb in a remote part of China. The cache of cannabis is about 2,700 years old and was clearly "cultivated for psychoactive purposes," rather than as fibre for clothing or as food, says a research paper in the Journal of Experimental Botany.

The 789 grams of dried cannabis was buried alongside a light-haired, blue-eyed Caucasian man, likely a shaman of the Gushi culture, near Turpan in northwestern China. The extremely dry conditions and alkaline soil acted as preservatives, allowing a team of scientists to carefully analyze the stash, which still looked green though it had lost its distinctive odour.

"To our knowledge, these investigations provide the oldest documentation of cannabis as a pharmacologically active agent," says the newly published paper, whose lead author was American neurologist Dr. Ethan B. Russo.

Remnants of cannabis have been found in ancient Egypt and other sites, and the substance has been referred to by authors such as the Greek historian Herodotus. But the tomb stash is the oldest so far that could be thoroughly tested for its properties.

The 18 researchers, most of them based in China, subjected the cannabis to a battery of tests, including carbon dating and genetic analysis. Scientists also tried to germinate 100 of the seeds found in the cache, without success. The marijuana was found to have a relatively high content of THC, the main active ingredient in cannabis, but the sample was too old to determine a precise percentage. Researchers also could not determine whether the cannabis was smoked or ingested, as there were no pipes or other clues in the tomb of the shaman, who was about 45 years old.

The large cache was contained in a leather basket and in a wooden bowl, and was likely meant to be used by the shaman in the afterlife. "This materially is unequivocally cannabis, and no material has previously had this degree of analysis possible," Russo said in an interview from Missoula, Mont. "It was common practice in burials to provide materials needed for the afterlife. No hemp or seeds were provided for fabric or food. Rather, cannabis as medicine or for visionary purposes was supplied." The tomb also contained bridles, archery equipment and a harp, confirming the man's high social standing.

Russo is a full-time consultant with GW Pharmaceuticals, which makes Sativex, a cannabis-based medicine approved in Canada for pain linked to multiple sclerosis and cancer. The company operates a cannabis-testing laboratory at a secret location in southern England to monitor crop quality for producing Sativex, and allowed Russo use of the facility for tests on 11 grams of the tomb cannabis.

Researchers needed about 10 months to cut red tape barring the transfer of the cannabis to England from China, Russo said. The inter-disciplinary study was published this week by the British-based botany journal, which uses independent reviewers to ensure the accuracy and objectivity of all submitted papers.

The substance has been found in two of the 500 Gushi tombs excavated so far in northwestern China, indicating that cannabis was either restricted for use by a few individuals or was administered as a medicine to others through shamans, Russo said. "It certainly does indicate that cannabis has been used by man for a variety of purposes for thousands of years."

Russo, who had a neurology practice for 20 years, has previously published studies examining the history of cannabis. "I hope we can avoid some of the political liabilities of the issue," he said, referring to his latest paper.

The region of China where the tomb is located, Xinjiang, is considered an original source of many cannabis strains worldwide.

New study indicates smallpox vaccination effective for decades

Implications for vaccine distribution in event of bioterrorist attack

New York, December 1, 2008 – Although naturally occurring smallpox was eradicated in 1977, there is concern that bioterrorists might obtain smallpox from a laboratory and release it into the population. Under such circumstances, the supply of smallpox vaccine may be insufficient for universal administration. In a study published in the December 2008 issue of The American Journal of Medicine, researchers found that lifetime protection is obtained from just one vaccination, even when that vaccination occurred as much as 88 years ago. They conclude that in the event of a smallpox bioterrorist attack, vaccinia smallpox vaccine should be used first on individuals who have not been vaccinated previously.

Examining 246 participants of the Baltimore Longitudinal Study of Aging, investigators from the National Institute on Aging and the National Institute of Allergy and Infectious Diseases, National Institutes of Health found permanent immunity was conferred by vaccination or by survival from an active smallpox infection. In the sample, 209 subjects were vaccinated one or more times 13 to 88 years prior to the study; an additional 18 had had childhood smallpox, and 29 with no history of vaccination or smallpox were included.

Although the vaccinia virus vaccine was used since the late 18th century, routine vaccination was discontinued more than 30 years ago in many countries. Most Americans under 35 have never been vaccinated and most over 35 have not received booster immunizations since the early 1970s. If a bioterrorist attack were to occur, it would be critical to know who already had effective immunity and would not need to be vaccinated, leaving another dose available for someone else.

Current recommendations relating to smallpox vaccination has been that people with repeated exposure to smallpox, for example travelers to endemic areas, should be revaccinated every five years. This study suggests that such reimmunizations may not be necessary because multiple vaccinations achieve only marginally higher levels of antibody and virus neutralizing activity than single vaccination.

Writing in the article, Dan L. Longo, MD, National Institute on Aging, states "A major question posed today is whether those individuals vaccinated 40 or more years ago would be protected in the event of smallpox exposure. This may be a critical question because the availability of smallpox vaccines is limited and currently inadequate for a mass inoculation program. We found that vaccinated subjects maintain what appear to be protective levels of neutralizing antibodies to vaccinia indefinitely and do not require booster vaccinations even if they are many decades removed from primary vaccination. These data imply that limited supplies of vaccine can be more usefully applied to individuals who have never been vaccinated, primarily individuals born after 1972."

The article is "Immunity from Smallpox Vaccine Persists for Decades: : A Longitudinal Study" by Dennis D. Taub, William B. Ershler, Mark Janowski, Andrew Artz, Michael L. Key, Julie McKelvey, Denis Muller, Bernard Moss, Luigi Ferrucci, Patricia L. Duffey and Dan L. Longo. It appears in The American Journal of Medicine, Volume 121, Issue 12 (December 2008) published by Elsevier.