

Pimped-up T-cells seek out and destroy HIV

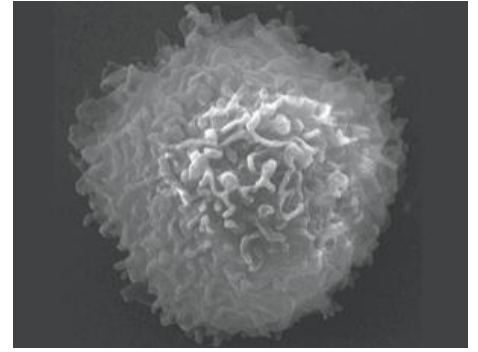
* 18:00 09 November 2008 by **Ewen Callaway**

Researchers have harnessed evolution to create souped-up immune cells able to recognise HIV far better than the regular "killer" T-cells our body produces.

The pimped up T-cell boasts a molecular receptor evolved in the lab to give the body the edge against a virus that has so far flummoxed our immune systems.

"When the body gets infected with HIV, the immune system doesn't know what the virus is going to do - but we do," says Andrew Sewell, an immunologist at Cardiff University, UK, who led the study.

Thanks to a custom-designed receptor, this killer T-cell slays HIV-infected cells far better than normal T-cells do
(Image: Andrew Sewell/University of Oxford)



One reason HIV has been able to skirt our immune systems, drugs and vaccines is the virus's chameleon-like behaviour - thanks to a genome that mutates with ease, HIV can quickly change guise to evade an attack.

But some parts of HIV are so vital to its functioning that changes result in dead or severely compromised viruses. Sewell's team targeted a part of one such protein, which holds the virus together.

The virus normally hides this protein from our immune system. But when HIV infects cells, small bits of this protein get trapped on the surface, warning the immune system of the danger that lurks inside.

The problem is that the killer T-cells our bodies produce do a mediocre job of recognizing SL9, Sewell says. So his team designed super T-cells that could recognize a portion of the protein called SL9, and then destroy the infected cell - thus preventing the virus from spreading.

Evolved killers

Beginning with a particularly potent T-cell collected from a patient in 1996, Sewell's team sought to redesign the receptor molecule that recognizes SL9.

This was done by letting one of evolution's guiding principles - survival of the fittest - take hold. In this case, the researchers selected for mutated receptors that grabbed the tightest to SL9.

In a Petri dish, the customised T-cells outperformed normal T-cells, slaying virus-infected cells with ease. The pimped up T-cells produced high levels of chemicals, called cytokines, which are indicative of a successful immune response. The engineered cells also recognised variations on SL9 that befuddle normal killer T-cells.

Sewell's team is preparing to test the cells in mice that have been engineered to produce human immune cells, capable of becoming infected with HIV. If those tests go well, his team hopes to try the approach in HIV-infected people.

Side effects?

One pitfall could be that the cells prove too strong for their own good, says James Riley, an immunologist at the University of Pennsylvania in Philadelphia, who also led the study.

The cells might be designed to see only SL9, but there is a chance they could recognise and attack human proteins, he says. "The big concern is autoimmunity - that these things will not only recognise things that we want, but they will also recognise things that we don't want them to," he says.

But with the recent failure of one major HIV vaccine trial and the cancellation of another, researchers are in a soul-searching mood, says Philip Goulder, an immunologist at the University of Oxford.

"I think the field as a whole has been taking a step back and thinking we need some different ideas all together," he says.

And while an expensive therapy that involves genetically engineering cells from a patient then re-injecting them back may never be feasible in sub-Saharan Africa, the approach could help researchers come up with more effective vaccines and therapeutics, Goulder says. *Journal reference: Nature Medicine (DOI: 10.1038/nm.1779)*

Cancer drugs may build and not tear down blood vessels

Scientists have thought that one way to foil a tumor from generating blood vessels to feed its growth – a process called angiogenesis – was by creating drugs aimed at stopping a key vessel growth-promoting protein. But now the opposite seems to be true.

Researchers at the Moores Cancer Center at the University of California, San Diego (UCSD) in La Jolla have found evidence that blocking that protein target, called VEGF, or vascular endothelial growth factor, doesn't really halt the process at all. Instead, cutting levels of VEGF in a tumor actually props up existing blood vessels, making them stronger and more normal, and in some cases the tumors larger. But as a result, the tumor is more vulnerable to the effects of chemotherapy drugs.

In a paper appearing online November 9, 2008 in the journal *Nature*, David Cheresh, Ph.D., professor and vice chair of pathology at the UC San Diego School of Medicine and the Moores UCSD Cancer Center and his co-workers mimicked the action of anti-angiogenesis drugs by genetically reducing VEGF levels in mouse tumors and inflammatory cells in various cancers, including pancreatic cancer. They also used drugs to inhibit VEGF receptor activity. In every case, blood vessels were made normal again.

The researchers say the findings provide an explanation for recent evidence showing that anti-angiogenesis drugs such as Avastin can be much more effective when combined with chemotherapy. The results may lead to better treatment strategies for a variety of cancers.

"We've discovered that when anti-angiogenesis drugs are used to lower the level of VEGF within a tumor, it's not so much a reduction in the endothelial cells and losing blood vessels as it is an activation of the tumor blood vessels supporting cells," said Cheresh. "This enables vessels to mature, providing a conduit for better drug delivery to the tumor. While the tumors initially get larger, they are significantly more sensitive to chemotherapeutic drugs." As a result, Cheresh said, the findings may provide a new strategy for treating cancer. "It means that chemotherapy could be timed appropriately. We could first stabilize the blood vessels, and then come in with chemotherapy drugs that are able to treat the cancer."

Co-author Randall Johnson, Ph.D., professor of biology at UCSD, Cheresh and their colleagues showed in a related paper in the same journal that tumors were more susceptible to drugs after inflammatory cells lost the ability to express VEGF.

"These two papers define a new mechanism of action for VEGF and for anti-angiogenesis drugs," Cheresh said. "It appears that the drugs, in shutting down VEGF activity, are actively maturing blood vessels, causing them to become stable and more normal, as opposed to reducing blood vessels."

VEGF normally promotes the growth of endothelial cells, which in turn helps build new blood vessels in tumors. But tumor blood vessels are built poorly and do a terrible job of carrying blood and oxygen – and drugs. Cutting VEGF levels in the tumor in turn increases the activity of cells called pericytes that surround the blood vessels, stabilizing them and making them more susceptible to chemotherapy, Cheresh explained.

Cheresh's group found that receptors for VEGF and another growth-promoting protein, PDGF, form a complex that turns off PDGF and the activity of the blood vessel-support cells. Tumors make too much VEGF in their haste to form blood vessels, which turns on the receptor complex. "When you take away the VEGF, you 'take the foot off of the brake,'" he said, allowing the pericytes to go to work, maturing blood vessels. The same mechanism is at work during wound repair.

Cheresh said that the results show that the host response to the cancer – whether or not it is making blood vessel-maturing cells, for example – is critical in terms of susceptibility to therapy. "It's not just about the therapy, but also what the host does in response to the cancer that makes a difference whether a tumor lives or dies, and if it's susceptible to a drug or not. We can change the host response to the cancer, which is otherwise resistant, and make the vessels more mature, temporarily increasing blood flow to the cancer. We're sensitizing the cancer."

The type of solid tumor should not matter, since the mechanism isn't specific to a particular kind of tumor, he noted. That the quality of the tumor's blood vessels could dictate the patient's response to chemotherapy could be one reason that two patients with similar cancers respond differently to the same therapy.

Cheresh believes that some drug regimens may need to be reexamined. "We have to test available regimens and perhaps restructure the way that we give drugs," he said. "We may be giving the right drugs, but we may not be giving them in the right order. We're just beginning to understand how it works."

Co-authors include Joshua I. Greenberg, M.D., David J. Shields, Ph.D., Samuel G. Barillas, Lisette M. Acevedo, Ph.D., Eric Murphy, Ph.D., Jianhua Huang, M.D., Lea Schepcke, Christian Stockmann, Ph.D., and Niren Angle, M.D.

Getting little sleep may be associated with risk of heart disease

Sleeping less than seven and a half hours per day may be associated with future risk of heart disease, according to a report in the November 10 issue of *Archives of Internal Medicine*, one of the JAMA/Archives journals. In addition, a combination of little sleep and overnight elevated blood pressure appears to be associated with an increased risk of the disease.

"Reflecting changing lifestyles, people are sleeping less in modern societies," according to background information in the article. Getting adequate sleep is essential to preventing health conditions such as obesity and diabetes as well as several risk factors for cardiovascular disease including sleep-disordered breathing and night-time hypertension (high blood pressure).

Kazuo Eguchi, M.D., Ph.D., at Jichi Medical University, Tochigi, Japan, and colleagues monitored the sleep of 1,255 individuals with hypertension (average age 70.4) and followed them for an average of 50 months.

Researchers noted patients' sleep duration, daytime and nighttime blood pressure and cardiovascular disease events such as stroke, heart attack and sudden cardiac death.

During follow-up, 99 cardiovascular disease events occurred. Sleep duration of less than 7.5 hours was associated with incident cardiovascular disease. "The incidence of cardiovascular disease was 2.4 per 100 person-years in subjects with less than 7.5 hours of sleep and 1.8 per 100 person-years in subjects with longer sleep duration," the authors write.

Patients with shorter sleep duration plus an overnight increase in blood pressure had a higher incidence of heart disease than those with normal sleep duration plus no overnight increase in blood pressure, but the occurrence of cardiovascular disease in those with a longer sleep duration vs. those with a shorter sleep duration was similar in those who did not experience an overnight elevation in blood pressure.

"In conclusion, shorter duration of sleep is a predictor of incident cardiovascular disease in elderly individuals with hypertension," particularly when it occurs with elevated nighttime blood pressure, the authors note. "Physicians should inquire about sleep duration in the risk assessment of patients with hypertension." (*Arch Intern Med.* 2008;168[20]:2225-2231. Available pre-embargo to the media at www.jamamedia.org.)

Editor's Note: This study was supported in part by grants-in-aid from the Foundation for the Development of the Community, Tochigi, Japan; the Banyu Fellowship Program, sponsored by Banyu Life Science Foundation International; and the National Heart, Lung and Blood Institute. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, funding and support, etc.

Vision screening law for older Floridians associated with lower fatality rates in car crashes

A vision screening law targeting Florida drivers age 80 and older appears to be associated with lower death rates from motor vehicle collisions in this age group, despite little evidence of an association between vision and car crashes, according to a report in the November issue of *Archives of Ophthalmology*, one of the JAMA/Archives journals.

"Older drivers represent the fastest-growing segment of the driving population," the authors write as background information in the article. "As this segment of the population expands, so too have public safety concerns, given older drivers' increased rate of motor vehicle collision involvement per mile driven. Research has suggested that this increase may be partly attributed to medical, functional and cognitive impairments."

Little evidence links visual acuity to involvement in motor vehicle collisions. However, in January 2004, Florida implemented a law requiring all drivers 80 years and older to pass a vision test before renewing their driver's licenses. Gerald McGwin Jr., M.S., Ph.D., and colleagues at the University of Alabama at Birmingham used data from the National Highway Traffic Safety Administration and the U.S. Census Bureau to study rates of motor vehicle collision deaths among all drivers and older drivers in Florida between 2001 and 2006. They also compared these rates to those in Alabama and Georgia, neighboring states that did not change their legal requirements during this time period.

Overall death rates from motor vehicle collisions in Florida increased non-significantly between 2001 and 2006, but showed a linear decrease in drivers age 80 and older. When comparing the period before the law (2001 to 2003) to the period after the law (2004 to 2006), the fatality rate among all drivers increased by 6 percent (from 14.61 per 100,000 persons per year to 14.75 per 100,000) while fatality rates among older drivers decreased by 17 percent (from 16.03 per 100,000 persons per year to 10.76 per 100,000). Death rates among older drivers did not change in Alabama or Georgia during the same time period.

Several potential reasons exist for the decline in Florida, the authors note. "Perhaps the most apparent reason is that the screening law removed visually impaired drivers from the road," the authors write. "However, in reality, the situation is significantly more complex."

About 93 percent of individuals who sought a license renewal were able to obtain one, suggesting that only a small percentage of drivers were removed from the road for failing to meet the vision standards. Another possibility is that the vision screening requirement improved visual function overall, because many of those who do not pass the test on the first try seek vision care and then return with improved vision. Finally, those who believe they have poor vision may have been discouraged from renewing their license at all, voluntarily removing themselves from the road.

"Ultimately, whether the vision screening law is responsible for the observed reduction in fatality rates because of the identification of visually impaired drivers or via another, yet related, mechanism may be inconsequential from a public safety perspective," the authors write. "However, the importance of driving to the well-being of older adults suggests that isolating the true mechanism responsible for the decline is in fact important." Future research identifying this mechanism would allow states to implement laws that accurately target high-risk drivers while allowing low-risk older drivers to retain their mobility.

Dirt won't stick to omniphobic material

* 22:00 10 November 2008 by **Colin Barras**

Water might run easily off a duck's back, but oil does not.

Now US chemists have created a material antisocial enough to repel liquids of both kinds. They have gone one better than nature, which is not known to have made materials with such properties.

Robert Cohen's team at the Massachusetts Institute of Technology, even had to coin a new word to describe their creation - "omniphobic" - literally meaning it hates everything.

Toadstool surface

The material forces away watery and oily liquids into tight droplets due to its surface texture, made up of 300-nanometer-tall "toadstools" with broad silicon dioxide caps and narrow silicon stems.

All liquids have a surface tension that attempts to pull a drop into a perfect sphere, like those seen in the zero gravity of space. But the strength of that tension varies between liquids.



Video: Omniphobic material repels water and oil

Water's very high surface tension, 72 milliNewtons per metre (mN/m) at room temperature, means it easily forms near-spherical drops when placed on a surface. Because of their near-spherical shape, the droplets meet the surface at a high angle - above 150° if the water is sitting on a superhydrophobic surface.

Oils such as pentane have a low surface tension - 15mN/m - so they sag under gravity and tend to form a flat pool rather than a spherical droplet, meeting the surface at a low angle.

All the angles

The shape of the omniphobic toadstools makes it possible for even that weak surface tension to hold a droplet together, allowing liquids like pentane to form a sphere without collapsing, Cohen told New Scientist.

"If you stand on top of one of these [toadstools] and start walking towards the edge, you'll pass through all angles and eventually you'll be standing upside down," he says.

That means even oily liquids can find their ideal angle with the surface and form a meniscus between adjacent toadstools that can support a spherical droplet. The meniscus rests on a layer of air beneath the toadstools' caps.

Although the toadstools are slightly omniphobic on their own, making it possible to knock droplets of water or oil around them like marbles with ease required adding a surface coating to enhance the effect.

The chemical used - fluorodecyl POSS - is more usually used to make surfaces more hydrophobic. After the coating, the new MIT material repels even oily liquids with low surface tension, such as pentane.

"Pentane is probably the lowest energy liquid you can have at atmospheric pressure, and we were able to get drops of that just rolling around on our surface," says Cohen.

It's so robust that even when droplets of hexadecane - with a surface tension of 27.5 mN/m - are dropped onto the surface, they simply bounce and retain their spherical shape (see video, above).

Philippe Brunet at the Mechanics Laboratory of Lille, France, is impressed with the material.

"To my knowledge, no such universal repelling properties have been observed before this work," he says. "What's quite convincing is that the robustness was evidenced by drop impact experiments."

But David Quéré at the Higher School of Industrial Physics and Chemistry of the City of Paris wonders how easy it will be to find real-world applications for the material.

Many concrete and glass companies have been interested in similar surfaces to improve their materials, he says. "But when you put this texture on the surface of a solid it is very easily destroyed - [the toadstools] are quite fragile."

If they could be made more robust, they could make easy-to-clean surfaces that are difficult to soil with either watery or oily dirt. *Journal reference: Proceedings of the National Academy of Sciences (DOI: 10.1073/pnas.0804872105)*

Researchers use chemical from medicinal plants to fight HIV

TAT2, used in Chinese herbal therapy, prolongs killer T-cells' ability to divide

Like other kinds of cells, immune cells lose the ability to divide as they age because a part of their chromosomes known as a telomere becomes progressively shorter with cell division. As a result, the cell changes in many ways, and its disease fighting ability is compromised.

But a new UCLA AIDS Institute study has found that a chemical from the Astragalus root, frequently used in Chinese herbal therapy, can prevent or slow this progressive telomere shortening, which could make it a key weapon in the fight against HIV.

"This has the potential to be either added to or possibly even replace the HAART (highly active antiretroviral therapy), which is not tolerated well by some patients and is also costly," said study co-author Rita Effros, a professor of pathology and laboratory medicine at the David Geffen School of Medicine at UCLA and member of the UCLA AIDS Institute.

The study, to be published in the Nov. 15 print edition of the Journal of Immunology, is available online at <http://www.jimmunol.org/cgi/content/full/181/10/7400>.

A telomere is a region at the end of every cell chromosome that contains repeated DNA sequences but no genes; telomeres act to protect the ends of the chromosomes and prevent them from fusing together — rather like the plastic tips that keep shoelaces from unraveling. Each time a cell divides, the telomeres get shorter, eventually causing the cell to reach a stage called replicative senescence, when it can no longer divide. This seems to indicate that the cell has reached an end stage, but, in fact, the cell has changed into one with new genetic and functional characteristics.

A great deal of cell division must take place within the immune system for the system to function properly. For example, the so-called "killer" CD8 T-cells that help fight infection have unique receptors for particular antigens. When a virus enters the body, the killer T-cells whose receptors recognize that virus create, through division, versions of themselves that fight the invader.

Generally, the telomeres in cells are sufficiently long that they can divide many times without a problem. Moreover, when fighting infections, T-cells can turn on an enzyme called telomerase, which can prevent the telomeres from shortening.

"The problem is that when we're dealing with a virus that can't be totally eliminated from the body, such as HIV, the T-cells fighting that virus can't keep their telomerase turned on forever," Effros said. "They turn off, and telomeres get shorter and they enter this stage of replicative senescence."

Previous studies have shown that injecting the telomerase gene into T-cells can keep the telomeres from shortening, enabling them to maintain their HIV-fighting function for much longer. This gene-therapy approach, however, is not a practical way to treat the millions of people living with HIV.

For the present study, rather than utilizing gene therapy, the researchers used a chemical called TAT2, which was originally identified from plants used in traditional Chinese therapy and which enhances telomerase activity in other cell types.

They tested TAT2 in several ways. First, they exposed the CD8 T-cells from HIV-infected persons to TAT2 to see if the chemical not only slowed the shortening of the telomeres but improved the cells' production of soluble factors called chemokines and cytokines, which had been previously shown to inhibit HIV replication. It did.

They then took blood samples from HIV-infected individuals and separated out the CD8 T-cells and the CD4 T-cells — those infected with HIV. They treated the CD8 T-cells with TAT2 and combined them with the CD4 T-cells in the dish and found that the treated CD8 cells inhibited production of HIV by the CD4 cells.

"The ability to enhance telomerase activity and antiviral functions of CD8 T-lymphocytes suggests that this strategy could be useful in treating HIV disease, as well as immunodeficiency and increased susceptibility to other viral infections associated with chronic diseases or aging," the researchers write.

In addition to Effros, researchers were Steven Russell Fauce, Beth D. Jamieson, Ronald T. Mitsuyasu, Stan T. Parish, Christina M. Ramirez Kitchen, and Otto O. Yang, all of UCLA, and Allison C. Chin and Calvin B. Harley of the Geron Corp. The Geron Corp., TA Therapeutics Ltd., the National Institutes of Health and the Frank Jernigan Foundation funded this study.

Maastricht University researchers produce 'neural fingerprint' of speech recognition

Published in Science: how the brain decodes human voice and speech processes

Scientists from Maastricht University have developed a method to look into the brain of a person and read out who has spoken to him or her and what was said. With the help of neuroimaging and data mining techniques the researchers mapped the brain activity associated with the recognition of speech sounds and voices. In their Science article "Who" is Saying "What"? Brain-Based Decoding of Human Voice and Speech the four authors demonstrate that speech sounds and voices can be identified by means of a unique 'neural fingerprint' in the listener's brain. In the future this new knowledge could be used to improve computer systems for automatic speech and speaker recognition.

Seven study subjects listened to three different speech sounds (the vowels /a/, /i/ and /u/), spoken by three different people, while their brain activity was mapped using neuroimaging techniques (fMRI). With the help of data mining methods the researchers developed an algorithm to translate this brain activity into unique patterns

that determine the identity of a speech sound or a voice. The various acoustic characteristics of vocal cord vibrations (neural patterns) were found to determine the brain activity. Just like real fingerprints, these neural patterns are both unique and specific: the neural fingerprint of a speech sound does not change if uttered by somebody else and a speaker's fingerprint remains the same, even if this person says something different.

Moreover, this study revealed that part of the complex sound-decoding process takes place in areas of the brain previously just associated with the early stages of sound processing. Existing neurocognitive models assume that processing sounds actively involves different regions of the brain according to a certain hierarchy: after a simple processing in the auditory cortex the more complex analysis (speech sounds into words) takes place in specialised regions of the brain. However, the findings from this study imply a less hierarchical processing of speech that is spread out more across the brain.

The research was partly funded by the Netherlands Organisation for Scientific Research (NWO): Two of the four authors, Elia Formisano and Milene Bonte carried out their research with an NWO grant (Vidi and Veni). The data mining methods were developed during the PhD research of Federico De Martino (doctoral thesis defended at Maastricht University on 24 October 2008).

Note for the press:

Title of the publication: Elia Formisano, Federico De Martino, Milene Bonte, Rainer Goebel, "Who" is Saying "What"? Brain-Based Decoding of Human Voice and Speech, Science, November 2008.

For further information about the content of this press release please contact Elia Formisano, tel. +31 43 3884040, e-mail e.formisano@psychology.unimaas.nl

Caring for the caregiver: Redefining the definition of patient

IU study finds 25 percent of family caregivers of AD patients go to ER Or are hospitalized

INDIANAPOLIS – One quarter of all family caregivers of Alzheimer's disease patients succumb to the stress of providing care to a loved one and become hospital patients themselves, according to an Indiana University study published in the November 2008 issue of the Journal of General Internal Medicine.

Researchers from the Indiana University School of Medicine, the Regenstrief Institute and the Indiana University Center for Aging Research report in a new study that a quarter of family caregivers of Alzheimer's dementia patients had at least one emergency room visit or hospitalization every six months.

While it has long been anecdotally recognized that caring for a family member with Alzheimer's disease is stressful, this work is the first to measure just how stressful providing care is and to examine the impact of this stress on both the physical and mental health of the family caregiver.

The study found that the behavior and functioning of the individual with Alzheimer's dementia, rather than cognitive ability, were the major factors determining whether the caregiver went to the emergency room or was hospitalized. "Our findings opened our minds to the fact that society needs to expand the definition of patient to include both the person with Alzheimer's dementia and that individual's family caregiver," said Malaz Boustani, M.D., corresponding author. Dr. Boustani is assistant professor of medicine and a Regenstrief Institute research scientist.

The researchers looked at 153 individuals with Alzheimer's disease and their family caregivers, a total of 366 people. Forty-four percent of the caregivers were spouses. Seventy percent of the caregivers resided with their charges. The average caregiver was 61 years of age. The researchers found that age, education and relationship to the individual with Alzheimer's disease did not impact caregiver use of acute medical services – either emergency room or inpatient facilities.

"While we've long known that Alzheimer's is a devastating disease to the patient, this study offers a look at how it also impacts the caregiver's health. If we don't offer help and support to the caregiver, too, the stress of caring for someone with dementia can be overwhelming, both mentally and physically," said Cathy C. Schubert, M.D., IU School of Medicine assistant professor of clinical medicine.

Approximately four million older adults in the United States have Alzheimer's disease and three million of them live in the community, often cared for by family members. This number is growing rapidly and by 2050 it is estimated that there will be 18.5 million cases of Alzheimer's dementia in the United States.

"For American society to respond to the growing epidemic of Alzheimer's disease, the health-care system needs to rethink the definition of patient. These findings alert health-care delivery planners that they need to restructure the health-care system to accommodate our new inclusive definition of patient," said Dr. Boustani.

Dr. Boustani directs the Healthy Aging Brain Center. Using the findings of this study, the center is leading the nation in expanding the definition of patient to include the individual with Alzheimer's disease and family caregivers and to provide care to both. The Healthy Aging Brain Center is part of the IU Center for Senior Health at Wishard Health Services.

Dr. Schubert is the medical director of the IU Center for Senior Health at Wishard and Acute Care for Elders at Indiana University Hospital.

Authors of the study are Cathy C. Schubert, M.D.; Malaz Boustani, M.D., MPH; Christopher M. Callahan, MD; Anthony J. Perkins, M.S.; Siu Hui, Ph.D.; and Hugh C. Hendrie, M.B., Ch.B., all of the Indiana University School of Medicine.

Forced evolution: Can we mutate viruses to death?

Analysis reveals role of gene swaps in evolution of disease

HOUSTON -- It sounds like a science fiction movie: A killer contagion threatens the Earth, but scientists save the day with a designer drug that forces the virus to mutate itself out of existence. The killer disease? Still a fiction. The drug? It could become a reality thanks to a new study by Rice University bioengineers.

The study, which is available online and slated for publication in the journal *Physical Review E*, offers the most comprehensive mathematical analysis to date of the mechanisms that drive evolution in viruses and bacteria. Rather than focusing solely on random genetic mutations, as past analyses have, the study predicts exactly how evolution is affected by the exchange of entire genes and sets of genes.

"We wanted to focus more attention on the roles that recombination and horizontal gene transfer play in the evolution of viruses and bacteria," said bioengineer Michael Deem, the study's lead researcher. "So, we incorporated both into the leading models that are used to describe bacterial and viral evolution, and we derived exact solutions to the models."

The upshot is a newer, composite formula that more accurately captures what happens in real world evolution. Deem's co-authors on the study include Rice graduate student Enrique Muñoz and longtime collaborator Jeong-Man Park, a physicist at the Catholic University of Korea in Bucheon.

In describing the new model, Deem drew an analogy to thermodynamics and discussed how a geneticist or drug designer could use the new formula in much the same way that an engineer might use thermodynamics formulas.

"Some of the properties that describe water are density, pressure and temperature," said Deem. "If you know any two of them, then you can predict any other one using thermodynamics.

"That's what we're doing here," he said. "If you know the recombination rate, mutation rate and fitness function, our formula can analytically predict the properties of the system. So, if you have recombination at a certain frequency, I can say exactly how much that helps or hurts the fitness of the population."

Deem, Rice's John W. Cox Professor in Biochemical and Genetic Engineering and professor of physics and astronomy, said the new model helps to better describe the evolutionary processes that occur in the real world, and it could be useful for doctors, drug designers and others who study how diseases evolve and how our immune systems react to that evolution.

One idea that was proposed about five years ago is "lethal mutagenesis." In a nutshell, the idea is to design drugs that speed up the mutation rates of viruses and push them beyond a threshold called a "phase transition." The thermodynamic analogy for this transition is the freezing or melting of water -- which amounts to a physical transition between water's liquid and solid phases.

"Water goes from a liquid to a solid at zero degrees Celsius under standard pressure, and you can represent that mathematically using thermodynamics," Deem said. "In our model, there's also a phase transition. If the mutation, recombination or horizontal gene transfer rates are too high, the system delocalizes and gets spread all over sequence space."

Deem said the new results predict which parameter values will lead to this delocalization.

A competing theory is that a mutagenesis drug may eradicate a virus or bacterial population by reducing the fitness to negative values. The new mathematical results allow calculation of this mechanism when the fitness function and the mutation, recombination and horizontal gene transfer rates are known.

Without theoretical tools like the new model, drug designers looking to create pills to induce lethal mutagenesis couldn't say for certain under what parameter ranges the drugs really worked. Deem said the new formula should provide experimental drug testers with a clear picture of whether the drugs -- or something else -- causes mutagenesis.

The research is supported by the Defense Advanced Research Projects Agency and the Korea Research Foundation.

Bone cancer treatment ineffective, despite promising laboratory data

San Francisco, Calif. -- Ewing sarcoma is the second most common type of primary bone cancer seen in children and young adults. Patients with relapsed or refractory Ewing sarcoma have a poor outcome with conventional therapies. Cytarabine decreases the levels of a certain key protein in Ewing sarcoma cells and has demonstrated preclinical activity against Ewing sarcoma cell lines in the laboratory. Treatment of Ewing sarcoma that relapses is difficult. A new study published in *Pediatric Blood & Cancer* evaluated a phase II clinical trial of a potential new treatment approach for relapsed Ewing sarcoma using cytarabine.

Ten patients were treated. While one patient's tumor stayed stable in size for approximately 4 months while receiving the drug, none of the ten patients had smaller tumors after treatment with cytarabine. This result is disappointing since laboratory studies indicated that cytarabine might be an effective drug for these patients. In addition, these patients with Ewing sarcoma developed lower blood counts than expected from these doses of cytarabine. The fact that the drug was not found to be effective is yet another example in which laboratory data do not always translate into success in treating patients.

"Cytarabine is not an effective agent for patients with Ewing sarcoma and this drug should be used with caution in heavily pretreated patients with solid tumors due to the significant impact of the drug on blood counts," says Steven DuBois, co-author of the study. This study demonstrates the difficulties of extending promising therapeutic targets observed in the laboratory to effective treatments in patients. It also emphasizes the need for more predictive preclinical models.

Brain scans demonstrate link between education and Alzheimer's

St. Louis, Nov. 10, 2007 —A test that reveals brain changes believed to be at the heart of Alzheimer's disease has bolstered the theory that education can delay the onset of the dementia and cognitive decline that are characteristic of the disorder.

Scientists at the Alzheimer's Disease Research Center at Washington University School of Medicine in St. Louis found that some study participants who appeared to have the brain plaques long associated with Alzheimer's disease still received high scores on tests of their cognitive ability. Participants who did well on the tests were likely to have spent more years in school.

"The good news is that greater education may allow people to harbor amyloid plaques and other brain pathology linked to Alzheimer's disease without experiencing decline of their cognitive abilities," says first author Catherine Roe, Ph.D., research instructor in neurology.

The findings are published in the November Archives of Neurology.

Roe and her colleagues at the Alzheimer's Disease Research Center used the study participants' education levels to approximate a theoretical quality called cognitive reserve: improved abilities in thinking, learning and memory that result from regularly challenging and making use of the brain. Neurologists have long speculated that this quality, roughly equivalent to the benefits that accrue in the body via regular physical exercise, can help the brain cope with the damage caused by Alzheimer's disease.

Doctors still cannot conclusively diagnose Alzheimer's disease in any manner other than post-mortem brain examination. But Washington University scientists have shown that an imaging agent for positron emission tomography scans, Pittsburgh Compound B (PIB), can reveal the presence of amyloid plaques, a key brain change that many neurologists suspect either causes Alzheimer's or is closely linked to its onset.

"This technique has been used before to analyze patients with dementia and their education levels, but our study is among the first, if not the first, to include both patients with Alzheimer's-type dementia and nondemented participants," says Roe.

In addition to scanning the participants' brains with PIB, the participants took several tests that assessed their cognitive abilities and status. They also ranked their educational experience: high-school degree or less, college experience up to an undergraduate degree, and graduate schooling.

As expected, those whose brains showed little evidence of plaque buildup scored high on all the tests. But while most participants with high levels of brain plaque scored poorly on the tests, those who had done postgraduate work still scored well. Despite signs that Alzheimer's might already be ravaging the brains of this subgroup, their cognitive abilities had not declined and they had not become demented.

Roe and her colleagues plan follow-up studies that will look at other potential indicators of increased cognitive reserve, including hobbies, social and intellectual activities and the mental challenges provided by professional duties.

Roe CM, Mintun MA, D'Angelo G, Xiong C, Grant EA, Morris JC. Alzheimer's disease and cognitive reserve. Archives of Neurology 2008;65[11]:1467-1471.

OHSU finds association between Epstein-Barr virus, inflammatory diseases of the mouth ***A new study, published in the Journal of Endodontics, finds a link between Epstein-Barr virus and the microorganisms that cause irreversible pulpitis and apical periodontitis***

PORTLAND, Ore. — Researchers at Oregon Health & Science University's School of Dentistry (www.ohsu.edu/sod) have found that a significant percentage of dental patients with the inflammatory diseases irreversible pulpitis and apical periodontitis also have the Epstein-Barr virus. The Epstein-Barr virus is an important human pathogen found in more than 90 percent of the world population. It is associated with many diseases, including infectious mononucleosis, malignant lymphomas, and nasopharyngeal carcinoma.

The findings are published online ([www.jendodon.com/article/S0099-2399\(08\)00879-0/abstract](http://www.jendodon.com/article/S0099-2399(08)00879-0/abstract)) in the

Journal of Endodontics, one of the leading peer-reviewed endodontology journals. The study also is expected to be published in the December 2008 (volume 34, issue 12) issue of the Journal of Endodontics.

Although the number of studies examining the role of herpesviruses in oral disease has been increasing, the majority of studies have focused on periodontitis, with no systematic attempt to examine herpesvirus in endodontic patients with varying inflammatory diseases. The OHSU study assessed the presence of human cytomegalovirus (HCMV), Epstein-Barr virus (EPV), herpes simplex virus (HSV-1), and Varicella zoster virus (VZV) in 82 endodontic patients, including patients with irreversible pulpitis and apical periodontitis, and compared them with 19 healthy patients. The goal of the study was to determine the potential association of herpesvirus with clinical symptoms, including acute pain and size of radiographic bone destruction.

Using a variety of methods, the OHSU team found the Epstein-Barr virus DNA and RNA in significantly higher percentages (43.9 percent and 25.6 percent respectively) compared with healthy patients (0 percent). Human cytomegalovirus DNA and RNA were found in measurable numbers in both endodontic patients (15.9 percent and 29.3 percent respectively) and in healthy patients (42.1 percent and 10.5 percent respectively). Herpes simplex virus DNA was found in low percentages of endodontic patients (13.4 percent) and only one patient showed the presence of Varicella zoster virus.

While a previous study examined the incidence of herpes viruses in apical periodontitis, "this is the first time irreversible pulpitis has been analyzed for the presence of herpes viruses and associated with Epstein-Barr virus," noted Curt Machida, Ph.D., OHSU professor of integrative biosciences and principal investigator, whose lab was host for the study. "The incidence of irreversible pulpitis and apical periodontitis, caused by bacteria and possibly the latent herpes virus, is painful and can greatly impair the body's natural immune system. Studies such as ours could someday lead to more effective treatments of inflammatory diseases of the mouth."

The OHSU team included Hong Li, D.D.S., M.Sc., Ph.D., a recent OHSU endodontology graduate; third-year OHSU dental student Vicky Chen, B.S.; second-year OHSU dental student Yanwen Chen, Ph.D.; J. Craig Baumgartner, D.D.S., M.Sc., Ph.D., chairman of the OHSU endodontology department; and Machida.

The research at OHSU was funded by grants from the American Association of Endodontists Foundation, the Oregon Clinical and Translational Research Institute, the NIH's National Center for Research Resources, and the NIH Roadmap for Medical Research.

Diuretic reduces risk for a type of heart failure that is more common among women

New research by The University of Texas School of Public Health shows that a medication for high blood pressure called a diuretic or water pill is particularly effective at reducing the risk for a type of heart failure that affects women more often than men. Findings appear in the Nov. 10 online issue of *Circulation: Journal of the American Heart Association*.

Heart failure is a clinical syndrome characterized by an inadequate supply of oxygen rich blood as a result of impaired cardiac pump function. More than 5 million Americans are living with heart failure and most had high blood pressure before developing this potentially deadly condition.

While much research has been focused on the impact of antihypertensive medications on the prevention of heart failure associated with reduced pumping capacity in the heart's all-important left ventricle, comparatively little research has been performed on the prevention of heart failure wherein the heart muscle is clearing a normal or preserved percentage of blood with each heart beat. This percentage is called left ventricular ejection fraction (LVEF).

"We showed that a diuretic was as good as or better than other classes of medication for high blood pressure in reducing the occurrence of heart failure in people with a wide range of left ventricular ejection fraction," said Barry Davis, M.D., Ph.D., the study's lead author, the Guy S. Parcel Chair in Public Health and director of the Coordinating Center for Clinical Trials at the UT School of Public Health.

The study involved 910 hypertensive adults who had been taking antihypertensive medications and who were subsequently diagnosed with heart failure in a hospital. Those with an ejection fraction of 50 percent or more were defined as Heart Failure Preserved Ejection Fraction (HFPEF) and those with an ejection fraction of 49 percent or less as Heart Failure Reduced Ejection Fraction (HFREF). Forty-four percent had preserved ejection fraction and 56 percent reduced ejection fraction.

Participants treated with a thiazide-type diuretic (chlorthalidone) had reduced risk of Heart Failure Preserved Ejection Fraction compared to those taking a calcium channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), or an alpha-adrenergic blocker (doxazosin). Chlorthalidone reduced the risk in people with reduced ejection fraction compared with amlodipine or doxazosin. Chlorthalidone was similar to lisinopril in preventing heart failure with reduced ejection fraction. "On the basis of the data from many heart failure trials, a combination of the last two agents would be expected to be particularly effective in preventing heart failure in this group," the authors wrote.

"In both heart failure with preserved and reduced ejection fraction, the diuretic is helping to remove excess fluid - which can reduce both pre load and after load and thus increase ejection fraction," Davis said.

Heart failure patients with preserved ejection fraction may still have big problems, Davis said. "Let's say the heart normally should pump 70 milliliters (ml) of blood. It fills up with 100 ml and pumps 70 for an EF of 70 percent (which is good). However with reduced ejection fraction it only pumps 30 ml or has an EF of only 30 percent. On the other hand you could have preserved ejection fraction and in this case the heart fill up with just 50 ml of blood but pumps 30 ml. The EF would be 60 percent. In both cases, only 30 ml is reaching the body."

Davis said heart failure is sometimes characterized as either systolic or diastolic heart failure. In systolic heart failure, there is reduced cardiac contractility, whereas in diastolic heart failure there is impaired cardiac relaxation and abnormal ventricular filling. Heart Failure Preserved Ejection Fraction is typically associated with the filling blood phase and Heart Failure Reduced Ejection Fraction with the forcing blood out phase.

Participants with preserved ejection fraction compared to those with reduced ejection fraction were more likely to be women (52 percent versus 38 percent) and less likely to have a history of coronary heart disease (32 percent versus 39 percent). People with heart failure with preserved ejection fraction have a subsequent mortality rate almost as high as those with reduced ejection fraction, about 50 percent at five years.

Participants in the study were from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, multi-center clinical trial that compared four classes of medications for high blood pressure. More than 42,000 people 55 years of age or more with hypertension were in the trial between 1994 and 2002.

Davis' collaborators from the UT School of Public Health were Charles E. Ford, Ph.D., associate professor of biostatistics and Lara M. Simpson, Ph.D., faculty associate. Also contributing were: John B. Kostis, M.D., UMDNJ-Robert Wood Johnson Medical School, New Brunswick, N.J. ; Henry R. Black, M.D., New York University School of Medicine, New York, N.Y.; William C. Cushman, M.D., Memphis Veteran's Affairs Medical Center, Memphis, Tenn.; Paula T. Einhorn, M.D., Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, Md.; Michael A. Farber, M.D., Crozer Keystone Health Network, Upland, Pa.; Daniel Levy, M.D., Framingham Heart Study/National Heart, Lung and Blood Institute Framingham, Mass.; Barry M. Massie, M.D., San Francisco Veterans Affairs Medical Center, San Francisco, Calif.; and Shah Nawaz, M.D., private practice in Sudbury, Ontario, Canada.

The study is titled "Heart Failure With Preserved and Reduced Left Ventricular Ejection Fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial." Research was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health and the U.S. Department of Health and Human Services, Bethesda, Md.

Rheumatoid arthritis breakthrough

Rheumatoid arthritis is a painful, inflammatory type of arthritis that occurs when the body's immune system attacks itself. A new paper, published in this week's issue of PLoS Biology, reports a breakthrough in the understanding of how autoimmune responses can be controlled, offering a promising new strategy for therapy development for rheumatoid arthritis.

Normally, immune cells develop to recognise foreign material – antigens; including bacteria - so that they can activate a response against them. Immune cells that would respond to 'self' and therefore attack the body's own cells are usually destroyed during development. If any persist, they are held in check by special regulatory cells that provide a sort of autoimmune checkpoint. A key player in these regulatory cells is a molecule called Foxp3. People who lack or have mutated versions of the Foxp3 gene lack or have dysfunctional immune regulation, which causes dramatic autoimmune disease.

Scientists at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, and funded by the Arthritis Research Campaign, have genetically engineered a drug-inducible form of Foxp3. Using this, scientists can 'switch' developing immune cells into regulatory cells that are then capable of suppressing the immune response.

Dr. Alexander Betz, Group Leader at the MRC laboratory, explains: "We have generated a modified form of Foxp3 which can be introduced into immune cells using genetic engineering techniques and then activated by a simple injection. When administered to and activated in animal models of arthritis, the modified cells inhibit or even reverse the disease process."

Further work is now aimed at elucidating the detailed molecular mechanisms involved in Foxp3 function, and transferring the experimental approach to human cells.

"First, we will develop a human Foxp3 factor and then assess its function in human arthritis models," said Dr Betz. "To be viable as a therapeutic option, the regulatory cells must fulfill certain criteria; they must be tissue matched to the patient for compatibility; they must only block the targeted disease and not the whole body immune response; and they have to home correctly to their target tissue. Establishing these criteria will be the key focus of our research.

"If Foxp3 functions as a key developmental switch in human immune cells, there is potential for a new avenue of therapy development that could transform arthritis treatment is substantial," he added.

Citation: Andersen KG, Butcher T, Betz AG (2008) Specific immunosuppression with inducible Foxp3-transduced polyclonal T cells. PLoS Biol 6(11): e276. doi:10.1371/journal.pbio.0060276

<http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pbio.0060276>

Joyful music may promote heart health

University of Maryland School of Medicine research team concludes the cardiovascular benefits of music are similar to those found in their previous study of laughter

Listening to your favorite music may be good for your cardiovascular system. Researchers at the University of Maryland School of Medicine in Baltimore have shown for the first time that the emotions aroused by joyful music have a healthy effect on blood vessel function.

Music, selected by study participants because it made them feel good and brought them a sense of joy, caused tissue in the inner lining of blood vessels to dilate (or expand) in order to increase blood flow. This healthy response matches what the same researchers found in a 2005 study of laughter. On the other hand, when study volunteers listened to music they perceived as stressful, their blood vessels narrowed, producing a potentially unhealthy response that reduces blood flow.

The results of the study, conducted at the University of Maryland Medical Center, will be presented at the Scientific Sessions of the American Heart Association, on November 11, 2008, in New Orleans.

"We had previously demonstrated that positive emotions, such as laughter, were good for vascular health. So, a logical question was whether other emotions, such as those evoked by music, have a similar effect," says principal investigator Michael Miller, M.D., director of preventive cardiology at the University of Maryland Medical Center and associate professor of medicine at the University of Maryland School of Medicine. "We knew that individual people would react differently to different types of music, so in this study, we enabled participants to select music based upon their likes and dislikes."

Study design

Ten healthy, non-smoking volunteers (70 percent male, average age 36 years) participated in all phases of the randomized study. There were four phases. In one, volunteers listened to music they selected that evoked joy. The volunteers brought recordings of their favorite music to the laboratory, or, if they did not own the music, the investigators acquired the recordings. Another phase included listening to a type of music that the volunteers said made them feel anxious. In a third session, audio tapes to promote relaxation were played and in a fourth, participants were shown videotapes designed to induce laughter.

Each volunteer participated in each of the four phases, but the order in which each phase occurred was determined at random.

To minimize emotional desensitization, the volunteers were told to avoid listening to their favorite music for a minimum of two weeks. "The idea here was that when they listened to this music that they really enjoyed, they would get an extra boost of whatever emotion was being generated," says Dr. Miller.

Prior to each phase of the study, the volunteers fasted overnight and were given a baseline test to measure what is known as flow-mediated dilation.

This test can be used to determine how the endothelium (the lining of blood vessels) responds to a wide range of stimuli, from exercise to emotions to medications. The endothelium has a powerful effect on blood vessel tone and regulates blood flow, adjusts coagulation and blood thickening, and secretes chemicals and other substances in response to wounds, infections or irritation. It also plays an important role in the development of cardiovascular disease.

During the blood vessel dilation test, blood flow in the brachial artery, located in the upper arm, is restricted by a blood pressure cuff and released. An ultrasound device measures how well the blood vessel responds to the sudden increase in flow, with the result expressed as a percentage change in vessel diameter.

After the baseline test, each volunteer was exposed to the music or humorous video for 30 minutes. Additional dilation measurements were obtained throughout each phase to assess changes from baseline. Participants returned a minimum of one week later for the next phase. Sixteen measurements per person or a total of 160 dilation measurements were taken during the course of the study, which took six to eight months to complete.

Study results

Compared to baseline, the average upper arm blood vessel diameter increased 26 percent after the joyful music phase, while listening to music that caused anxiety narrowed blood vessels by six percent. "I was impressed with the highly significant differences both before and after listening to joyful music as well as between joyful and anxious music," says Dr. Miller.

During the laughter phase of the study, a 19 percent increase in dilation showed a significant trend. The relaxation phase increased dilation by 11 percent on average; a number that the investigators determined was not statistically significant.

Most of the participants in the study selected country music as their favorite to evoke joy, according to Dr. Miller, while they said "heavy metal" music made them feel anxious. "You can't read into this too much, although you could argue that country music is light, spirited, a lot of love songs." says Dr. Miller, who enjoys rock, classical, jazz and country music. He says he could have selected 10 other individuals and the favorite could have been a different type of music.

Could other types of music produce similar positive effects on blood vessels? It's possible, according to Dr. Miller. "The answer, in my opinion, is how an individual is 'wired.' We're all wired differently, we all react differently. I enjoy country music, so I could appreciate why country music could cause that joyful response," he says.

Dr. Miller believes that a physiological reaction to the type of music is behind the formation of positive and negative blood vessel reaction. "We don't understand why somebody may be drawn to certain classical music, for example. There are no words in that, and yet the rhythm, the melody and harmony, may all play a role in the emotional and cardiovascular response."

That physiological impact may also affect the activity of brain chemicals called endorphins. "The emotional component may be an endorphin-mediated effect," says Dr. Miller. "The active listening to music evokes such raw positive emotions likely in part due to the release of endorphins, part of that mind-heart connection that we yearn to learn so much more about. Needless to say, these results were music to my ears because they signal another preventive strategy that we may incorporate in our daily lives to promote heart health."

Dr. Miller's funding sources include the American Heart Association, Veterans Administration and the National Institutes of Health.

"Positive Emotions and the Endothelium: Does Joyful Music Improve Vascular Health?" Miller M, Beach V, Mangano C, Vogel RA. Oral Presentation. American Heart Association Scientific Sessions, 11/11/2008.

Doctors must look after their health too

Research paper: Counselling for burnout in Norwegian doctors: one year cohort study BMJ Online

Short term counselling followed by a modest cut in work hours may help reduce emotional exhaustion (burnout) and sick leave in doctors, according to a study published on bmj.com today.

It is well known that doctors have higher rates of depression and suicide than the general population and are less likely to seek help. There have been calls for early intervention programmes to help doctors with mental distress and burnout before their problems interfere with the welfare of patients.

Although such programmes have been shown to reduce stress and exhaustion, it is not clear what type of intervention is best suited to which individual or personal characteristics, or which factors contribute to positive changes.

Dr Karin Rø and colleagues from Norway examined levels of burnout and predictors of reduction in emotional exhaustion after one year, in 227 stressed doctors who participated in voluntary counselling.

Initially, 187 doctors attended a one day individual session, and 40 a one week group based course. Of the 185 doctors who completed follow-up assessments, 70 returned for an additional intervention during the follow-up year, 51 to a one week course and 19 to an individual session.

They completed self report assessments in the four weeks before and the three weeks after the counselling, and a follow-up questionnaire after one year. The data was compared with data obtained from a representative sample of Norwegian doctors in 2003.

One year after a counselling intervention stressed doctors reported a reduction in emotional exhaustion and job stress similar to the level found in a representative sample of Norwegian doctors.

The researchers also found that the number of doctors on full time sick leave had reduced substantially in the year after counselling (35% to 6%), and that the use of psychotherapy also substantially increased from 20% to 53% in the follow-up year.

Interestingly, they found that reduction in work hours after the intervention was also associated with a reduction in emotional exhaustion.

"Our findings indicate that seeking a counselling intervention could be conducive to reduction of burnout among doctors. Considering doctors' reluctance to seek help...it is important to offer interventions that facilitate access", conclude the authors.

Without enzyme, biological reaction essential to life takes 2.3 billion years

CHAPEL HILL – All biological reactions within human cells depend on enzymes. Their power as catalysts enables biological reactions to occur usually in milliseconds. But how slowly would these reactions proceed spontaneously, in the absence of enzymes – minutes, hours, days? And why even pose the question?

One scientist who studies these issues is Richard Wolfenden, Ph.D., Alumni Distinguished Professor Biochemistry and Biophysics and Chemistry at the University of North Carolina at Chapel Hill. Wolfenden holds posts in both the School of Medicine and in the College of Arts and Sciences and is a member of the National Academy of Sciences.

In 1995, Wolfenden reported that without a particular enzyme, a biological transformation he deemed "absolutely essential" in creating the building blocks of DNA and RNA would take 78 million years.

"Now we've found a reaction that – again, in the absence of an enzyme – is almost 30 times slower than that," Wolfenden said. "Its half-life – the time it takes for half the substance to be consumed – is 2.3 billion years, about half the age of the Earth. Enzymes can make that reaction happen in milliseconds."

With co-author Charles A. Lewis, Ph.D., a postdoctoral scientist in his lab, Wolfenden published a report of their new findings recently in the online early edition of the Proceedings of the National Academy of Science. The study is also due to appear in the Nov. 11 print edition.

The reaction in question is essential for the biosynthesis of hemoglobin and chlorophyll, Wolfenden noted. But when catalyzed by the enzyme uroporphyrinogen decarboxylase, the rate of chlorophyll and hemoglobin production in cells "is increased by a staggering factor, one that's equivalent to the difference between the diameter of a bacterial cell and the distance from the Earth to the sun."

"This enzyme is essential for both plant and animal life on the planet," Wolfenden said. "What we're defining here is what evolution had to overcome, that the enzyme is surmounting a tremendous obstacle, a reaction half-life of 2.3 billion years."

Knowing how long reactions would take without enzymes allows biologists to appreciate their evolution as prolific catalysts, Wolfenden said. It also enables scientists to compare enzymes with artificial catalysts produced in the laboratory.

"Without catalysts, there would be no life at all, from microbes to humans," he said. "It makes you wonder how natural selection operated in such a way as to produce a protein that got off the ground as a primitive catalyst for such an extraordinarily slow reaction."

Experimental methods for observing very slow reactions can also generate important information for rational drug design based on cellular molecular studies.

"Enzymes that do a prodigious job of catalysis are, hands-down, the most sensitive targets for drug development," Wolfenden said. "The enzymes we study are fascinating because they exceed all other known enzymes in their power as catalysts."

Wolfenden has carried out extensive research on enzyme mechanisms and water affinities of biological compound. His work has also influenced rational drug design, and findings from his laboratory helped spur development of ACE inhibitor drugs, now widely used to treat hypertension and stroke. Research on enzymes as proficient catalysts also led to the design of protease inhibitors that are used to treat HIV infection. "We've only begun to understand how to speed up reactions with chemical catalysts, and no one has even come within shouting distance of producing, or predicting the magnitude of, their catalytic power," Wolfenden said. *Support for this research came from the National Institute of General Medicine, a component of the National Institutes of Health.*

Note: Wolfenden can be reached at (919) 966-1203 or water@med.unc.edu. Lewis can be contacted at (919) 966-7409 or clewisjr@med.unc.edu.

New technology could revolutionize breast cancer screening

The world's first radar breast imaging system developed at Bristol University that could revolutionise the way women are scanned for breast cancer, is being trialled at North Bristol NHS Trust (NBT).

Professor Alan Preece and Dr Ian Craddock from the University of Bristol have been working for a number of years to develop a breast-imaging device which uses radio waves and therefore has no radiation risk unlike conventional mammograms.

The team began developing and researching a prototype around five years ago and have received funding from organisations including the Engineering and Physical Sciences Research Council (EPSRC), the trustees of the United Bristol Hospitals and the University of Bristol spin-out company, Micrima Ltd.

Dr Ian Craddock from the University's Department of Electrical and Electronic Engineering, said: "This new imaging technique works by transmitting radio waves of a very low energy and detecting reflected signals, it

then uses these signals to make a 3D image of the breast. This is basically the same as any radar system, such as the radars used for air traffic control at our airports."

Mike Shere, Associate Specialist Breast Clinician at NBT, added: "Currently women are diagnosed in three ways: firstly by a clinician then by using imaging such as mammography and ultrasound and lastly by a needle biopsy.

"The radar breast imaging system came to Frenchay in September this year and so far around 60 women have been examined using it. "It takes less time to operate than a mammogram approximately six minutes for both breasts compared with 30-45 minutes for an MRI, and like an MRI it provides a very detailed 3D digital image. "Women love it as they compare it to a mammogram and find the whole experience much more comfortable."

The radar breast imaging system is built using transmitters and receivers arranged around a ceramic cup, which the breast sits in. These transmitters view the breast from several different angles.

In the initial stages of the study the team used mammogram images to compare similar abnormalities in the new 3D image produced from the radio breast imaging system.

Professor Preece from the University's Medical Physics, said: "I started off looking at breast tumour imaging in 1990 using a hand held scanner similar to ultrasound however it did not have enough sensitivity and that's when I got to know some people in engineering and together we approached the EPSRC to help.

"Using this engineering knowledge we built the machine using ground penetrating radar, a similar technique to land mine detection to take four hundred quarter of a second pictures of the breast to form a 3D image.

"Women do not feel any sensation and it equates to the same type of radiation exposure as speaking into a mobile phone at arms length which makes it much safer. "We are extremely grateful for North Bristol NHS Trust help in getting the project underway with so much enthusiasm. "We are constantly learning and adapting and it has been particularly easy to work with NBT, we have seen some very promising results so far."

In the coming months the team plan on "testing blind", this means looking at images taken by both machines and examining each independently to check whether the radio breast imaging system's 3D image picks up the same abnormalities as a mammogram would and if anything else is identified in the new image.

They hope that if the results continue, further trials will be scheduled for the next 12 months. These trials will focus specifically on young women as these can prove the most challenging. They also hope that two new prototypes will be made for further trials in other hospitals around the country.

"This technology will ultimately only benefit the patient if it can be successfully commercialised", said Roy Johnson, CEO of Micrima Ltd, "this new invention could provide a safe, more comfortable experience for women as well as giving clinicians a better image of the breast allowing them to pick up abnormalities at an earlier stage. We particularly hope that it may work well in younger women who can pose a problem to conventional mammography."

In this stage of the process the system provides an additional picture of the breast to complement the other imaging devices available, and also has the potential to be made cheaply en-mass.

Pitt Research Finds That Low Concentrations of Pesticides Can Become Toxic Mixture ***Concentrations of 10 most popular pesticides that fall within EPA safe-exposure levels, when combined, cause 99 percent mortality in leopard frog tadpoles***

PITTSBURGH-Ten of the world's most popular pesticides can decimate amphibian populations when mixed together even if the concentration of the individual chemicals are within limits considered safe, according to University of Pittsburgh research published Nov. 11 in the online edition of "Oecologia." Such "cocktails of contaminants" are frequently detected in nature, the paper notes, and the Pitt findings offer the first illustration of how a large mixture of pesticides can adversely affect the environment.

Study author Rick Relyea, an associate professor of biological sciences in Pitt's School of Arts and Sciences, exposed gray tree frog and leopard frog tadpoles to small amounts of the 10 pesticides that are widely used throughout the world. Relyea selected five insecticides-carbaryl, chlorpyrifos, diazinon, endosulfan, and malathion-and five herbicides-acetochlor, atrazine, glyphosate, metolachlor, and 2,4-D. He administered the following doses: each of the pesticides alone, the insecticides combined, a mix of the five herbicides, or all 10 of the poisons.

Relyea found that a mixture of all 10 chemicals killed 99 percent of leopard frog tadpoles as did the insecticide-only mixture; the herbicide mixture had no effect on the tadpoles. While leopard frogs perished, gray tree frogs did not succumb to the poisons and instead flourished in the absence of leopard frog competitors.

Relyea also discovered that endosulfan-a neurotoxin banned in several nations but still used extensively in U.S. agriculture-is inordinately deadly to leopard frog tadpoles. By itself, the chemical caused 84 percent of the leopard frogs to die. This lethality was previously unknown because current regulations from the U.S. Environmental Protection Agency (EPA) do not require amphibian testing, Relyea said. His results showed that

endosulfan was not only highly toxic to leopard frogs, but also that it served as the linchpin of the pesticide mixture that eliminated the bulk of leopard frog tadpoles.

“Endosulfan appears to be about 1,000-times more lethal to amphibians than other pesticides that we have examined,” Relyea said. “Unfortunately, pesticide regulations do not require amphibian testing, so very little is known about endosulfan's impact on amphibians, despite being sprayed in the environment for more than five decades.”

For most of the pesticides, the concentration Relyea administered (2 to 16 parts per billion) was far below the human-lifetime-exposure levels set by the EPA and also fell short of the maximum concentrations detected in natural bodies of water. But the research suggests that these low concentrations—which can travel easily by water and, particularly, wind—can combine into one toxic mixture. In the published paper, Relyea points out that declining amphibian populations have been recorded in pristine areas far downwind from areas of active pesticide use, and he suggests that the chemical cocktail he describes could be a culprit.

The results of this study build on a nine-year effort by Relyea to understand potential links between the global decline in amphibians, routine pesticide use, and the possible threat to humans in the future. Amphibians are considered an environmental indicator species because of their unique sensitivity to pollutants. Their demise from pesticide overexposure could foreshadow the fate of less sensitive animals, Relyea said. Leopard frogs, in particular, are vulnerable to contamination; once plentiful across North America, including Pennsylvania, their population has declined in recent years as pollution and deforestation have increased.

Relyea published a paper in the Oct. 1 edition of “Ecological Applications” reporting that gradual amounts of malathion—the most popular insecticide in the United States—that were too small to directly kill developing leopard frog tadpoles instead sparked a biological chain of events that deprived them of their primary food source. As a result, nearly half the tadpoles in the experiment did not reach maturity and would have died in nature. Relyea published papers in 2005 in the same journal suggesting that the popular weed-killer Roundup® is “extremely lethal” to amphibians in concentrations found in the environment. News releases about Relyea's previous work are available on Pitt's Web site at www.news.pitt.edu

The paper can be found on the Oecologia Web site at www.springerlink.com/content/3420j3486k108805/ or by contacting Morgan Kelly.

Basics

Scientists and Philosophers Find That ‘Gene’ Has a Multitude of Meanings

By NATALIE ANGIER

I owe an apology to my genes. For years I offhandedly blamed them for certain personal defects conventionally associated with one's hereditary starter pack — my Graves' autoimmune disease, for example, or my hair, which looks like the fibers left behind on the rim of an aspirin bottle after the cotton ball has been removed, only wispier.

Now it turns out that genes, per se, are simply too feeble to accept responsibility for much of anything. By the traditional definition, genes are those lineups of DNA letters that serve as instructions for piecing together the body's proteins, and, I'm sorry, but the closer we look, the less instructive they seem, less a “blueprint for life” than one of those disappointing two-page Basic Setup booklets that comes with your computer, tells you where to plug it in and then directs you to a Web site for more information.

Scientists have learned that the canonical “genes” account for an embarrassingly tiny part of the human genome: maybe 1 percent of the three billion paired subunits of DNA that are stuffed into nearly every cell of the body qualify as indisputable protein codes. Scientists are also learning that many of the gene-free regions of our DNA are far more loquacious than previously believed, far more willing to express themselves in ways that have nothing to do with protein manufacture.

In fact, I can't even make the easy linguistic transition from blaming my genes to blaming my whole DNA, because it's not just about DNA anymore. It's also about DNA's chemical cousin RNA, doing complicated things it wasn't supposed to do. Not long ago, RNA was seen as a bureaucrat, the middle molecule between a gene and a protein, as exemplified by the tidy aphorism, “DNA makes RNA makes protein.” Now we find cases of short clips of RNA acting like DNA, transmitting genetic secrets to the next generation directly, without bothering to ask permission. We find cases of RNA acting like a protein, catalyzing chemical reactions, pushing other molecules around or tearing them down. RNA is like the vice presidency: it's executive, it's legislative, it's furtive.

For many scientists, the increasingly baroque portrait of the genome that their latest research has revealed, along with the muddying of molecular categories, is to be expected. “It's the normal process of doing science,” said Jonathan R. Beckwith of Harvard Medical School. “You start off simple and you develop complexity.” Nor are researchers disturbed by any linguistic turbulence that may arise, any confusion over what they mean

when they talk about genes. “Geneticists happily abuse ‘gene’ to mean many things in many settings,” said Eric S. Lander of the Broad Institute. “This can be a source of enormous consternation to onlookers who want to understand the conversation, but geneticists aren’t bothered.”

In Dr. Lander’s view, the “kluges upon kluges” are an occupational hazard. “We’re trying to parse an incredibly complex system,” he said. “It’s like the U.S. economy. What are your functional units? Employees and employers? Consumers and producers? What if you’re a freelancer with multiple employers? Where do farmers’ markets and eBay map onto your taxonomy?”

“You shouldn’t be worried about the fact that you have to layer on other things as you go along,” he said. “You can never capture something like an economy, a genome or an ecosystem with one model or one taxonomy — it all depends on the questions you want to ask.”

Dr. Lander added: “You have to be able to say, this is Tuesday’s simplification; Wednesday’s may be different, because incredible progress has been made by those simplifications.”

For other researchers, though, the parlance of molecular biology is desperately in need of an overhaul, starting with our folksy friend, gene. “The language is historical baggage,” said Evelyn Fox Keller, a science historian and professor emerita at M.I.T. “It comes from the expectation that if we could find the fundamental units that make stuff happen, if we could find the atoms of biology, then we would understand the process.”

“But the notion of the gene as the atom of biology is very mistaken,” said Dr. Keller, author of “The Century of the Gene” and other books. “DNA does not come equipped with genes. It comes with sequences that are acted on in certain ways by cells. Before you have cells you don’t have genes. We have to get away from the underlying assumption of the particulate units of inheritance that we seem so attached to.”

Dr. Keller is a big fan of the double helix considered both in toto and in situ — in its native cellular setting. “DNA is an enormously powerful resource, the most brilliant invention in evolutionary history,” she said. “It is a far richer and more interesting molecule than we could have imagined when we first started studying it.”

Still, she said, “it doesn’t do anything by itself.” It is a profoundly relational molecule, she said, and it has meaning only in the context of the cell. To focus endlessly on genes, she said, keeps us stuck in a linear, unidirectional and two-dimensional view of life, in which instructions are read out and dutifully followed.

“What makes DNA a living molecule is the dynamics of it, and a dynamic vocabulary would be helpful,” she said. “I talk about trying to verb biology.” And to renoun it as well. Writing last year in the journal *PloS One*, Dr. Keller and David Harel of the Weizmann Institute of Science suggested as an alternative to gene the word *dene*, which they said could be used to connote any DNA sequence that plays a role in the cell. So far, Dr. Keller admits, it has yet to catch on.

Complex as our genome is, it obviously can be comprehended: our cells do it every day. Yet as the physician and essayist Lewis Thomas once noted, his liver was much smarter than he was, and he would rather be asked to pilot a 747 jet 40,000 feet over Denver than to assume control of his liver. “Nothing would save me or my liver, if I were in charge,” he wrote.

In a similar vein, we may never understand the workings of our cells and genomes as comfortably and cockily as we understand the artifacts of our own design. “We have evolved to solve problems,” Dr. Keller said. “Those do not include an understanding of the operation of our own systems — that doesn’t have much evolutionary advantage.” It’s quite possible, she said, that biology is “irreducibly complex,” and not entirely accessible to rational analysis. Which is not to say we’re anywhere near being stymied, she said: “Our biology is stretching our minds. It’s another loop in the evolutionary process.”

And if canonical genes are too thin a gruel to explain yourself to yourself, you can always reach for the stalwart of scapegoats. Blame it all on your mother, who surely loved you too much or too little or in all the wrong ways.

In a Novel Theory of Mental Disorders, Parents’ Genes Are in Competition

By BENEDICT CAREY

Two scientists, drawing on their own powers of observation and a creative reading of recent genetic findings, have published a sweeping theory of brain development that would change the way mental disorders like autism and schizophrenia are understood.

The theory emerged in part from thinking about events other than mutations that can change gene behavior. And it suggests entirely new avenues of research, which, even if they prove the theory to be flawed, are likely to provide new insights into the biology of mental disease.

At a time when the search for the genetic glitches behind brain disorders has become mired in uncertain and complex findings, the new idea provides psychiatry with perhaps its grandest working theory since Freud, and one that is grounded in work at the forefront of science. The two researchers — Bernard Crespi, a biologist at Simon Fraser University in Canada, and Christopher Badcock, a sociologist at the London School of

Economics, who are both outsiders to the field of behavior genetics — have spelled out their theory in a series of recent journal articles.

“The reality, and I think both of the authors would agree, is that many of the details of their theory are going to be wrong; and it is, at this point, just a theory,” said Dr. Matthew Belmonte, a neuroscientist at Cornell University. “But the idea is plausible. And it gives researchers a great opportunity for hypothesis generation, which I think can shake up the field in good ways.”

Their idea is, in broad outline, straightforward. Dr. Crespi and Dr. Badcock propose that an evolutionary tug of war between genes from the father’s sperm and the mother’s egg can, in effect, tip brain development in one of two ways. A strong bias toward the father pushes a developing brain along the autistic spectrum, toward a fascination with objects, patterns, mechanical systems, at the expense of social development. A bias toward the mother moves the growing brain along what the researchers call the psychotic spectrum, toward hypersensitivity to mood, their own and others’. This, according to the theory, increases a child’s risk of developing schizophrenia later on, as well as mood problems like bipolar disorder and depression.

In short: autism and schizophrenia represent opposite ends of a spectrum that includes most, if not all, psychiatric and developmental brain disorders. The theory has no use for psychiatry’s many separate categories for disorders, and it would give genetic findings an entirely new dimension.

“The empirical implications are absolutely huge,” Dr. Crespi said in a phone interview. “If you get a gene linked to autism, for instance, you’d want to look at that same gene for schizophrenia; if it’s a social brain gene, then it would be expected to have opposite effects on these disorders, whether gene expression was turned up or turned down.”

The theory leans heavily on the work of David Haig of Harvard. It was Dr. Haig who argued in the 1990s that pregnancy was in part a biological struggle for resources between the mother and unborn child. On one side, natural selection should favor mothers who limit the nutritional costs of pregnancy and have more offspring; on the other, it should also favor fathers whose offspring maximize the nutrients they receive during gestation, setting up a direct conflict.

The evidence that this struggle is being waged at the level of individual genes is accumulating, if mostly circumstantial. For example, the fetus inherits from both parents a gene called IGF2, which promotes growth. But too much growth taxes the mother, and in normal development her IGF2 gene is chemically marked, or “imprinted,” and biologically silenced. If her gene is active, it causes a disorder of overgrowth, in which the fetus’s birth weight swells, on average, to 50 percent above normal.

Biologists call this gene imprinting an epigenetic, or “on-genetic,” effect, meaning that it changes the behavior of the gene without altering its chemical composition. It is not a matter of turning a gene on or off, which cells do in the course of normal development. Instead it is a matter of muffling a gene, for instance, with a chemical marker that makes it hard for the cell to read the genetic code; or altering the shape of the DNA molecule, or what happens to the proteins it produces. To illustrate how such genetic reshaping can give rise to behavioral opposites — the yin and yang that their theory proposes — Dr. Crespi and Dr. Badcock point to a remarkable group of children who are just that: opposites, as different temperamentally as Snoopy and Charlie Brown, as a lively Gaugin and a brooding Goya.

Those with the genetic disorder called Angelman syndrome typically have a jerky gait, appear unusually happy and have difficulty communicating. Those born with a genetic problem known as Prader-Willi syndrome often are placid, compliant and as youngsters low maintenance.

Yet these two disorders, which turn up in about one of 10,000 newborns, stem from disruptions of the same genetic region on chromosome 15. If the father’s genes dominate in this location, the child develops Angelman syndrome; if the mother’s do, the result is Prader-Willi syndrome, as Dr. Haig and others have noted. The former is associated with autism, and the latter with mood problems and psychosis later on — just as the new theory predicts.

Emotional problems like depression, anxiety and bipolar disorder, seen through this lens, appear on Mom’s side of the teeter-totter, with schizophrenia, while Asperger’s syndrome and other social deficits are on Dad’s.

It was Dr. Badcock who noticed that some problems associated with autism, like a failure to meet another’s gaze, are direct contrasts to those found in people with schizophrenia, who often believe they are being watched. Where children with autism appear blind to others’ thinking and intentions, people with schizophrenia see intention and meaning everywhere, in their delusions. The idea expands on the “extreme male brain” theory of autism proposed by Dr. Simon Baron-Cohen of Cambridge.

“Think of the grandiosity in schizophrenia, how some people think that they are Jesus, or Napoleon, or omnipotent,” Dr. Crespi said, “and then contrast this with the underdeveloped sense of self in autism. Autistic kids often talk about themselves in the third person.”

Such observations and biological evidence are hardly enough to overturn current thinking about disorders as distinct as autism and schizophrenia, experts agree. “I think his work is often brilliant,” Dr. Stephen Scherer, of the University of Toronto and the Hospital for Sick Children, said by e-mail message of Dr. Crespi. At the same time, Dr. Scherer added, “For autism there will not be one unifying theory but perhaps for a proportion of families there are underlying common variants” of genes that together cause the disorder.

The theory also does not fit all of the various quirks of autism and schizophrenia on flip sides of the same behavioral coin. The father of biological psychiatry, Emil Kraepelin, in the late 1800s made a distinction between mood problems, like depression and bipolar disorder, and the thought distortions of schizophrenia — a distinction that, to most psychiatrists, still holds up. Many people with schizophrenia, moreover, show little emotion; they would seem to be off the psychosis spectrum altogether, as the new theory describes it.

But experts familiar with their theory say that the two scientists have, at minimum, infused the field with a shot of needed imagination and demonstrated the power of thinking outside the gene. For just as a gene can carry a mark from its parent of origin, so it can be imprinted by that parent’s own experience.

The study of such markers should have a “significant impact on our understanding of mental health conditions,” said Dr. Bhisadev Chakrabarti, of the Autism Research Center at the University of Cambridge, “as, in some ways, they represent the first environmental influence on the expression of the genes.”

The Promise and Power of RNA

By ANDREW POLLACK

People whose bodies make an unusually active form of a certain protein tend to have dangerously high levels of cholesterol. Those with an inactive form of the protein have low cholesterol and a low risk of heart attacks.

Needless to say, pharmaceutical companies would love to find a drug that can attach itself to the protein and block its activity. That might be difficult for this protein, which is called PCSK9.

But a powerful new approach, called RNA interference, may surmount that obstacle. Instead of mopping up a protein after it has been produced, as a conventional drug would do, RNA interference turns off the faucet, halting production of a protein by silencing the gene that contains its recipe.

In monkeys, a single injection of a drug to induce RNA interference against PCSK9 lowered levels of bad cholesterol by about 60 percent, an effect that lasted up to three weeks. Alnylam Pharmaceuticals, the biotechnology company that developed the drug, hopes to begin testing it in people next year.

The drug is a practical application of scientific discoveries that are showing that RNA, once considered a mere messenger boy for DNA, actually helps to run the show. The classic, protein-making genes are still there on the double helix, but RNA seems to play a powerful role in how genes function. “This is potentially the biggest change in our understanding of biology since the discovery of the double helix,” said John S. Mattick, a professor of molecular biology at the University of Queensland in Australia. And the practical impact may be enormous.

RNA interference, or RNAi, discovered only about 10 years ago, is attracting huge interest for its seeming ability to knock out disease-causing genes. There are already at least six RNAi drugs being tested in people, for illnesses including cancer and an eye disease. And while there are still huge challenges to surmount, that number could easily double in the coming year. “I’ve never found a gene that couldn’t be down-regulated by RNAi,” said Tod Woolf, president of RXi Pharmaceuticals, one of the many companies that have sprung up in the last few years to pursue RNA-based medicines.

The two scientists credited with discovering the basic mechanism of RNA interference won the Nobel Prize in Physiology or Medicine in 2006, only eight years after publishing their seminal paper. And three scientists credited with discovering the closely related micro-RNA in the 1990s won Lasker Awards for medical research this year.

RNA and DNA are strands made up of the chemical units that represent the letters of the genetic code. Each letter pairs with only one other letter, its complement. So two strands can bind to each other if their sequences are complementary.

Genes, which contain the recipes for proteins, are made of DNA. When a protein is to be made, the genetic code for that protein is transcribed from the DNA onto a single strand of RNA, called messenger RNA, which carries the recipe to the cell’s protein-making machinery. Proteins then perform most functions of a cell, including activating other genes.

But scientists are now finding that a lot of DNA is transcribed into RNA without leading to protein production. Rather, the RNA itself appears to be playing a role in determining which genes are active and which proteins are produced.

Much attention has focused on micro-RNAs, which are short stretches of RNA, about 20 to 25 letters long. They interfere with messenger RNA, reducing protein production.

More than 400 micro-RNAs have been found in the human genome, and a single micro-RNA can regulate the activity of hundreds of genes, said David P. Bartel, a biologist at the Whitehead Institute in Cambridge, Mass., and at the Massachusetts Institute of Technology.

As a result, Dr. Bartel said, the activity of more than half the genes in the human genome is affected by micro-RNA. “It’s going to be very difficult to find a developmental process or a disease that isn’t influenced by micro-RNAs,” he said.

Indeed, scientists have found that some micro-RNAs contribute to the formation of cancer and others help block it. Other studies have found micro-RNAs important for the proper formation and functioning of the heart and blood cells. Scientists are also finding other types of RNA, some of which may work differently from micro-RNA. By now, there are so many types of RNA that one needs a scorecard to keep track.

Besides micro-RNA (miRNA), the new ones include small interfering RNA (siRNA), piwi-interacting RNAs (piRNA), chimeric RNA, and promoter-associated and terminus-associated long and short RNAs. They join an existing stable that included messenger RNA (mRNA), transfer RNA (tRNA), and small nucleolar RNA (snoRNA), which all play roles in protein production.

Scientists do not know what all the newly discovered RNA is doing. Some of it may be just a nonfunctional byproduct of other cellular processes. And there is still uncertainty over how big a role RNA plays. Some scientists say proteins are like a light switch, turning genes on and off, while RNA usually does fine tuning, like a dimmer.

Still, the many new discoveries are “revealing a level of regulation and complexity that I don’t think the current organizational model of the genome ever envisioned,” said Thomas R. Gingeras, professor and head of functional genomics at Cold Spring Harbor Laboratory.

Despite the remaining mysteries, researchers and companies are moving rapidly to exploit the latest findings. While micro-RNAs are getting some attention, the biggest effort is on RNA interference.

RNA interference is induced when a short snippet of double-stranded RNA — called a small interfering RNA, or siRNA — enters a cell. The cell treats it much like a micro-RNA it might make on its own. That results in the silencing of a gene that corresponds to the inserted RNA.

Scientists believe that RNA interference evolved as a way to fight viruses, since double-stranded RNA is rare outside viruses. Given that the sequences of genes are now known, it is fairly straightforward to synthesize a small interfering RNA that can serve as a drug to silence a gene. Still, there has not yet been a truly convincing demonstration that such drugs will work in people.

One risk is that the small RNA snippets might silence genes beyond the intended target. And that could mean that a drug based on these snippets would have unwanted side effects.

But the biggest challenge is getting the RNA into the cells where it is needed. Double-stranded RNA is rare outside viruses, so the cell is not likely to welcome it. “Double-stranded RNA basically to the body means one thing: a virus,” said Jonas Alsenas, a biotechnology analyst at the securities firm Leerink Swann who is skeptical about RNAi drugs. Double-stranded RNA can set off an immune response. Enzymes in the blood tear RNA apart. And even if the RNA survives a trip through the bloodstream, it can have difficulty entering the target cells. “Most of the cell membranes are negatively charged and the RNA is negatively charged, so they won’t get close to each other,” said Dr. Mohammad Azab, president of Intradigm, an RNA interference company.

Still, startups like Intradigm, Tekmira Pharmaceuticals, Calando Pharmaceuticals, MDRNA and Traversa Therapeutics are developing delivery methods.

Chemical changes can be made to RNA to make it more stable and to avoid setting off the immune system. And the RNA can be inserted into little globules of fat or attached to polymers to help it get through the bloodstream and enter cells. RXi is developing an oral delivery method for treating certain immune diseases. In some cases, though, these packages can introduce their own toxicities.

Delivery problems tripped up an earlier gene-silencing technology called antisense, which uses single strands of RNA instead of double strands. But progress is now being made in antisense as well, so it may turn out that antisense drugs will compete with RNAi drugs. Given the delivery challenges, the first RNAi drugs are for uses that do not require delivery through the bloodstream. Alnylam is testing a drug that can be inhaled to treat a respiratory virus. Three other companies are testing drugs to treat age-related macular degeneration, the leading cause of blindness among the elderly. The drugs are injected directly into the eye.

The most advanced of the eye drugs, developed by the Miami-based Opko Health, is in the final stage of clinical trials, which would give it a shot at being the first RNAi drug to reach the market.

But some systemic delivery is now being tried. Quark Pharmaceuticals has started early human testing of a drug to prevent kidney damage. Since the kidney removes RNA from blood for excretion, much of the drug is expected to end up there anyway.

Similarly, lipids tend to end up in the liver. Since cholesterol is also processed in the liver, lipid particles will be used to deliver Alnylam's PCSK9 anticholesterol drug, as well as one it plans to test against liver cancer. "If all we ever get to is the liver, we'll be having our hands full with human disease," said John Maraganore, chief executive of Alnylam. But he and other industry executives say they will eventually learn to deliver RNAi drugs anywhere in the body.

One shortcoming of RNA interference is that it can only turn genes off. But to treat some diseases, like those in which the body makes too little of a protein, it might be desirable to turn genes on or to increase their activity levels.

In one of the latest surprises in this field, scientists have found that RNA can do this too. They have discovered what they call RNA activation, or RNAa. The molecules that perform it are called either small activating RNAs (saRNA) or antigene RNAs (agRNA). "We weren't looking for it," said David Corey, a professor of pharmacology at the University of Texas Southwestern Medical Center in Dallas, who was one of those to discover the phenomenon about two years ago. Scientists in his lab were attempting to silence genes using RNAi directed at the promoters of genes. A promoter is a region of DNA that helps activate a gene. Instead of being silenced, the genes became more active and protein production increased. Dr. Corey said it appeared that the RNA enhanced the activity of proteins that bind to the gene promoters.

Whether RNA activation can be used for therapy remains to be seen. It does show, however, that the limits of RNA activity have yet to be understood. There is more to come.

Gender matching aids long-term survival after heart transplants

Abstract 5852

Study highlights:

• *Men who received heart transplants from a male donor and women who had female donors had lower chances of death than patients who received a transplant from the opposite sex, according to a new 10-year study.*

• *Pairing female patients with male donors had the greatest risk for death during the study.*

• *Researchers said heart size and perhaps differences in the immune system explain the correlation.*

NEW ORLEANS, La.- Gender matching between donors and recipients is important to short- and long-term survival in heart transplantation, according to a retrospective study presented at the American Heart Association's Scientific Sessions 2008.

"Heart size would seem to be the most obvious factor; beyond that, no one knows why sex matching is important to transplant survival," said Eric Weiss, M.D., first author of the study and a post doctoral research fellow in the Division of Cardiac Surgery at The Johns Hopkins University Medical Institutions in Baltimore, Md. "In clinical transplantation, we generally don't assume that organs from male and female donors have inherent differences affecting long-term outcomes, but our data suggest that there are important differences which must be taken into account."

Researchers analyzed data from the United Network of Organ Sharing (UNOS), identifying 18,240 patients who received their first orthotopic (replacing a failing organ with a healthy one) heart transplant between 1998 and 2007. In this dataset, patients were followed for 10 years, with the average follow-up time being 3.4 years. Patients were sorted into four groups: male donor with male recipient, female donor with male recipient, male donor with female recipient, and female donor with female recipient.

Overall, 71 percent were matched by gender to their donor (77 percent of male recipients and 51 percent of female recipients). Twenty-five percent of patients died during the study.

Matching donor and recipient by gender resulted in:

- 13 percent lower risk of graft rejection within the first year;
- 14 percent lower rate of graft rejection over the study period;
- 25 percent drop in 30-day death rate; and
- 20 percent lower one-year death rate.

Statistical modeling revealed that the greatest chance for death during the study occurred when pairing a male donor with a female recipient, which made the risk of death an estimated 20 percent higher compared to a male donor with male recipient. The most successful transplants occurred between male recipients and male donors, when the cumulative chance for survival was 61 percent.

"These results fit with our hypothesis that sex matching in heart transplantation leads to improved survival rates," said Weiss, the Irene Piccinini Investigator in Cardiac Surgery.

“We hypothesized that we would see a big difference in the short-term survival - which we did, most likely because of heart-size issues - but what was interesting was the substantial difference in the long term, as well.” More than 2,000 transplant surgeries are done each year. Almost 87.5 percent of male recipients and 85.5 percent of female recipients live for more than a year after the transplant, according to American Heart Association statistics. “We don’t recommend that patients wait longer for a same-sex organ,” Weiss said. “Clearly receiving a heart transplant from a donor of opposite sex is preferable to severe heart failure. If equivalent donors exist for a given patient, our data suggest that picking a sex matched donor may lead to improved short- and long-term survival.”

Co-authors are: Nishant D. Patel, B.A.; Stuart D. Russell, M.D.; William A. Baumgartner, M.D.; Ashish S. Shah, M.D.; and John V. Conte, M.D. Individual author disclosures can be found on the abstract.

A Health Resources and Services Administration contract and a Ruth L. Kirschstein National Research Service Award from the National Institutes of Health funded the study.

Statements and conclusions of study authors that are presented at American Heart Association scientific meetings are solely those of the study authors and do not necessarily reflect association policy or position. The association makes no representation or warranty as to their accuracy or reliability. The association receives funding primarily from individuals; foundations and corporations (including pharmaceutical, device manufacturers and other companies) also make donations and fund specific association programs and events. The association has strict policies to prevent these relationships from influencing science content. Revenues from pharmaceutical and device corporations are available at www.americanheart.org/corporatefunding. NR08-1136 (SS08/Weiss)

Hormone shows promise in reversing Alzheimer's disease and stroke **SLU researchers find strategy to get it past vigilant blood-brain barrier**

ST. LOUIS -- Saint Louis University researchers have identified a novel way of getting a potential treatment for Alzheimer's disease and stroke into the brain where it can do its work.

"We found a unique approach for delivering drugs to the brain," says William A. Banks, M.D., professor of geriatrics and pharmacological and physiological science at Saint Louis University. "We're turning off the guardian that's keeping the drugs out of the brain."

The brain is protected by the blood-brain barrier (BBB), a gate-keeping system of cells that lets in nutrients and keeps out foreign substances. The blood-brain barrier passes no judgment on which foreign substances are trying to get into the brain to treat diseases and which are trying to do harm, so it blocks them without discrimination. "The problem in treating a lot of diseases of the central nervous system – such as Alzheimer's disease, HIV and stroke – is that we can't get drugs past the blood-brain barrier and into the brain," says Banks, who also is a staff physician at Veterans Affairs Medical Center in St. Louis. "Our new research shows a way of getting a promising treatment for these types of devastating diseases to where they need to be to work."

The therapy – known as PACAP27 -- is a hormone produced by the body that is a general neuro-protectant. PACAP stands for pituitary adenylate cyclase-activating polypeptide. "It is a general protector of the brain against many types of insult and injury," Banks says.

He compares a specific guarding mechanism in the BBB -- efflux pumps – to bouncers at exclusive nightclubs. While they welcome those on the approved guest list, they look for trouble-makers trying to crash the party, refuse to let them in and evict them if they do get in.

The scientists isolated the particular gatekeeper that evicts PACAP27. Then they designed an antisense, a specific molecule that turned off the impediment. "We went after the guard and essentially told him to go on break for a while so PACAP27 could get into the brain," Banks says.

They used mouse models of Alzheimer's disease and stroke to test what would happen if PACAP27 could get into the brain. "We reversed the symptoms of the illnesses," Banks says. "The mice that had a version of Alzheimer's disease became smarter and in the stroke model, we reduced the amount of damage caused by the blockage of blood to the brain and improved brain recovery."

Simply turning off the gatekeeper that kept PACAP27 out of the brain allowed enough of the hormone that already is in the body to get inside the brain, where it effectively treated strokes. However, the mice that had a version of Alzheimer's disease needed both an extra dose of PACAP27 and the antisense that turned off the gatekeeper to improve learning.

"These findings are significant for three reasons. We have found a therapy that reverses symptoms of Alzheimer's disease and stroke in a mouse model. We have isolated the particular roadblock that keeps the treatment from getting into the brain. And we have found a way to finesse that obstacle so the medicine can get into the brain to do its work," Banks says. "This could have implications in treating many diseases of the central nervous system."

The findings were published in the Nov. 12 early online issue of the Journal of Cerebral Blood Flow & Metabolism.

Placebo acupuncture is associated with a higher pregnancy rate after IVF than real acupuncture

A study comparing the effects of real and placebo acupuncture on pregnancy rates during assisted reproduction has found that, surprisingly, placebo acupuncture was associated with a significantly higher overall pregnancy rate than real acupuncture. The study, published online in Europe's leading reproductive medicine journal *Human Reproduction* today (Thursday 13 November), looked at real and placebo acupuncture given on the day of embryo transfer in 370 patients in a randomised, double blind trial (where neither the patients nor the doctors knew which treatment was being given). [1]

The researchers found that the overall pregnancy rate (defined by a positive urinary pregnancy test) for placebo acupuncture was 55.1%, versus 43.8% for the real acupuncture.

Dr Ernest Hung Yu Ng, Associate Professor in the Department of Obstetrics and Gynaecology at the University of Hong Kong (People's Republic of China), said: "We found a significantly higher overall pregnancy rate following placebo acupuncture when compared with that of real acupuncture. In addition, there was a trend towards higher rates of clinical pregnancy, ongoing pregnancy, live birth and embryo implantation in the placebo acupuncture group, although the differences did not reach statistical significance."

The authors say that their results suggest that placebo acupuncture may not act as an inert control for real acupuncture, and that it may be having a real effect. This theory is supported by the fact that measurements for the receptivity of the uterus and the levels of patient stress changed significantly for both the real and control groups after the women had received the real or placebo acupuncture.

It is difficult to design a suitable control for acupuncture – a treatment that involves the insertion of fine needles into particular points on the body. In this study, the researchers used a placebo needle that looked identical to a real acupuncture needle, but which was blunt and retracted into the handle of the needle when pressed on the skin, while still giving the appearance and sensation of entering the skin. A trained acupuncturist applied the placebo to the same acupuncture points as for the real acupuncture.

Dr Ng gave two possible explanations for the results: "Placebo acupuncture is similar to acupressure and therefore is good enough to improve the pregnancy rate. Or else, it's possible that real acupuncture may, in some way, reduce the pregnancy rate of acupuncture. "So far there is no evidence that real acupuncture would adversely affect IVF outcomes because, in a previous meta-analysis of several acupuncture studies, the pregnancy rate was higher in the acupuncture groups than in the control groups. However, we cannot draw a firm conclusion about this from our current study as we did not compare the two groups with a third control group patients who received neither forms of acupuncture. Further studies should be conducted to compare placebo or non-invasive acupuncture and controls without acupuncture."

Dr Ng was the lead author of the previous meta-analysis mentioned here, and an associated sub-group analysis detected a significant improvement in pregnancy rates for acupuncture treatment when it was delivered on the day of embryo transfer, but not if it was given only on the day when the oocytes were retrieved from the women's ovaries.

However, Dr Ng's current study takes the research a step forward because it is double blinded. "The meta-analysis showed that acupuncture on the day of embryo transfer leads to a significantly higher pregnancy rate when compared to controls. But in the vast majority of the studies included in the meta-analysis, the controls received no acupuncture and the patients were not blinded. My current study compared real and placebo acupuncture in a double blind setting, which should be the ideal model in research. However, the results suggest that placebo acupuncture may not be inert."

Infertile patients can suffer from high levels of stress and anxiety, which can adversely affect the outcome of IVF. Dr Ng said: "We found a significant decrease in serum cortisol concentration and the anxiety level following placebo and real acupuncture. Reduction in stress in both groups may also contribute to a better pregnancy rate following placebo and real acupuncture."

Assessing the sometimes contradictory evidence about the effects of acupuncture on IVF success so far, Dr Ng concluded: "Based on my previous meta-analysis, I believe that acupuncture on the day of embryo transfer can improve the pregnancy rate. However, there are still some unresolved issues. The improvement in the pregnancy rates of IVF treatment with acupuncture are higher than that for drugs or other procedures given to enhance the success of this treatment, and the underlying biological mechanism is difficult to explain.

"In addition, the sub-group analysis shows no improvement in the pregnancy rate after acupuncture if the pregnancy rate of the IVF unit was good i.e. achieving a clinical pregnancy rate of more than 28% per cycle. In 2005 the pregnancy rate per embryo transfer in our unit was 35%, so this aspect requires further investigation."

[1] A randomized double blind comparison of real and placebo acupuncture in IVF treatment. *Human Reproduction*. Published online under advance access. doi:10.1093/humrep/den380

A large waist can almost double your risk of premature death, says huge Europe-wide study

Having a large waistline can almost double your risk of dying prematurely even if your body mass index is within the 'normal' range, according to a new study of over 350,000 people across Europe, published today in the *New England Journal of Medicine*.

The study provides strong evidence that storing excess fat around the waist poses a significant health risk, even in people not considered to be overweight or obese. It suggests that doctors should measure a patient's waistline and their hips as well as their body mass index as part of standard health checks, according to the researchers, from Imperial College London, the German Institute of Human Nutrition, and other research institutions across Europe.

Comparing subjects with the same body mass index, the risk of premature death increased in a linear fashion as the waist circumference increased. The risk of premature death was around double for subjects with a larger waist (more than 120cm or 47.2in for men and more than 100cm or 39.4in for women) compared to subjects with a smaller waist (less than 80cm or 31.5in for men and less than 65cm or 25.6in for women). Body mass index is commonly used to assess if a person is of 'normal' weight.

Each 5cm increase in waist circumference increased the mortality risk by 17% in men and 13% in women.

The ratio of waist to hips was also revealed as an important indicator of health in the study. Lower waist-hip ratios indicate that the waist is comparatively small in relation to the hips. The ratio is calculated by dividing the waist measurement by the hip measurement.

Waist to hip ratio varied quite widely in the European populations in the study. In 98 percent of the study population, waist to hip ratio ranged between 0.78 and 1.10 in men and between 0.66 and 0.98 in women. Within these ranges, each 0.1 unit higher waist-hip-ratio was related to a 34% higher mortality risk in men and a 24% higher risk in women.

An increased risk of mortality may be particularly related to storing fat around the waistline because fatty tissue in this area secretes cytokines, hormones and metabolically active compounds that can contribute to the development of chronic diseases, particularly cardiovascular diseases and cancers, suggest the authors.

Although the main new finding of this study is that waist size increases the risk of premature death independently of body mass index (BMI), the study does support earlier findings showing that a higher body mass index is significantly related to mortality. The lowest risk of death was at a BMI of approximately 25.3 in men and 24.3 in women.

The new research forms part of the European Prospective Investigation into Cancer and Nutrition (EPIC), one of the largest long-term prospective studies in the world.

Professor Elio Riboli, the European coordinator of the EPIC study from the Department of Epidemiology and Public Health at Imperial College London, said: "Although smaller studies have suggested a link between mortality and waist size, we were surprised to see the waist size having such a powerful effect on people's health and premature death. Our study shows that accumulating excess fat around your middle can put your health at risk even if your weight is normal based on body mass index scores. There aren't many simple individual characteristics that can increase a person's risk of premature death to this extent, independently from smoking and drinking. "

Privatdozent Dr Tobias Pischon, the lead author of the paper from the German Institute of Human Nutrition in Potsdam-Rehbrücke, said: "The most important result of our study is the finding that not just being overweight, but also the distribution of body fat, affects the risk of premature death of each individual. Abdominal fat is not only a mere energy depot, but it also releases messenger substances that can contribute to the development of chronic diseases. This may be the reason for the link."

The new research does not reveal why some people have a larger waist than others but the researchers believe that a sedentary lifestyle, poor diet and genetic predisposition are probably key factors.

Professor Riboli added: "The good news is that you don't need to take an expensive test and wait ages for the result to assess this aspect of your health - it costs virtually nothing to measure your waist and hip size. Doctors and nurses can easily identify people who need to take certain steps to improve their health by routinely monitoring these measurements. If you have a large waist, you probably need to increase the amount of exercise you do every day, avoid excessive alcohol consumption and improve your diet. This could make a huge difference in reducing your risk of an early death."

Professor Riboli leads a new Interventional Public Health Clinical Programme Group at the UK's first Academic Health Science Centre (AHSC). The AHSC is a unique partnership between Imperial College London and Imperial College Healthcare NHS Trust, which aims to ensure that the benefits of research reach

patients more quickly than ever before. Professor Riboli's Interventional Public Health group will find new ways of improving people's health in order to prevent them developing conditions such as diabetes and obesity.

For today's prospective EPIC study the researchers looked at 359,387 participants from 9 European countries. The average age of the participants when data were first collected was 51.5 years of age, and 65.4% of the participants were women. During the follow-up period, which averaged 9.7 years, 14,723 of the participants died. Participants with a high BMI, compared with those in the medium range, died more often from cardiovascular diseases or from cancer. Participants with a low BMI tended to die more frequently from respiratory diseases.

Thar she blows: Snot offers clues to whale health

What is the strangest thing you could do with a remote-controlled toy helicopter? To strap on a few Petri dishes and fly it through whale snot must be high on the list. That is how Karina Acevedo-Whitehouse, a veterinarian and conservation biologist with the Zoological Society of London, has spent much of her time over the past few years. Of course, there's a serious reason for such work - Acevedo-Whitehouse is, for the first time, making it possible to study the viruses, fungi and bacteria that hitch a ride in whale lungs.

Researchers can fairly easily take blood samples from other marine mammals, such as seals and sea lions, but whales' sheer bulk rules out such sampling without killing them. "Scientists have always found it difficult to study diseases in whales because of their size," explains Acevedo-Whitehouse. "Most studies on whale pathogens have focused on dead, stranded or captive animals, which are hardly representative of the normal population."

Whales are too big to take blood samples, but their breath can also give insight into their health (Image: ZSL)

Snot collector

After witnessing the sheer power of whale "blows" in the Gulf of California, she realised that this would be the best way of sampling the insides of a live whale in the ocean. She first tried tying herself to a research boat and leaning overboard to catch a bit of whale "snot" in Petri dishes. "It worked," she says, "but it wasn't very safe."

Her technique is now somewhat more sophisticated. For species like grey and sperm whales that do not mind being close to a boat, the researchers attach their Petri dishes to a long pole and hold them out over the blows. With the shy blue whale, they have had to resort to toy-sized helicopters. The Petri dishes are attached beneath the metre-long choppers, which are remotely flown through whale blows. "The whales definitely notice the helicopter," says Acevedo-Whitehouse, "they turn on their sides to look at it. But they don't seem bothered. We are collecting very relevant biological information without harming them in the least - we don't even touch them."

The team has taken samples from more than 120 whales in the Gulf of California and off Gibraltar. Each time also sampling the background ocean spray as a control. This lets them identify which bugs come from the whales, and which are present in the sea.

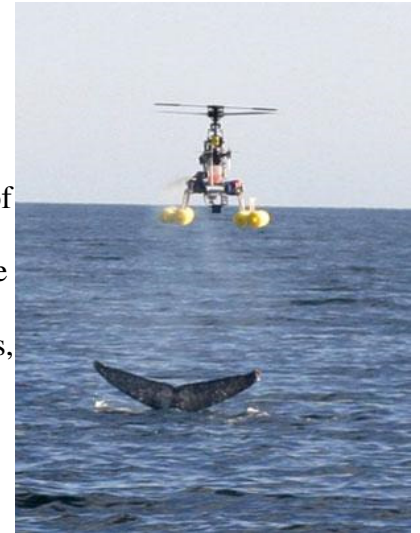
Poo too

The samples are taken back to the lab and scanned for specific DNA sequences that identify individual bacteria, fungi and viruses. As well as looking for pathogenic bugs similar to flu or TB, the researchers are trying to build a profile of what microbes a healthy whale normally carries in its lungs.

In the long run, these microbe profiles will be compared to ones sampled from beached whales. With the help of colleagues at Cicimar in Mexico, who have been tracking the Gulf of California whales for over 20 years, the team also hope to study how bacteria and viruses spread through whale populations.

The team is still analysing its data but enough has been processed to know that different species carry different bacteria. There are also differences between the bacteria they have collected from healthy whales and those collected from stranded whales - though Acevedo-Whitehouse cautiously notes that the bacteria on stranded whales may have grown after the whales died.

Other attempts to study the physiology of healthy, live whales have included collecting floating poo to study their diet, hormones and parasites in their digestive tract, and taking skin samples to look at contaminants. Whale scat is harder to find than the whales that left them behind, which is why researchers use sniffer dogs to help them out ([see Sniffing out a whale's doo-doo](#)).



Female spiders make a meal out of lazy lovers

* 15:46 12 November 2008 by **David Robson**

Men that are "only after one thing" should be grateful that they are dating women. Female redback spiders kill and eat partners that demand quick sex in place of extended courtship.

In contrast, a little bit of wooing goes a long way in arousing her passions for the male, new research reveals.

Jeffrey Stoltz from the University of Toronto Scarborough, Canada, studied the courting habits of redback spiders by setting up females with either one or two males. They then filmed the courtships as they unfolded.



Video: [Watch what happens if a male does keep a female happy](#)

The single males spent up to five hours courting the female by alternately plucking the web and beating on her abdomen before attempting to mate. During copulation, the female always started to eat the male, but roughly 90% of the time she would let him escape after a quick nibble to have another try at courtship and mating. When a rival was present, the story changed, although this depended on the strength of the competition.

Size matters

When the males were of differing size, the smaller of the two competitors would often try to sneak past its rival and copulate quickly, leaving just 45 minutes for courtship. The females seemed to resent this, since the team observed a greater probability of cannibalism following shorter courtships. Overall, the females ate roughly half of the "sneaking" partners in these cases.

"Prolonged courtship probably gives information on a male's endurance," says Stoltz. "We speculate that it might indicate whether the male had been able to find good food reserves when they were young." Killing the lazy suitors prevents them from mating for a second time and fathering more of her young.

The female redbacks didn't seem to take such umbrage at the shorter courtships if there wasn't an obvious size difference between the two males - eating just 35% of their suitors after the first copulation while allowing the majority to stay within the competition.

However, she was still wary of allowing him to father more of her offspring, being far more likely to have repeated sex with the male's rivals if he didn't pay enough initial attention.

Journal reference: Animal Behaviour (DOI: 10.1016/j.anbehav.2008.09.012)

How warfare shaped human evolution

* 12 November 2008 by **Bob Holmes**

IT'S a question at the heart of what it is to be human: why do we go to war? The cost to human society is enormous, yet for all our intellectual development, we continue to wage war well into the 21st century.

Now a new theory is emerging that challenges the prevailing view that warfare is a product of human culture and thus a relatively recent phenomenon. For the first time, anthropologists, archaeologists, primatologists, psychologists and political scientists are approaching a consensus. Not only is war as ancient as humankind, they say, but it has played an integral role in our evolution.

The theory helps explain the evolution of familiar aspects of warlike behaviour such as gang warfare. And even suggests the cooperative skills we've had to develop to be effective warriors have turned into the modern ability to work towards a common goal.

These ideas emerged at a conference last month on the evolutionary origins of war at the University of Oregon in Eugene. "The picture that was painted was quite consistent," says Mark Van Vugt, an evolutionary psychologist at the University of Kent, UK. "Warfare has been with us for at least several tens, if not hundreds, of thousands of years." He thinks it was already there in the common ancestor we share with chimps. "It has been a significant selection pressure on the human species," he says. In fact several fossils of early humans have wounds consistent with warfare.

Studies suggest that warfare accounts for 10 per cent or more of all male deaths in present-day hunter-gatherers. "That's enough to get your attention," says Stephen LeBlanc, an archaeologist at Harvard University's Peabody Museum in Boston.

Primatologists have known for some time that organised, lethal violence is common between groups of chimpanzees, our closest relatives. Whether between chimps or hunter-gatherers, however, intergroup violence is nothing like modern pitched battles. Instead, it tends to take the form of brief raids using overwhelming force, so that the aggressors run little risk of injury. "It's not like the Somme," says Richard Wrangham, a primatologist at Harvard University. "You go off, you make a hit, you come back again." This opportunistic violence helps the aggressors weaken rival groups and thus expand their territorial holdings.

Such raids are possible because humans and chimps, unlike most social mammals, often wander away from the main group to forage singly or in smaller groups, says Wrangham. Bonobos - which are as closely related to humans as chimps are - have little or no intergroup violence because they tend to live in habitats where food is easier to come by, so that they need not stray from the group.

If group violence has been around for a long time in human society then we ought to have evolved psychological adaptations to a warlike lifestyle. Several participants presented the strongest evidence yet that males - whose larger and more muscular bodies make them better suited for fighting - have evolved a tendency towards aggression outside the group but cooperation within it. "There is something ineluctably male about coalitional aggression - men bonding with men to engage in aggression against other men," says Rose McDermott, a political scientist at Stanford University in California.

Aggression in women, she notes, tends to take the form of verbal rather than physical violence, and is mostly one on one. Gang instincts may have evolved in women too, but to a much lesser extent, says John Tooby, an evolutionary psychologist at the University of California at Santa Barbara. This is partly because of our evolutionary history, in which men are often much stronger than women and therefore better suited for physical violence. This could explain why female gangs only tend to form in same-sex environments such as prison or high school. But women also have more to lose from aggression, Tooby points out, since they bear most of the effort of child-rearing.

Not surprisingly, McDermott, Van Vugt and their colleagues found that men are more aggressive than women when playing the leader of a fictitious country in a role-playing game. But Van Vugt's team observed more subtle responses in group bonding. For example, male undergraduates were more willing than women to contribute money towards a group effort - but only when competing against rival universities. If told instead that the experiment was to test their individual responses to group cooperation, men coughed up less cash than women did. In other words, men's cooperative behaviour only emerged in the context of intergroup competition (Psychological Science, vol 18, p 19).

Some of this behaviour could arguably be attributed to conscious mental strategies, but anthropologist Mark Flinn of the University of Missouri at Columbia has found that group-oriented responses occur on the hormonal level, too. He found that cricket players on the Caribbean island of Dominica experience a testosterone surge after winning against another village. But this hormonal surge, and presumably the dominant behaviour it prompts, was absent when the men beat a team from their own village, Flinn told the conference. "You're sort of sending the signal that it's play. You're not asserting dominance over them," he says. Similarly, the testosterone surge a man often has in the presence of a potential mate is muted if the woman is in a relationship with his friend. Again, the effect is to reduce competition within the group, says Flinn. "We really are different from chimpanzees in our relative amount of respect for other males' mating relationships."

The net effect of all this is that groups of males take on their own special dynamic. Think soldiers in a platoon, or football fans out on the town: cohesive, confident, aggressive - just the traits a group of warriors needs.

Chimpanzees don't go to war in the way we do because they lack the abstract thought required to see themselves as part of a collective that expands beyond their immediate associates, says Wrangham. However, "the real story of our evolutionary past is not simply that warfare drove the evolution of social behaviour," says Samuel Bowles, an economist at the Santa Fe Institute in New Mexico and the University of Siena, Italy. The real driver, he says, was "some interplay between warfare and the alternative benefits of peace".

Though women seem to help broker harmony within groups, says Van Vugt, men may be better at peacekeeping between groups.

Our warlike past may have given us other gifts, as well. "The interesting thing about war is we're focused on the harm it does," says Tooby. "But it requires a super-high level of cooperation." And that seems to be a heritage worth hanging on to. The interesting thing about war is that we're focused on the harm it does. But it requires a super-high level of cooperation

The mindset for modern warfare

Modern warfare with its complex strategies, and advanced, long-distance weapons bears little resemblance to the hand-to-hand skirmishes of our ancestors. This may mean we're left with battle instincts unsuited to our time, suggested several participants at the Oregon conference. Overconfidence in the strength of numbers is one example, says Dominic Johnson of the University of Edinburgh, UK. He found that in a simulated war game, men tended to overestimate their chance of winning, making them more likely to attack (Proceedings of the Royal Society B, vol 273, p 2513). Thus, a dictator surveying his soldiers on parade may vastly overrate his military strength. "In the Pleistocene, nobody would have been able to beat that," says John Tooby at the University of California at Santa Barbara. Soldiers going into battle today don't make the decisions, says

Richard Wrangham of Harvard University, which may make them more fearful fighters. "In primitive warfare, men were fighting because they wanted to."

How war spread like the plague

The threat of disease could have driven the evolution of war - at least within a nation. This controversial idea is the brainchild of Randy Thornhill, an evolutionary biologist at the University of New Mexico in Albuquerque. He argues that cultures become more insular and xenophobic where diseases and parasites are common, preferring to drive away strangers who may carry new diseases. In contrast, cultures with a low risk of disease are more open to outsiders. Thornhill thinks these attitudes to outsiders colour each culture's propensity for war. Sure enough, when Thornhill and his colleagues gathered data from 125 civil wars, they found that such wars were far more common in nations with higher rates of infectious disease, such as Indonesia and Somalia. Participants at the conference at the University of Oregon in Eugene greeted Thornhill's theory with interested scepticism. It is "a very different way of thinking that has to be taken seriously", says primatologist Francis White who works at the university. John Orbell, a political scientist also at the university, says the idea is "pretty persuasive". Thornhill admits his ideas are hard to test, because countries with high disease levels are often poor, multi-ethnic and authoritarian, all of which can drive civil unrest. However, he says, when infectious disease fell in western nations in the 20th century thanks to antibiotics and sanitation, those same societies also became less xenophobic.

Humans may have prevented super ice age

* 18:00 12 November 2008 by Michael Le Page

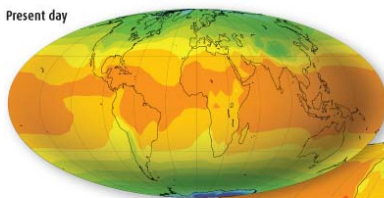
Our impact on Earth's climate might be even more profound than we realise. Before we started pumping massive amounts of carbon dioxide into the atmosphere, the planet was on the brink of entering a semi-permanent ice age, two researchers have proposed.

Had we not radically altered the atmosphere, say Thomas Crowley of the University of Edinburgh, UK, and William Hyde of the University of Toronto in Canada, the current cycle of ice ages and interglacials would have given way in the not-too-distant future to an ice age lasting millions of years. "It's not proven but it's more than just an interesting idea," says Crowley. For much of the 500 million years or so since complex life evolved, Earth's climate has been much hotter than it is now, with no ice at the poles. During the last of these "hothouse Earth" phases, from around 100 to 50 million years ago, the Antarctic was covered by lush forests and shallow seas submerged vast areas of America, Europe and Africa.

A DIFFERENT WORLD

From around 100 million to 40 million years ago, our planet was much hotter with no permanent ice at the poles

Present day

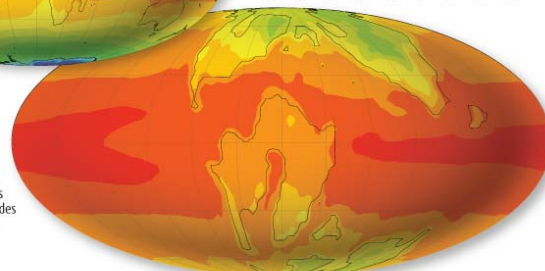


Annual mean temperature °C



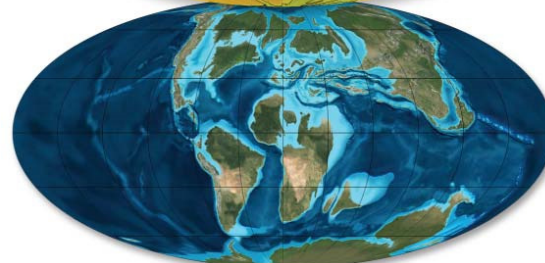
100 million years ago

A model simulation of temperatures. Fossil evidence, however, suggests the interiors of the continents in high latitudes were somewhat warmer than models predict



90 million years ago

What the world might have looked like, showing how shallow oceans covered large parts of what is land today



A different world

Oscillating wildly

Since that time, though, CO2 levels have slowly fallen, possibly due to the rise of the Himalayas. As a result Earth has gradually cooled, with permanent ice sheets starting to form in Antarctica around 30 million years ago and later in the Arctic. Then, 2.5 million years ago, the climate entered a curious new phase: it started oscillating wildly, see-sawing between interglacial periods with conditions similar to today's and ice ages during which the amount of permanent ice in the northern hemisphere expanded hugely. At the peaks of these transient ice ages, much of northern Europe, northern Asia and North America were covered in ice sheets up to 4 kilometres thick, and sea levels were 120 metres lower than today. From a "deep time" perspective, this ice age-interglacial cycle may be just another brief transitional phase. It has been becoming ever more variable, Crowley says.

Bigger swings

When the cycle began, the climate went from ice age to interglacial and back roughly every 41,000 years. More recently, it has been happening every 100,000 years.

The temperature swings have also become greater: the interglacials have been no warmer but the ice ages have become much colder. So the overall cooling trend was continuing - until the arrival of the Anthropocene, the period in which humans have started to have a major affect on Earth's climate and ecosystems.

According to a simple climate model developed by Crowley and Hyde, this increasing variability was a sign that the climate was about to flip into a new stable state - a semi-permanent ice age. This ice age might well have lasted for tens of millions of years or more, Crowley says. In the model runs best resembling actual climate history, the switch to a long-lasting ice age happened as early as 10,000 to 100,000 years from now. However, Crowley stresses that not too much confidence can be placed on the results of single runs out of many.

Hello snowball

The idea of the world becoming locked in an ice age is certainly plausible, says James Zachos of the University of California, Santa Cruz, who studies past climate. It's not that rare for the climate to switch from one state into another, he says.

And there were extensive and long-lived ice ages during the Carboniferous period, around 300 million years, points out climate modeller Andy Ridgwell of the University of Bristol, UK. Further back, around 700 million years ago, there was an even colder period known as "Snowball Earth", when the planet froze over nearly completely.

However, Crowley and Hyde are going to have to do a lot more work to convince their peers. Because of the vast lengths of time involved, they used a very basic model to simplify calculations. "It is not as complex as everyone wants it to be, but you can run it for a very long time," says Crowley.

Handle with care

None of the researchers contacted by New Scientist thought the model's predictions are worth taking seriously. It appears to have a bias to forming large and stable ice sheets, says Ridgwell. "So it does not come as a shock that they find a transition point to an even greater ice mass state."

Still, everyone agrees that it is an intriguing idea. "It is worth delving into deeper," says Ridgwell. The idea that humans have averted an ice age may ring a bell with regular New Scientist readers. Climatologist Bill Ruddiman has suggested that Stone Age farmers prevented an ice age by releasing greenhouse gases.

However, the two ideas are quite distinct: Ruddiman thinks that without human intervention we would now be entering another transient ice age like all the previous ones, while Crowley thinks that at some time in the future the whole ice age-interglacial cycle would have ended.

It's possible they could both be right - or wrong - but we will never know for sure. We have pumped so much carbon dioxide into the atmosphere in little more than a century that levels are higher now than they have been for at least 800,000 years. This will have delayed any switch to a long-lasting ice age indefinitely. "We are probably very comfortably away from it happening now," Crowley stresses.

Instead, we are putting the planet's climate on the opposite trajectory, back towards "hothouse Earth" conditions. *Journal reference: Nature (DOI: 10.1038/nature07365)*

Common anesthetic induces Alzheimer's-associated changes in mouse brains

For the first time researchers have shown that a commonly used anesthetic can produce changes associated with Alzheimer's disease in the brains of living mammals, confirming previous laboratory studies. In their *Annals of Neurology* report, which has received early online release, a team of Massachusetts General Hospital (MGH) investigators shows how administration of the gas isoflurane can lead to generation of the toxic amyloid-beta (A-beta) protein in the brains of mice.

"These are the first in vivo results indicating that isoflurane can set off a time-dependent cascade inducing apoptosis [cell death] and enhanced levels of the Alzheimer's-associated proteins BACE and A-beta," says Zhongcong Xie, MD, PhD, of the MassGeneral Institute for Neurodegenerative Disease (MGH-MIND) and the MGH Department of Anesthesia and Critical Care, the study's lead and corresponding author. "This work needs to be confirmed in human studies, but it's looking like isoflurane may not be the best anesthesia to use for patients who already have higher A-beta levels, such as the elderly and Alzheimer's patients."

Alzheimer's disease is characterized by deposition of A-beta plaques within the brain. The A-beta protein is formed when the larger amyloid precursor protein (APP) is clipped by two enzymes – beta-secretase, also known as BACE, and gamma-secretase – to release the A-beta fragment. Normal processing of APP by an enzyme called alpha-secretase produces an alternative, non-toxic protein.

Several studies have suggested that surgery and general anesthesia may increase the risk of developing Alzheimer's disease, and it is well known that a small but significant number of surgical patients experience a transient form of dementia in the postoperative period. Last year the MGH team showed that applying isoflurane to cultured neural cells increased activation of the cell-death protein caspase and raised levels of BACE and gamma-secretase as part of a pathway leading to the generation of A-beta. The current study was designed to see if the same process takes place in mice.

Neurologically normal mice received isoflurane for two hours at doses comparable to what would be administered to human patients. Their brains were examined 2, 6, 12 and 24 hours after they received the

anesthesia and compared with the brains of control mice. Results at 6 hours showed that caspase levels were elevated and BACE had modestly increased in mice that received isoflurane. At 12 hours moderate caspase activation persisted, and BACE levels were even higher in the treated mice; and at 24 hours BACE levels were more than four times higher than in controls, and A-beta levels had also risen, while caspase activation had fallen off.

Another group of mice had been treated for seven days with the drug clioquinol before the two-hour isoflurane administration. Laboratory studies have found that clioquinol inhibits the aggregation of A-beta into neurotoxic deposits, and a clioquinol derivative is currently in clinical trials as an Alzheimer's treatment drug. Six hours after they received isoflurane, caspase levels in the clioquinol-treated mice were significantly less than in other animals that had received the anesthetic, suggesting both that A-beta aggregation contributes to a vicious cycle of further cell death – echoing a finding from the team's 2007 study – and that a drug like clioquinol might block isoflurane's neurotoxic effects.

"This study cannot tell us about the long-term effects of isoflurane administration; that's something we will examine in future investigations," notes Xie, who is an assistant professor of Anesthesia at Harvard Medical School (HMS) and director of the Geriatric Anesthesia Research Unit in the MGH Department of Anesthesia and Critical Care.

"Until we can directly assess the impact of isoflurane on biomarkers like A-beta levels in the plasma or cerebrospinal fluid of human patients, we cannot conclusively determine its role in increasing the risk for Alzheimer's or postoperative dementia," adds Rudolph Tanzi, PhD, director of the MGH-MIND Genetics and Aging Research Unit, senior author of the study, and the Joseph P. and Rose F. Kennedy Professor of Neurology at HMS.

Gregory Crosby, MD, of Brigham and Women's Hospital (BWH) is a co-corresponding author of the Annals of Neurology paper. Additional co-authors are Yuanlin Dong, Guohua Zhang, and Bin Zhang, MGH-MIND and MGH Anesthesia; Robert D. Moir, PhD, MGH-MIND; Matthew Frosch, MD, PhD, MGH Neurology, and Deborah Culley, MD, BWH.

The study was supported by grants from the National Institutes of Health, the American Geriatrics Society, the Alzheimer's Association, Harvard University and the Cure Alzheimer's Fund. Tanzi is a co-founder, consultant and holds equity in Prana Biotechnology, Ltd, the company conducting a clinical trial of clioquinol derivative PBT2. Xie is a consultant of Baxter Healthcare, the company that produces isoflurane. Neither company supported or had any other connection with the current study.

Mineral kingdom has co-evolved with life

Washington, DC— Evolution isn't just for living organisms. Scientists at the Carnegie Institution have found that the mineral kingdom co-evolved with life, and that up to two thirds of the more than 4,000 known types of minerals on Earth can be directly or indirectly linked to biological activity. The finding, published in *American Mineralogist**, could aid scientists in the search for life on other planets.

Robert Hazen and Dominic Papineau of the Carnegie Institution's Geophysical Laboratory, with six colleagues, reviewed the physical, chemical, and biological processes that gradually transformed about a dozen different primordial minerals in ancient interstellar dust grains to the thousands of mineral species on the present-day Earth. (Unlike biological species, each mineral species is defined by its characteristic chemical makeup and crystal structure.)

"It's a different way of looking at minerals from more traditional approaches," says Hazen. "Mineral evolution is obviously different from Darwinian evolution—minerals don't mutate, reproduce or compete like living organisms. But we found both the variety and relative abundances of minerals have changed dramatically over more than 4.5 billion years of Earth's history."

All the chemical elements were present from the start in the Solar Systems' primordial dust, but they formed comparatively few minerals. Only after large bodies such as the Sun and planets congealed did there exist the extremes of temperature and pressure required to forge a large diversity of mineral species. Many elements were also too dispersed in the original dust clouds to be able to solidify into mineral crystals.

As the Solar System took shape through "gravitational clumping" of small, undifferentiated bodies - fragments of which are found today in the form of meteorites - about 60 different minerals made their appearance. Larger, planet-sized bodies, especially those with volcanic activity and bearing significant amounts of water, could have given rise to several hundred new mineral species. Mars and Venus, which Hazen and coworkers estimate to have at least 500 different mineral species in their surface rocks, appear to have reached this stage in their mineral evolution.

However, only on Earth - at least in our Solar System - did mineral evolution progress to the next stages. A key factor was the churning of the planet's interior by plate tectonics, the process that drives the slow shifting continents and ocean basins over geological time. Unique to Earth, plate tectonics created new kinds of physical

and chemical environments where minerals could form, and thereby boosted mineral diversity to more than a thousand types.

What ultimately had the biggest impact on mineral evolution, however, was the origin of life, approximately 4 billion years ago. "Of the approximately 4,300 known mineral species on Earth, perhaps two thirds of them are biologically mediated," says Hazen. "This is principally a consequence of our oxygen-rich atmosphere, which is a product of photosynthesis by microscopic algae." Many important minerals are oxidized weathering products, including ores of iron, copper and many other metals.

Microorganisms and plants also accelerated the production of diverse clay minerals. In the oceans, the evolution of organisms with shells and mineralized skeletons generated thick layered deposits of minerals such as calcite, which would be rare on a lifeless planet.

"For at least 2.5 billion years, and possibly since the emergence of life, Earth's mineralogy has evolved in parallel with biology," says Hazen. "One implication of this finding is that remote observations of the mineralogy of other moons and planets may provide crucial evidence for biological influences beyond Earth."

Stanford University geologist Gary Ernst called the study "breathtaking," saying that "the unique perspective presented in this paper may revolutionize the way Earth scientists regard minerals."

**Robert M. Hazen, Dominic Papineau, Wouter Bleeker, Robert T. Downs, John M. Ferry, Timothy J. McCoy, Dimitri Sverjensky and Hexiong Yang (2008) Mineral evolution. American Mineralogist.*

Clean results: University of Michigan researchers learn how bleach kills bacteria

ANN ARBOR, Mich.- Developed more than 200 years ago and found in households around the world, chlorine bleach is among the most widely used disinfectants, yet scientists never have understood exactly how the familiar product kills bacteria.

New research from the University of Michigan, however, reveals key details in the process by which bleach works its antimicrobial magic.

In a study published in the Nov. 14 issue of the journal *Cell*, a team led by molecular biologist Ursula Jakob describes a mechanism by which hypochlorite, the active ingredient of household bleach, attacks essential bacterial proteins, ultimately killing the bugs.

"As so often happens in science, we did not set out to address this question," said Jakob, an associate professor of molecular, cellular and developmental biology. "But when we stumbled on the answer midway through a different project, we were all very excited."

Jakob and her team were studying a bacterial protein known as heat shock protein 33 (Hsp33), which is classified as a molecular chaperone. The main job of chaperones is to protect proteins from unfavorable interactions, a function that's particularly important when cells are under conditions of stress, such as the high temperatures that result from fever.

"At high temperatures, proteins begin to lose their three-dimensional molecular structure and start to clump together and form large, insoluble aggregates, just like when you boil an egg," said lead author Jeannette Winter, who was a postdoctoral fellow in Jakob's lab. And like eggs, which once boiled never turn liquid again, aggregated proteins usually remain insoluble, and the stressed cells eventually die.

Jakob and her research team figured out that bleach and high temperatures have very similar effects on proteins. Just like heat, the hypochlorite in bleach causes proteins to lose their structure and form large aggregates.

"Many of the proteins that hypochlorite attacks are essential for bacterial growth, so inactivating those proteins likely kills the bacteria," said second author Marianne Ilbert, a postdoctoral fellow in Jakob's lab.

These findings are not only important for understanding how bleach keeps our kitchen countertops sanitary, but they may lead to insights into how we fight off bacterial infections. Our own immune cells produce significant amounts of hypochlorite as a first line of defense to kill invading microorganisms. Unfortunately, hypochlorite damages not just bacterial cells, but ours as well. It is the uncontrolled production of hypochlorite acid that is thought to cause tissue damage at sites of chronic inflammation.

How did studying the protein Hsp33 lead to the bleach discovery? The researchers learned that hypochlorite, rather than damaging Hsp33 as it does most proteins, actually revs up the molecular chaperone. When bacteria encounter the disinfectant, Hsp33 jumps into action to protect bacterial proteins against bleach-induced aggregation.

"With Hsp33, bacteria have evolved a very clever system that directly senses the insult, responds to it and increases the bacteria's resistance to bleach," Jakob said.

Artificial diamonds - now available in extra large

* 18:11 13 November 2008 by Catherine Brahic

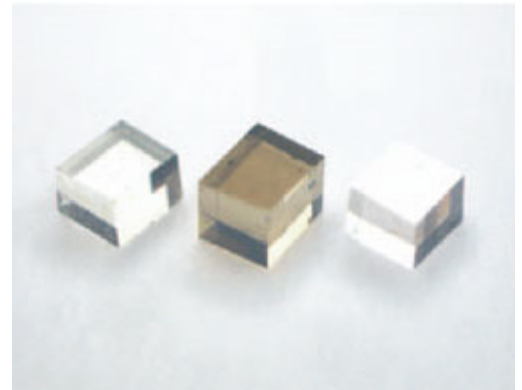
Diamonds are a girl's best friend, they say - and soon they could be every girl's best friend.

A team in the US has brought the world one step closer to cheap, mass-produced, perfect diamonds. The improvement also means there is no theoretical limit on the size of diamonds that can be grown in the lab.

A team led by Russell Hemley, of the Carnegie Institute of Washington, makes diamonds by chemical vapour deposition (CVD), where carbon atoms in a gas are deposited on a surface to produce diamond crystals.

The CVD process produces rapid diamond growth, but impurities from the gas are absorbed and the diamonds take on a brownish tint.

These defects can be purged by a costly high-pressure, high-temperature treatment called annealing. However, only relatively small diamonds can be produced this way: the largest so far being a 34-carat yellow diamond about 1 centimetre wide.



The CVD diamond in the centre has not been annealed, the ones to the left and right have (Image: Hemley /PNAS)

Microwaved gems

Now Hemley and his team have got around the size limit by using microwaves to "cook" their diamonds in a hydrogen plasma at 2200 °C but at low pressure. Diamond size is now limited only by the size of the microwave chamber used.

"The most exciting aspect of this new annealing process is the unlimited size of the crystals that can be treated. The breakthrough will allow us to push to kilocarat diamonds of high optical quality," says Hemley's Carnegie Institute colleague Ho-kwang Mao.

"The microwave unit is also significantly less expensive than a large high-pressure apparatus," adds Yufei Meng, who also participated in the experiments. The new technique is so efficient that the synthetic diamonds contain fewer impurities than those found in nature, says Meng. "We once sent one of our lab-grown diamonds for jewellery identification, it wasn't told apart from natural ones," she says.

One immediate application will be to make ultra-high quality windows that are optically transparent to lasers.

Threat to commerce

The team's method "could be routinely run in any laboratory where it is needed," says Alexandre Zaitsev, a physicist at the City University of New York, whose work also includes diamonds. "When considered in combination with the high-growth-rate technique of CVD diamonds, it seems to be a starting point of mass-scale production of perfect diamond material at a low price." Zaitsev considers low-pressure annealing at temperatures greater than 2000 °C to be a "breakthrough in diamond research and technology".

The improving quality of synthetic diamonds threatens the natural diamond market. While 20 tonnes of natural diamonds are mined annually, some 600 tonnes of synthetic diamonds are produced each year for industrial use alone. They are used in a range of high-end technologies, such as lasers and high-pressure anvils. Some companies have also started to sell synthetic diamonds as gemstones. In response, diamond giant De Beers has set up a "Gem Defensive Programme" with the aim of finding ways to tell apart synthetic and natural diamonds. *Journal reference: Proceedings of the National Academy of Sciences (DOI: 10.1073/pnas.0808230105)*

Now in Sight: Far-Off Planets

By DENNIS OVERBYE

A little more of the universe has been pried out of the shadows. Two groups of astronomers have taken the first pictures of what they say — and other astronomers agree — are most likely planets going around other stars.

The achievement, the result of years of effort on improved observational techniques and better data analysis, presages more such discoveries, the experts said, and will open the door to new investigations and discoveries of what planets are and how they came to be formed.

"It's the tip of the iceberg," said Christian Marois of the Herzberg Institute of Astrophysics in Victoria, British Columbia. "Now that we know they are there, there is going to be an explosion."

Dr. Marois is the leader of a team that recorded three planets circling a star known as HR 8799 that is 130 light-years away in the constellation Pegasus. The other team, led by Paul Kalas of the University of California, Berkeley, found a planet orbiting the star Fomalhaut, only 25 light-years from Earth, in the constellation Piscis Austrinus.

In an interview by e-mail, Dr. Kalas said that when he finally confirmed his discovery last May, "I nearly had a heart attack."

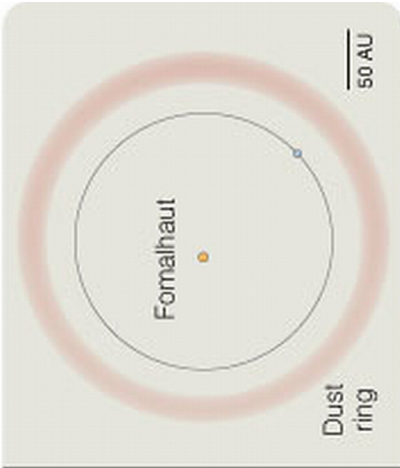
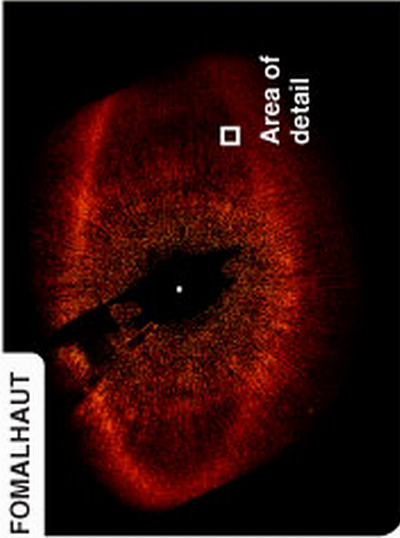
New Extrasolar Planets

Two groups of astronomers have taken the first widely accepted pictures of planets orbiting other stars.

HR 8799

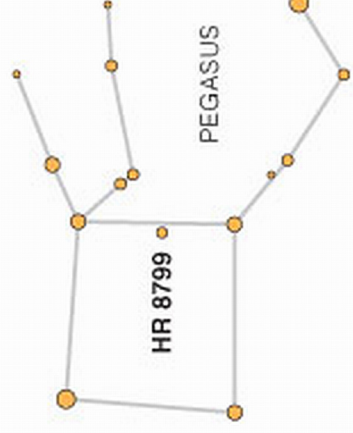


FOMALHAUT

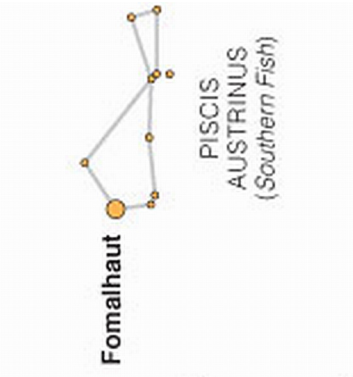


One group used the Gemini and Keck telescopes on Mauna Kea in Hawaii to record three planets circling the star HR 8799, 130 light-years away.

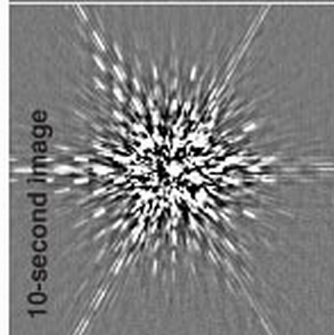
The group used adaptive optics, in which the telescope mirrors are warped several times a second, and software filtering to compensate for atmospheric turbulence and glare from the star.



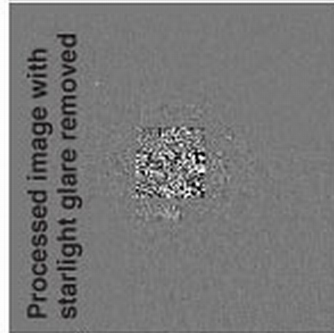
Another group used the Hubble Space Telescope to spot a planet orbiting the bright star Fomalhaut, 25 light-years away. Using a mask called a coronagraph to block the star's direct light (above, in black), the team was able to take detailed images of Fomalhaut's huge dust ring in 2004 and again in 2006. One bright spot inside the ring had moved slightly—a massive planet.



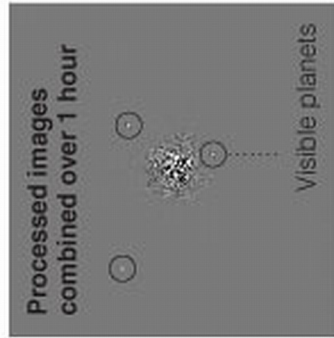
10-second image



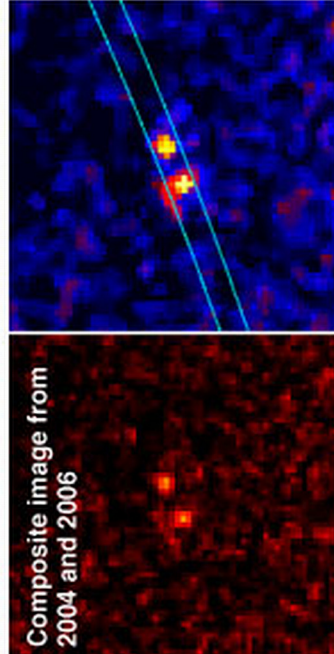
Processed image with starlight glare removed



Processed images combined over 1 hour



Composite image from 2004 and 2006



Planet Fomalhaut b



Sources: *Science Express*; *Space Telescope Science Institute*; *Christian Marois*; *Paul Kalas* wrote in an e-mail message elaborating on HR 8799. More than 300 so-called extrasolar planets have been found circling distant stars, making their discovery the hottest and fastest-growing field in astronomy.

In scratchy telescope pictures released Thursday in *Science Express*, the online version of the journal *Science*, the planets appear as fuzzy dots that move slightly around their star from exposure to exposure. Astronomers who have seen the new images agreed that these looked like the real thing. “I think Kepler himself would recognize these as planets orbiting a star following his laws of orbital motion,” Mark S. Marley of the Ames Research Center in Mountain View, Calif.,

But the observations have been made mostly indirectly, by dips in starlight as planets cross in front of their home star or by wobbles they induce going by it.

Astronomers being astronomers, they want to actually see these worlds, but a few recent claims of direct observations have been clouded by debates about whether the bodies were really planets or failed stars. “Every extrasolar planet detected so far has been a wobble on a graph,” said Bruce Macintosh, an astrophysicist from Lawrence Livermore National Laboratory in California and a member of Dr. Marois’s team. “These are the first pictures of an entire system.”

The new planetary systems are anchored by young bright stars more massive than our own Sun and swaddled in large disks of dust, the raw material of worlds. The three planets orbiting HR 8799 are roughly 10, 9 and 6 times the mass of Jupiter, and orbit their star in periods of 450, 180 and 100 years respectively, all counterclockwise.

The Fomalhaut planet is about three times as massive as Jupiter, according to Dr. Kalas’s calculations, and is on the inner edge of a huge band of dust, taking roughly 872 years to complete a revolution of its star.

Both systems appear to be scaled-up versions of our own solar system, with giant planets in the outer reaches, leaving plenty of room for smaller planets to lurk undetected in the warmer inner regions. Dust rings lie even farther out, like the Kuiper belt of icy debris extending beyond the orbit of Neptune.

“This is a window into what our own solar system might have looked like when it was 60 million years old,” Dr. Marois said.

Sara Seager, a planetary theorist at the Massachusetts Institute of Technology, said it was significant that the planets in both cases seemed to be associated with disks of dust, particularly Fomalhaut, one of the brightest and closest stars known to be host to a massive disk.

“Fomalhaut is like a Hollywood star to astronomers, so we have some personal excitement here,” Dr. Seager said. “It feels like finding out that one of your four closest friends just won the lottery big time”

Alan Boss, a planetary theorist at the Carnegie Institution of Washington, said the triple-planet system in Pegasus was particularly promising, “as we expect planets to form in systems in general, whereas spurious background interlopers will generally appear as single ‘planets.’ ” But he and others cautioned that much more study of these objects was necessary and that the masses imputed to them were still highly uncertain.

Being able to see planets directly opens the door to spectroscopic observations that can help determine the composition, temperature and other physical characteristics of planets and allow for comparisons with one another and with their parent stars. Dr. Macintosh said he hoped to train a spectroscope on his new planets as early as Monday.

The new images are the fruits of a long campaign by astronomers to see more and more of the unseeable. In particular, it is a triumph for the emerging technology of adaptive optics, in which telescope mirrors are jiggled and warped slightly many times a second to compensate for the atmospheric turbulence that blurs star images.

The problem in seeing other planets is picking them out of the glare of their parent stars, which are millions of times brighter, at least in visible light. As a result, planet hunters usually look for infrared, or heat radiation, which is emitted copiously by planets still shedding heat from the process of formation.

For their observations, Dr. Marois and his colleagues used the 8-meter in diameter Gemini North and the 10-meter Keck telescopes on Mauna Kea in Hawaii, both of which had been fitted with adaptive optics. Then they processed the images with a special computer program, which Dr. Marois described as “a software coronagraph,” for processing the images.

The team first spied a pair of dots about four billion and six billion miles out from HR 8799 in October last year. Following up, they discovered a third planet closer in, at about two billion miles. Then they discovered an old observation from 2004, which also showed the planets and how far they had moved around the star in three years. “Seeing the orbit is one of the coolest things,” Dr. Macintosh said.

Dr. Kalas did his work with the Hubble Space Telescope, which is immune to turbulence because it is in space. He used a coronagraph to block light from the actual star.

He said he had been driven to look for a planet around Fomalhaut after Hubble photographs in October 2004 showed that a dust ring around the star had a suspiciously sharp inner edge, often a clue that the ring is being sculpted by the gravity of some body orbiting nearby.

A second set of Hubble observations, in July 2006, revealed a dot moving counterclockwise around the star. “I basically held my breath for three days until I could confirm the existence of Fomalhaut in all of my data,” Dr. Kalas recalled.

Fomalhaut is also a young star, about 200 million years old, and its dust ring extends 11 billion to 20 billion miles from its planet, Dr. Kalas said. In order not to disturb or roil the dust ring, Fomalhaut’s planet must be less than three Jupiter masses, well within regulation planet size, Dr. Kalas and his collaborators calculated.

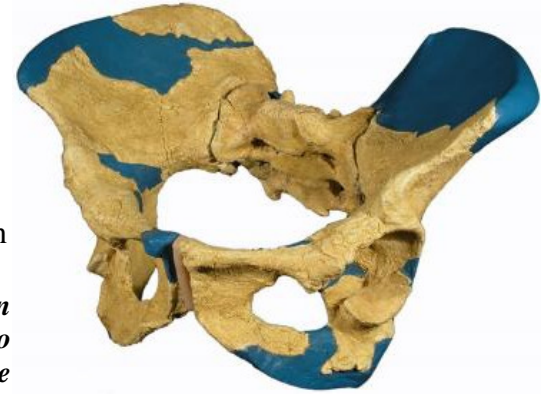
A more detailed analysis, with another team member, Eugene Chiang of the University of California, Berkeley, as lead author will appear in the *Astrophysical Journal*, Dr. Kalas said.

In an e-mail message, Dr. Kalas pointed out that Fomalhaut was the closest exoplanet yet discovered, "close enough to contemplate sending spacecraft there."

Prehistoric pelvis offers clues to human development

BLOOMINGTON, Ind. -- Discovery of the most intact female pelvis of *Homo erectus* may cause scientists to reevaluate how early humans evolved to successfully birth larger-brained babies. "This is the most complete female *Homo erectus* pelvis ever found from this time period," said Indiana University Bloomington paleoanthropologist Sileshi Semaw. "This discovery gives us more accurate information about the *Homo erectus* female pelvic inlet and therefore the size of their newborns."

A reconstruction of the 1.2 million-year-old pelvis discovered in 2001 in the Gona Study Area at Afar, Ethiopia, that has led researchers to speculate early man was better equipped than first thought to produce larger-brained babies. The actual fossils remain in Ethiopia.



A reconstruction of the 1.2 million-year-old pelvis discovered in 2001 in the Gona Study Area at Afar, Ethiopia, that has led researchers to speculate early man was better equipped than first thought to produce larger-brained babies. The actual fossils remain in Ethiopia. Scott W.

Simpson, Case Western Reserve University

The discovery will be published in *Science* this week (Nov. 14) by Semaw, leader of the Gona Project in Ethiopia, where the fossil pelvis was discovered with a group of six other scientists that includes IU Department of Geosciences graduate student Melanie Everett.

Reconstructing pelvis bone fragments from the 1.2 million-year-old adult female, Semaw and his co-workers determined the early ancestor's birth canal was more than 30 percent larger than earlier estimates based on a 1.5-million-year-old juvenile male pelvis found in Kenya. The new female fragments were discovered in the Gona Study Area in Afar, Ethiopia, in 2001 and excavation was completed in 2003.

Scientists also were intrigued by other unique attributes of the specimen, such as its shorter stature and broader body shape more likely seen in hominids adapted to temperate climates, rather than the tall and narrow body believed to have been efficient for endurance running.

Early humans became taller and narrower over time, scientists believe, partly due to long distance running and to help them maintain a constant body temperature. One consequence, however, is that a narrower pelvis would have been less accommodating to producing larger-brained offspring. But rather than a tall, narrow hominid with the expected slight pelvic region, Semaw and the Gona researchers found evidence of a hominid ready to produce offspring with a much larger brain size. "The female *Homo erectus* pelvic anatomy is basically unknown," Semaw said. "And as far as the fossil pelvis of ancestral hominids goes, all we've had is Lucy (dated at 3.2 million years and also found in Ethiopia), and she is very much farther back in time from modern humans."

Scientists studying early man predominantly find fragments of craniums and dental remains, while fossil bones from the neck down are rarely discovered. Even more difficult to verify are *Homo erectus* fossil bones that can be identified as those belonging to a female.

Scientists had thought early adult *Homo erectus* females, because of the assumed small birth canal, would produce offspring with only a limited neonatal brain size. These young would have then experienced rapid brain growth while still developmentally immature, leading researchers to envision a scenario of maternal involvement and child-rearing on par with that of modern humans. But those theories had been based upon extrapolations from the existing male skeleton from Kenya.

"This find will give us far more accurate information," Semaw said. Semaw is also a research scientist at the Stone Age Institute, a research center near Bloomington dedicated to the study of early human evolution and culture. It is affiliated with Indiana University's CRAFT, the Center for Research into the Anthropological Foundations of Technology.

Gona has turned out to be a productive dig site for Semaw. In 1997 Semaw and colleagues reported the oldest known stone tools used by ancestral humans. Then in 2004 he coauthored a paper summarizing Gona's geological properties and the site's cornucopia of hominid fossils spanning several million years. At the time, *Science* gave the article an "Editor's Choice" recognition. In 2005 he and colleagues published an article in

Nature announcing the discovery of *Ardipithecus ramidus*, one of the earliest ancestral hominids, dating between 4.3 and 4.5 million years ago.

Scott Simpson (Case Western Reserve University School of Medicine and the Cleveland Museum of Natural History), Jay Quade (University of Arizona), Naomi Levin (University of Utah), Robert Butler (University of Portland) and Guillaume Dupont-Nivet (Utrecht University, Netherlands) also contributed to the report. Support for the research was provided by the Leakey Foundation, the National Science Foundation, the National Geographic Society and the Wenner-Gren Foundation. The authors thank Ethiopia's Authority for Research and Conservation of Cultural Heritage and the National Museum of Ethiopia for research permits and support.

Soluble fiber, antispasmodics and peppermint oil should be used to treat IBS

Effect of fiber, antispasmodics and peppermint oil in irritable bowel syndrome: Systematic review and meta-analysis

Fibre, antispasmodics and peppermint oil are all effective therapies for irritable bowel syndrome (IBS) and should become first-line treatments, according to a study on *bmj.com* today.

National guidelines on the management of IBS should be updated in light of this evidence, say the authors.

IBS is characterised by abdominal pain and an irregular bowel habit, and affects between 5% and 20% of the population. Because the exact cause of IBS is unknown it is difficult to treat. A wide range of therapies are currently used including fibre supplements, probiotics, antidepressants, hypnotherapy and laxatives.

Because of a lack of suitable drug treatments, international and national guidelines promote the use of complementary and alternative treatments, including the recently published National Institute of Health and Clinical Excellence (NICE) guidelines on the management of IBS.

Fibre, antispasmodics and peppermint oil are used to treat IBS, but evidence of their effectiveness is unclear because of conflicting conclusions and errors in previous studies.

In an attempt to resolve this uncertainty, Dr Alex Ford and colleagues performed a systematic review and meta-analysis of randomised trials comparing fibre, antispasmodics and peppermint oil with placebo or no treatment in more than 2500 adult patients with IBS.

Fibre, antispasmodics and peppermint oil were all found to be effective treatments for IBS. The number needed to treat to prevent IBS symptoms in one patient was 11 for fibre, 5 for antispasmodics, and 2.5 for peppermint oil. None of the treatments had serious adverse effects.

The researchers analysed 12 studies which compared fibre with placebo or no treatment involving 591 patients. Interestingly, insoluble fibre such as bran was not beneficial, only isphaghula husk (soluble fibre) significantly reduced symptoms.

They identified 22 studies comparing various antispasmodics with placebo in 1778 patients. Hyoscine was the most successful at preventing symptoms of IBS. The authors suggest that hyoscine, which is extracted from the cork wood tree, be used as the first-line antispasmodic therapy in primary care.

Peppermint oil seemed to be the most effective treatment of the three, based on four trials involving 392 patients.

These treatments have been overlooked because of the introduction of newer more expensive drugs which were withdrawn due to lack of efficacy and safety concerns, say the authors. All three treatments have been shown to be potentially effective therapies for IBS and current national and international guidelines need to be revised to include this new evidence, they add.

The results of this study should "reawaken interest in the pharmacotherapy of irritable bowel syndrome and stimulate further research", says Professor Roger Jones from King's College London.

However, he cautions that this new evidence must not detract from the need to make a holistic diagnosis and integrated approach to the treatment of IBS which takes account of the physical, psychological, and social factors involved.

Wasabi receptor can sense ammonia that causes pain

Japanese research group, led by Prof Makoto Tominaga of National Institute for Physiological Sciences in Japan, found that the receptor for hot taste of WASABI, Japanese horseradish usually eaten with Sushi, can sense alkaline pH caused by base such as ammonia. The team reports their finding in *Journal of Clinical Investigation* on November 13, 2008.

Clinically, alkaline pH is known to cause pain but the mechanism has been not known. By electrophysiological experiments, the team found that the WASABI receptor, namely transient receptor potential (TRP) A1 receptor, can be activated by alkalization inside of cells by application of base such as ammonia. Administration of such base to the foot of mice caused transient pain-related behaviors. However, it did not in TRPA1 deficient mice.

"It has the first report showing molecular entity for the alkali-sensor. You could feel pain when you eat too much WASABI with Japanese Sushi. We found that this pain sensation is the same with that caused by ammonia", said Prof Tominaga.

How eating red meat can spur cancer progression

Researchers at the University of California, San Diego School of Medicine, led by Ajit Varki, M.D., have shown a new mechanism for how human consumption of red meat and milk products could contribute to the increased risk of cancerous tumors. Their findings, which suggest that inflammation resulting from a molecule introduced through consumption of these foods could promote tumor growth, are published online this week in advance of print publication in the Proceedings of the National Academy of Sciences (PNAS).

Varki, UC San Diego School of Medicine distinguished professor of medicine and cellular and molecular medicine, and co-director of the UCSD Glycobiology Research and Training Center, and colleagues studied a non-human cellular molecule called N-glycolylneuraminic acid (Neu5Gc). Neu5Gc is a type of glycan, or sugar molecule, that humans don't naturally produce, but that can be incorporated into human tissues as a result of eating red meat. The body then develops anti-Neu5Gc antibodies – an immune response that could potentially lead to chronic inflammation, as first suggested in a 2003 PNAS paper by Varki.

"We've shown that tumor tissues contain much more Neu5Gc than is usually found in normal human tissues," said Varki. "We therefore surmised that Neu5Gc must somehow benefit tumors."

It has been recognized by scientists for some time that chronic inflammation can actually stimulate cancer, Varki explained. So the researchers wondered if this was why tumors containing the non-human molecule grew even in the presence of Neu5Gc antibodies.

"The paradox of Neu5Gc accumulating in human tumors in the face of circulating antibodies suggested that a low-grade, chronic inflammation actually facilitated the tumor growth, so we set out to study that hypothesis," said co-author Nissi M. Varki, M.D., UCSD professor of pathology.

Using specially bred mouse models that lacked the Neu5Gc molecule – mimicking humans before the molecule is absorbed into the body through ingesting red meat – the researchers induced tumors containing Neu5Gc, and then administered anti-Neu5Gc antibodies to half of the mice. In mice that were given antibodies inflammation was induced, and the tumors grew faster. In the control mice that were not treated with antibodies, the tumors were less aggressive

Others have previously shown that humans who take non-steroidal anti-inflammatory drugs (commonly known as NSAIDs) have a reduced risk of cancer. Therefore, the mice with cancerous tumors facilitated by anti-Neu5Gc antibodies were treated with an NSAID. In these animals, the anti-inflammatory treatment blocked the effect of the Neu5Gc antibodies and the tumors were reduced in size.

"Taken together, our data indicate that chronic inflammation results from interaction of Neu5Gc accumulated in our bodies from eating red meat with the antibodies that circulate as an immune response to this non-human molecule – and this may contribute to cancer risk," said Varki.

Additional contributors to the paper are Maria Hedlund and Vered Padler-Karavani, UCSD Departments of Medicine and Cellular and Molecular Medicine. The study was funded in part by a grant from the National Cancer Institute, of the National Institutes of Health.

Unhappy people watch TV, happy people read/socialize, says study **Channeling unhappiness, in good and bad economic times**

COLLEGE PARK, Md. – A new study by sociologists at the University of Maryland concludes that unhappy people watch more TV, while people who describe themselves as very happy spend more time reading and socializing. The study appears in the December issue of the journal Social Indicators Research.

Analyzing 30-years worth of national data from time-use studies and a continuing series of social attitude surveys, the Maryland researchers report that spending time watching television may contribute to viewers' happiness in the moment, with less positive effects in the long run.

"TV doesn't really seem to satisfy people over the long haul the way that social involvement or reading a newspaper does," says University of Maryland sociologist John P. Robinson, the study co-author and a pioneer in time-use studies. "It's more passive and may provide escape - especially when the news is as depressing as the economy itself. The data suggest to us that the TV habit may offer short-run pleasure at the expense of long-term malaise."

Tv Viewing During A Financial Crisis

Based on data from time use surveys, Robinson projects that TV viewing might increase significantly as the economy worsens in the next few months and years.

"Through good and bad economic times, our diary studies, have consistently found that work is the major activity correlate of higher TV viewing hours," Robinson says. "As people have progressively more time on their hands, viewing hours increase."

But Robinson cautions that some of that extra time also might be spent sleeping. "As working and viewing hours increase, so do sleep hours," he says. "Sleep could be the second major beneficiary of job loss or reduced working hours."

Study Findings And Data

In their new study, Robinson and his co-author, University of Maryland sociologist Steven Martin, set out to learn more about the activities that contributed to happiness in people's lives. They analyzed two sets of data spanning nearly 30 years (1975-2006) gathered from nearly 30,000 adults:

- * A series of time-use studies that asked people to fill out diaries for a 24-hour period and to indicate how pleasurable they found each activity;

- * General Social Survey attitude studies, which Robinson calls the national premier source for monitoring changes in public attitudes – in-depth surveys that over the years consistently asked subjects how happy they feel, how they spend their time among a number of other questions.

Unhappy People View Significantly More

Robinson and Martin found that the two sets of data largely coincided for most activities – with the exception of television.

From the General Social Survey, the researchers found that self-described happy people were more socially active, attended more religious services, voted more and read more newspapers. By contrast, unhappy people watched significantly more television in their spare time.

According to the study's findings, unhappy people watch an estimated 20 percent more television than very happy people, after taking into account their education, income, age and marital status – as well as other demographic predictors of both viewing and happiness.

Unhappy People Are Happy With Tv

Data from time-diaries told a somewhat different story. Responding in "real time," much closer to daily events, survey respondents tended to rate television viewing more highly as a daily activity.

"What viewers seem to be saying is that 'While TV in general is a waste of time and not particularly enjoyable, the shows I saw tonight were pretty good,'" Robinson says.

The data also suggested to Robinson and Martin that TV viewing was "easy." Viewers don't have to go anywhere, dress up, find company, plan ahead, expend energy, do any work or spend money in order to view. Combine these advantages with the immediate gratification offered by television, and you can understand why Americans spend more than half their free time as TV viewers, the researchers say.

Unhappy people were also more likely to feel they have unwanted extra time on their hands (51 percent) compared to very happy people (19 percent) and to feel rushed for time (35 percent vs. 23 percent). Having too much time and no clear way to fill it was the bigger burden of the two.

An Addict's Fix

Martin likens the short, temporary pleasure of television to addiction: "Addictive activities produce momentary pleasure but long-term misery and regret," he says. "People most vulnerable to addiction tend to be socially or personally disadvantaged. For this kind of person, TV can become a kind of opiate in a way. It's habitual, and tuning in can be an easy way of tuning out."

On the Farm

A Seafood Snob Ponders the Future of Fish

By MARK BITTMAN

I suppose you might call me a wild-fish snob. I don't want to go into a fish market on Cape Cod and find farm-raised salmon from Chile and mussels from Prince Edward Island instead of cod, monkfish or haddock. I don't want to go to a restaurant in Miami and see farm-raised catfish from Vietnam on the menu but no grouper.

Those have been my recent experiences, and according to many scientists, it may be the way of the future: most of the fish we'll be eating will be farmed, and by midcentury, it might be easier to catch our favorite wild fish ourselves rather than buy it in the market.

It's all changed in just a few decades. I'm old enough to remember fishermen unloading boxes of flounder at the funky Fulton Fish Market in New York, charging wholesalers a nickel a pound. I remember when local mussels and oysters were practically free, when fresh tuna was an oxymoron, and when monkfish, squid and now-trendy skate were considered "trash."

But we overfished these species to the point that it now takes more work, more energy, more equipment, more money to catch the same amount of fish — roughly 85 million tons a year, a yield that has remained mostly stagnant for the last decade after rapid growth and despite increasing demand.

Still, plenty of scientists say a turnaround is possible. Studies have found that even declining species can quickly recover if fisheries are managed well. It would help if the world's wealthiest fish-eaters (they include us, folks) would broaden their appetites. Mackerel, anyone?

It will be a considerable undertaking nonetheless. Global consumption of fish, both wild and farm raised, has doubled since 1973, and 90 percent of this increase has come in developing countries. (You'll sometimes hear that Americans are now eating more seafood, but that reflects population growth; per capita consumption has remained stable here for 20 years.)

The result of this demand for wild fish, according to the United Nations' Food and Agricultural Organization, is that "the maximum wild-capture fisheries potential from the world's oceans has probably been reached."

One study, in 2006, concluded that if current fishing practices continue, the world's major commercial stocks will collapse by 2048.

Already, for instance, the Mediterranean's bluefin tuna population has been severely depleted, and commercial fishing quotas for the bluefin in the Mediterranean may be sharply curtailed this month. The cod fishery, arguably one of the foundations of North Atlantic civilization, is in serious decline. Most species of shark, Chilean sea bass, and the cod-like orange roughy are threatened.

Scientists have recently become concerned that smaller species of fish, the so-called forage fish like herring, mackerel, anchovies and sardines that are a crucial part of the ocean's food chain, are also under siege.

These smaller fish are eaten not only by the endangered fish we love best, but also by many poor and not-so-poor people throughout the world. (And even by many American travelers who enjoy grilled sardines in England, fried anchovies in Spain, marinated mackerel in France and pickled or raw herring in Holland — though they mostly avoid them at home.)

But the biggest consumers of these smaller fish are the agriculture and aquaculture industries. Nearly one-third of the world's wild-caught fish are reduced to fish meal and fed to farmed fish and cattle and pigs. Aquaculture alone consumes an estimated 53 percent of the world's fish meal and 87 percent of its fish oil. (To make matters worse, as much as a quarter of the total wild catch is thrown back — dead — as "bycatch.")

"We've totally depleted the upper predator ranks; we have fished down the food web," said Christopher Mann, a senior officer with the Pew Environmental Group.

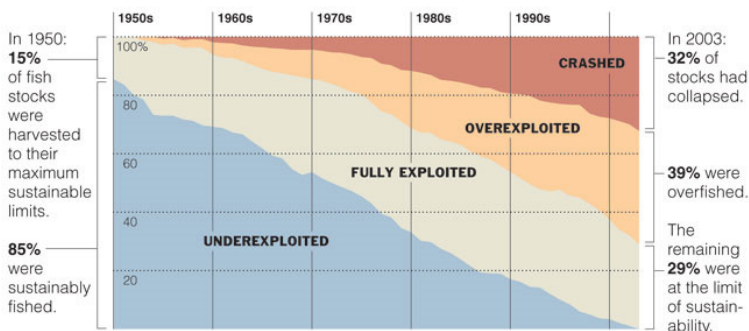
Using fish meal to feed farm-raised fish is also astonishingly inefficient. Approximately three kilograms of forage fish go to produce one kilogram of farmed salmon; the ratio for cod is five to one; and for tuna — the most beef-like of all — the so-called feed-to-flesh ratio is 20 to 1, said John Volpe, an assistant professor of marine systems conservation at the University of Victoria in British Columbia.

Industrial aquaculture — sometimes called the blue revolution — is following the same pattern as land-based agriculture. Edible food is being used to grow animals rather than nourish people.

This is not to say that all aquaculture is bad. China alone accounts for an estimated 70 percent of the world's aquaculture — where it is small in scale, focuses on herbivorous fish and is not only sustainable but environmentally sound. "Throughout Asia, there are hundreds of thousands of small farmers making a living by

At the Breaking Point

The condition of the world's fisheries has declined drastically because of overfishing.



Source: Sea Around Us Project (seararoundus.org)

BILL MARSH/THE NEW YORK TIMES

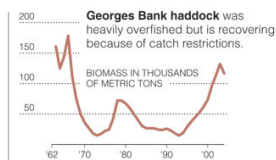
Threatened

Here are the total stocks of several species that have faced collapse from overfishing.

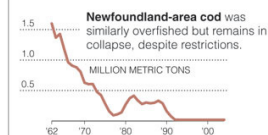


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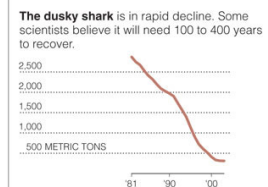
Sharks of all kinds are vulnerable to destruction as "bycatch" — unintentionally caught by industrial fishing methods and largely discarded as waste (above). One study found that nearly a quarter of the catch from U.S. marine fisheries was wasted.



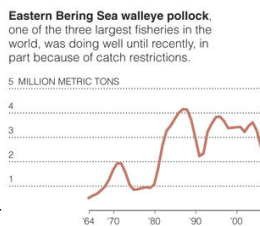
Georges Bank haddock was heavily overfished but is recovering because of catch restrictions.



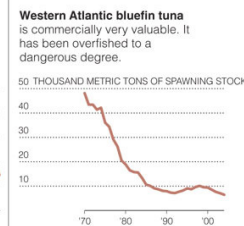
Newfoundland-area cod was similarly overfished but remains in collapse, despite restrictions.



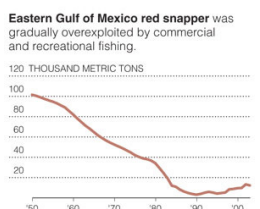
The dusky shark is in rapid decline. Some scientists believe it will need 100 to 400 years to recover.



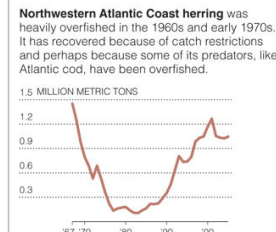
Eastern Bering Sea walleye pollock, one of the three largest fisheries in the world, was doing well until recently, in part because of catch restrictions.



Western Atlantic bluefin tuna is commercially very valuable. It has been overfished to a dangerous degree.



Eastern Gulf of Mexico red snapper was gradually overexploited by commercial and recreational fishing.



Northwestern Atlantic Coast herring was heavily overfished in the 1960s and early 1970s. It has recovered because of catch restrictions and perhaps because some of its predators, like Atlantic cod, have been overfished.

Sources: Boris Worm, Dalhousie University; National Marine Fisheries Service

BILL MARSH/THE NEW YORK TIMES

farming fish,” said Barry Costa-Pierce, professor of fisheries at University of Rhode Island.

But industrial fish farming is a different story. The industry spends an estimated \$1 billion a year on veterinary products; degrades the land (shrimp farming destroys mangroves, for example, a key protector from typhoons); pollutes local waters (according to a recent report by the Worldwatch Institute, a salmon farm with 200,000 fish releases nutrients and fecal matter roughly equivalent to as many as 600,000 people); and imperils wild populations that come in contact with farmed salmon.

Not to mention that its products generally don’t taste so good, at least compared to the wild stuff. Farm-raised tilapia, with the best feed-to-flesh conversion ratio of any animal, is less desirable to many consumers, myself included, than that nearly perfectly blank canvas called tofu. It seems unlikely that farm-raised striped bass will ever taste remotely like its fierce, graceful progenitor, or that anyone who’s had fresh Alaskan sockeye can take farmed salmon seriously.

If industrial aquaculture continues to grow, said Carl Safina, the president of Blue Ocean Institute, a conservation group, “this wondrously varied component of our diet will go the way of land animals — get simplified, all look the same and generally become quite boring.”

Why bother with farm-raised salmon and its relatives? If the world’s wealthier fish-eaters began to appreciate wild sardines, anchovies, herring and the like, we would be less inclined to feed them to salmon raised in fish farms. And we’d be helping restock the seas with larger species.

Which, surprisingly, is possible. As Mr. Safina noted, “The ocean has an incredible amount of productive capacity, and we could quite easily and simply stay within it by limiting fishing to what it can produce.”

This sounds almost too good to be true, but with monitoring systems that reduce bycatch by as much as 60 percent and regulations providing fishermen with a stake in protecting the wild resource, it is happening. One regulatory scheme, known as “catch shares,” allows fishermen to own shares in a fishery — that is, the right to catch a certain percentage of a scientifically determined sustainable harvest. Fishermen can buy or sell shares, but the number of fish caught in a given year is fixed.

This method has been a success in a number of places including Alaska, the source of more than half of the nation’s seafood. A study published in the journal *Science* recently estimated that if catch shares had been in place globally in 1970, only about 9 percent of the world’s fisheries would have collapsed by 2003, rather than 27 percent.

“The message is optimism,” said David Festa, who directs the oceans program at the Environmental Defense Fund. “The latest data shows that well-managed fisheries are doing incredibly well. When we get the rules right the fisheries can recover, and if they’re not recovering, it means we have the rules wrong.”

(The world’s fishing countries would need to participate; right now, the best management is in the United States, Australia and New Zealand; even in these countries, there’s a long way to go.)

An optimistic but not unrealistic assessment of the future is that we’ll have a limited (and expensive) but sustainable fishery of large wild fish; a growing but sustainable demand for what will no longer be called “lower-value” smaller wild fish; and a variety of traditional aquaculture where it is allowed. This may not sound ideal, but it’s certainly preferable to sucking all the fish out of the oceans while raising crops of tasteless fish available only to the wealthiest consumers.

Myself, I’d rather eat wild cod once a month and sardines once a week than farm-raised salmon, ever.

Mark Bittman writes the Minimalist column for the Dining section of The Times and is the author of “How to Cook Everything.”