Disease Caused By Insect Bites Can Be Transmitted To Children At Birth, NC State Researcher Finds

Tracey Peake

A North Carolina State University researcher has discovered that bacteria transmitted by fleas–and potentially ticks–can be passed to human babies by the mother, causing chronic infections and raising the possibility of bacterially induced birth defects.

Dr. Ed Breitschwerdt, professor of internal medicine in the Department of Clinical Sciences, is among the world's leading experts on Bartonella, a bacteria that is maintained in nature by fleas, ticks and other biting insects, but which can be transmitted by infected cats and dogs as well. The most commonly known Bartonella-related illness is cat scratch disease, caused by B. henselae, a strain of Bartonella that can be carried in a cat's blood for months to years. Cat scratch disease was thought to be a self-limiting, or "one-time" infection; however, Breitschwerdt's previous work discovered cases of children and adults with chronic, blood-borne Bartonella infections–from strains of the bacteria that are most often transmitted to cats (B. henselae) and dogs (B. vinsonii subsp. berkhoffii) by fleas and other insects.

In his most recent case study, Breitschwerdt's research group tested blood and tissue samples taken over a period of years from a mother, father and son who had suffered chronic illnesses for over a decade. Autopsy samples from their daughter–the son's twin who died shortly after birth–contained DNA evidence of B. henselae and B. vinsonii subsp. berkhoffi infection, which was also found in the other members of the family.

Both parents had suffered recurring neurological symptoms including headaches and memory loss, as well as shortness of breath, muscle weakness and fatigue before the children were born. In addition, their 10-year-old son was chronically ill from birth and their daughter died due to a heart defect at nine days of age.

Results of the parents' medical histories and the microbiological tests indicated that the parents had been exposed to Bartonella prior to the birth of the twins, and finding the same bacteria in both children, one shortly after birth and the other 10 years later, indicates that they may have become infected while in utero.

Breitschwerdt's research appears online in the April 14 Journal of Clinical Microbiology.

"This is yet more evidence that Bartonella bacteria cause chronic intravascular infections in people with otherwise normal immune systems, infections that can span a decade or more," Breitschwerdt says. "Also this new evidence supports the potential of trans-placental infection and raises the possibility that maternal infection with these bacteria might also cause birth defects."

The Department of Clinical Sciences is part of NC State's College of Veterinary Medicine. Dr. Breitschwerdt is also an adjunct professor of medicine at Duke University Medical Center.

Note to editors: An abstract of the paper follows.

Molecular evidence of perinatal transmission of Bartonella vinsonii subsp. berkhoffii and B.henselae to a child"
Authors: Edward B. Breitschwerdt, Ricardo G. Maggi and Patricia E. Mascarelli, NC State University; Peter Farmer, Department of Pathology, North Shore University Hospital Published: April 14, 2010 in Journal of Clinical Microbiology
Abstract:
Bartonella vinsonii subsp. berkhoffii, Bartonella henselae or DNA of both organisms was amplified and sequenced from blood, enrichment blood cultures or autopsy tissues from four family members. Historical and microbiological results support perinatal transmission of Bartonella species in this family.

Standard heel-stick test ineffective at screening for CMV in newborns

DALLAS – A national study involving a UT Southwestern Medical Center neonatologist and pediatric infectious diseases specialist suggests that a screening test routinely performed in newborns is not very good at identifying cytomegalovirus (CMV) infection, a leading cause of hearing loss in children.

The findings, published in the April 14 issue of the Journal of the American Medical Association, suggest that testing blood drawn from a newborn's heel has limited value in detecting CMV infection.

The heel-stick procedure involves pricking a newborn's heel and drawing a small amount of blood that is then absorbed onto a filter paper and dried. The dried blood is analyzed for several diseases including sickle cell disease. Because the procedure already is used to test for several metabolic and genetic disorders, researchers hoped it would be a good candidate for a universal screening program for CMV.

"Our findings tell us that if we rely on the standard heel-stick test to detect CMV, more than half of the babies who are infected will be missed," said Dr. Pablo Sanchez, professor of pediatrics at UT Southwestern and a co-author of the study. "The fact that this screening test is virtually ineffective has major public health implications because congenital CMV infection is the most common nongenetic cause of hearing loss in the United States."

Each year, 30,000 to 50,000 U.S. infants are born with CMV, the most common infection passed from a mother to her unborn child. Although only about 10 percent of infected babies have any clinically detectable

abnormalities, half of those with clinical signs and 10 percent to 15 percent of those who appear well are at risk for developing hearing loss.

The study is part of a multicenter investigation seeking to find the most effective screening test for CMV infections in newborns and study the natural history of hearing loss among these babies. Currently, the only way to identify accurately a CMV infection is to culture a urine or saliva sample collected from the patient, a process unlikely to be widely adopted because it is labor-intensive and requires a tissue culture facility.

Prior research has shown that dried blood spots can be used to identify CMV infection. Because no studies have compared it to the gold standard CMV rapid culture test, however, researchers have been unable to say whether the heel-stick method is effective at identifying all infected babies.

For the study, the researchers used a new molecular diagnostic technique, polymerase chain reaction (PCR), to analyze dried blood samples obtained using the heel-stick procedure from more than 20,000 infants born between March 2007 and May 2008 at seven medical institutions nationwide, including Parkland Memorial Hospital in Dallas. Parkland has one of the country's largest and busiest obstetrics services, with about 16,000 births a year. Attending physicians are faculty members of UT Southwestern's obstetrics and gynecology and pediatrics departments.

Of the more than 20,000 babies screened in this study, 92 were confirmed to have congenital CMV infection. The CMV rapid culture method identified all but one of those children.

In contrast, of the 11,422 children screened with a basic version of the diagnostic test of dried blood spots, only 17 out of 60 infected children were identified. Eleven out of 32 infected babies were identified in a group screened with a slightly more sensitive test.

The next step, Dr. Sanchez said, is to determine whether using the molecular technique to analyze saliva samples rather than blood spots is as effective as the CMV rapid culture test.

The project is part of the ongoing CMV and Hearing Multicenter Screening (CHIMES) Study. The other participating centers are the University of Alabama at Birmingham; Saint Peter's University Hospital in New Brunswick, N.J.; the University of Mississippi Medical Center in Jackson; the Carolinas Medical Center in Charlotte, N.C.; the University of Pittsburgh and the Children's Hospital of Pittsburgh; and the University of Cincinnati and Cincinnati Children's Hospital Medical Center.

Weird, ultra-small microbes turn up in acidic mine drainage

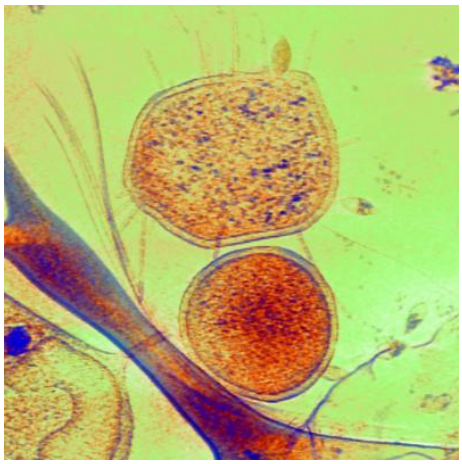
Microbes have among smallest genomes, plus unusual interactions with other Archaea

In the depths of a former copper mine in Northern California dwell what may be the smallest, most stripped-down forms of life ever discovered.

The microbes – members of the domain of one-celled creatures called Archaea – are smaller than other known microorganisms, rivaled in size only by a microbe that can survive solely as a parasite attached to the outside of other cells. Their genomes, reconstructed by a group at the University of California, Berkeley, are among the smallest ever reported.

The researchers also discovered another mine-dwelling microbe that occasionally produces weird protuberances unlike any structures seen before in Archaea and uses them to penetrate the ultra-small microbes.

"Other cells in the mine have what looks like a needle that sometimes pokes right into the cells," said Brett J. Baker, a researcher in UC Berkeley's Department of Earth and Planetary Science and first author of a new paper describing the findings. "It is really remarkable and suggests an interaction that has never been described before in nature."



An ARMAN cell (center, orange) is penetrated by a needle-like protrusion from Thermoplasma (lower left), an Archaea that lives in the same acidic pools as ARMAN. The much smaller, yellow lozenges are viruses that also infect ARMAN cells. A probably dying ARMAN cell (top) has grown to a diameter of about 1,000 nanometers -- less than one hundredth the width of a human hair. **Luis R. Comolli/LBNL**

These cellular extensions are only present when this interaction between the microbes is seen, noted co-author Luis R. Comolli, a microscopist at Lawrence Berkeley National Laboratory (LBNL).

Baker, Comolli and a team led by Jillian Banfield, UC Berkeley professor of earth and planetary science and of environmental science, policy and management and staff scientist at LBNL, published their findings last week in the online early edition of the journal Proceedings of the National Academy of Sciences.

Under a light microscope, the ultra-small microbes look like specks of dust. But Comolli used a state-of-the-art cryoelectron microscope, or cryoEM, to obtain high-resolution, 3-D images and even measure an individual microbe's internal volume – between one-tenth and one-hundredth the volume of an E. coli bacterium. Each of

the microbes, dubbed ARMAN, for archaeal Richmond Mine acidophilic nanoorganisms, is ellipsoidal and only 200-400 nanometers in diameter, one-third the diameter of the rod-shaped E. coli.

The team reconstructed the genomes of three distinct lineages of ARMAN and found them to be tiny – a mere 1 million base pairs, in contrast to hundreds of billions in humans. In the smallest of the three, the average gene length is only 774 base pairs, in contrast to the average gene length in humans of 10,000 to 15,000 base pairs. Base pairs, the smallest chemical units of the gene, are nucleic acids that come in four forms. The base pairs are chained together to make DNA, and a gene is a sequence of base-pairs coding for a unique protein.

The genomes are so small that the researchers initially suspected that the ARMAN microbes are parasites upon other microbes, since parasites can afford to lose genes that their host already has.

But of the 70 individual specimens so far imaged in 3-D, 90 percent seem to be free-living. The other 10 percent are impaled on the mysterious needle-like spines of Thermoplasmatales, the other Archaea living alongside ARMAN in the mine. The researchers suspect that the penetrating spines may mean that the microbes live off other microbes at least part of the time, unlike symbiotic organisms or parasites, which must always associate with other organisms to live.

"ARMAN are among the smallest microbes we know of that, if not free-living, are at least not permanently obliged to be a parasite or symbiont," Comolli said. The cells are about as large as the largest viruses, which can replicate only in living organisms and are not considered to be "living."

"The genome is very compact," Baker added." A microbial genome 10 percent larger has the same number of genes as ARMAN." The organism has a much higher percentage – 45 percent – of unknown genes than any other organism sequenced, he said.

"ARMAN share a lot of genes with Euryarchaeota and Crenarchaeaota, but they also have a lot of genes not seen before in these branches of Archaea," he said, suggesting that ARMAN may have been around since these two branches split billions of years ago.

Three-dimensional cryoEM tomographic reconstructions show the unique architecture of ARMAN, Comolli said. It has very few ribosomes – the machines that build proteins per unit volume, for example; in the same volume, E coli would have 100 times more. The ribosomes also are distributed close to the cell wall. ARMAN cells also have an enigmatic internal tube. Like other Archaea, however, they have no nucleus or other internal organelles.

Banfield's group first described the ARMAN microbes four years ago, after identifying the organisms in acidic pools in the Richmond Mine, which is owned by Ted Arman, in Iron Mountain, Calif. The team's continued analysis has revealed amazing organization within the mine drainage biofilm communities that grow on solutions with the acidity of battery acid. The new data will help the researchers explore even further the community of organisms in the mine and determine how the organisms are able to live in such harsh environs and convert iron sulfides to sulfuric acid.

"Having these microbes described at the genomic level allows us to develop molecular identification methods and combine these methods with a 3-D view of the microbes to study the distribution of these organisms within this little ecological system, this little society, in the mine," Comolli said.

The work was supported by the Department of Energy and the National Aeronautics and Space Administration Astrobiology Institute. Sequencing was provided by the Community Sequencing Program at the Department of Energy Joint Genome Institute.

The Claim: Green Tea Can Help Lower Blood Pressure

By ANAHAD O'CONNOR

THE FACTS Few foods have a reputation for soothing stress quite like a hot cup of tea.

Green tea, in particular, has been linked to reduced stress and anxiety, and it contains compounds that are said to relax blood vessels. But when scientists have looked at whether it lowers blood pressure, even by a little, the evidence is fairly weak. Some small studies have found that a few cups a day can shave some points from blood pressure levels, but others have found that it provides no help at all, and may even be counterproductive.

Still, the news is not all bad for tea drinkers.

In a recent randomized study financed in part by the Department of Agriculture, scientists at Tufts University recruited 65 men and women with modestly high blood pressure who were not taking medication. Some were randomly assigned to drink a cup of hibiscus tea three times a day, while others received a tea-flavored placebo.

After six weeks, the tea group saw a respectable drop in systolic pressure - the top number in the reading - compared with the placebo group, suggesting that the tea made a small impact. Of course, replication is the cornerstone of good science, and one study is nothing to base conclusions on. Experts say more study is needed.

THE BOTTOM LINE Green tea doesn't seem to have much effect on blood pressure; hibiscus tea may have potential.

Enhancing the Placebo

By OLIVIA JUDSON

The placebo effect is, potentially, one of the most powerful forces in medicine. The challenge is to harness that power in a reliable and systematic way.

First, what is the placebo effect?

It's the improvement in health that some patients experience because of the feeling that they are receiving medical care. A classic example comes from drug trials. Suppose patients are randomly divided into three groups: those who get no treatment, those who get the drug that's being tested, and those who get the placebo treatment - typically a pill that looks and tastes like the drug, but doesn't contain it, or any other active ingredient.

The idea is that the "no treatment" group shows how many people would have gotten better by themselves; the "placebo" group shows any effect of participating in medical rituals (like taking pills); the "drug" group shows any effect of the drug over and above the effect of medical rituals. Simple.

Or not. Different studies of the placebo effect report wildly different results. One survey of 117 trials of two ulcer drugs found that, depending on the trial, patients in the placebo group had anywhere from zero to a 100 percent recovery rate.

The drugs also varied in their effectiveness from one trial to the next; sometimes patients on the placebo did better than those on the drug. Intriguingly, the results varied from country to country, with Brazilians showing no placebo effect and Germans having a strong one. Why? No one knows, but it doesn't appear to be because of anything inherently German: trials of drugs for hypertension found a weaker placebo effect in Germany than in other countries.

The problem is that humans are not machines, and emotions are not abstractions. Hope and expectation, anxiety and fear, trust and suspicion — these cause physiological changes in the brain that can interact with drugs, changing their effects.

This is even true for a drug like morphine. Yes, it's a powerful painkiller. But it's far more powerful if a doctor marches in, tells you he's going to give you morphine, and injects you, than it is if it is administered secretly by a hidden machine.

Differences in hopes and fears, and the resulting physiological changes, may explain why the placebo effect varies so much: individual experiences matter. Some people are more anxious than others, or may find the thought of a particular disease especially alarming. Moreover, in different cultures, similar diseases may be treated with different degrees of gravity.

Expectations around medical rituals may also explain why placebos tend to be more powerful if the pills are expensive or you take them several times a day; why injections and exotic machines are more powerful than pills; and why surgery is more powerful than injections. (In placebo surgery, the patient is anaesthetized, cut, and sewn back up again, but no manipulation is done. For obvious reasons, there have been few tests of this. But when it has been done, it has often produced good results for the patients.)

However, the most reliable source of a strong placebo effect appears to be: the doctor.

Placebo treatments are more powerful if your doctor believes in them. They are also more powerful if the doctor tells you so. In one study, for example, patients who had just come out of surgery were given a saline infusion, and — whenever they asked for it — the pain killer buprenorphine. However, some patients were told the saline infusion was a powerful painkiller, others that it might be one, while a third group wasn't told anything. Over the course of three days, those in the "know-nothing" group asked for more buprenorphine than those in the "maybe" group, who in turn asked for more than those told they were getting a real drug.

Which highlights a problem. Since deception of patients is unethical, some argue that the placebo has no place in the actual practice of medicine.

But the matter is more nuanced. As the morphine example shows, the placebo effect also enhances "real" treatments. So the key is to figure out how to maximize that enhancement without lying. One idea would be to deliberately increase the element of formal ritual in medicine. Studies of "alternative" therapies show that strong placebo effects can be induced by ritual. Indeed, in mainstream medicine, surgery is the treatment most surrounded by ritual; perhaps this is one reason it appears to be the most powerful placebo.

To be sure, many questions still need to be answered. But one thing is clear. It's time we stopped treating the placebo effect as a nuisance — something that rational humans shouldn't have. Instead, we must learn to purposefully enhance its power.

Notes:

The placebo effect has generated a vast and complex literature; my treatment of the topic is necessarily brief.

For anyone interested in a fascinating overview of the complexities of the placebo effect, see Moerman, D. 2002. "Meaning, Medicine, and the 'Placebo Effect.' " Cambridge University Press. I particularly recommend chapters 4 and 5; the first is on the importance of doctors, the second is on how different placebo regimes (pills, shots, surgery) compare with each other, and also how different regimens (taking pills four times a day as against once a day) can change the effectiveness of the placebo.

Anyone interested in the history of the placebo effect should read Shapiro, A. K. and Shapiro, E. 1997. "The Powerful Placebo: From Ancient Priest to Modern Physician." Johns Hopkins University Press. Note that the understanding of the physiology of the placebo effect has advanced considerably since this book was published.

A number of authors have written thoughtfully about enhancing the placebo effect. See, for example, Greene, C. S. et al. 2009. "Placebo responses and therapeutic responses. How are they related?" Journal of Orofacial Pain 23: 93-107; Finnis, D. G. et al. 2010. "Biological, clinical, and ethical advances of placebo effects." The Lancet 375: 686-695; and Miller, F. G., Colloca, L. and Kaptchuk, T. J. 2009. "The placebo effect: illness and interpersonal healing." Perspectives in Biology and Medicine 52: 518-539. See also Pacheco-López, G., et al. 2006. "Expectations and associations that heal: immunomodulatory placebo effects and its neurobiology." Brain, Behavior, and Immunity 20: 430-446.

For the 117 studies of ulcer drugs, see Moerman, D. E. 2000. "Cultural variations in the placebo effect: ulcers, anxiety, and blood pressure." Medical Anthropology Quarterly 14: 51-72. For physiological changes to the brain in response to the anticipation of receiving pain killers, see Colloca, L. and Benedetti, F. 2005. "Placebos and painkillers: is mind as real as matter?" Nature Reviews Neuroscience 6: 545-552; and Price, D. D., Finniss, D. G. and Benedetti, F. 2008. "A comprehensive review of the placebo effect: recent advances and current thought." Annual Reviews of Psychology 59: 565-590. This paper also discusses ways in which conditioning and memory may contribute to placebo responses. A number of papers have considered hidden versus open injections of drugs; for morphine in particular, see for example, figure 2 of Colloca, L. et al. 2004. "Open versus covert treatment for pain, anxiety, and Parkinson's disease." The Lancet Neurology 3: 679-684.

For expensive placebo pills being more effective than cheap ones, see Waber, R. L. et al. 2008. "Commercial features of placebo and therapeutic efficiency." Journal of the American Medical Association 299: 1016-1017. For sham devices being more powerful than placebo pills, see Kaptchuk, T. J. et al. 2006. "Sham device versus inert pill: randomised control trial of two placebo treatments." British Medical Journal 332: 391-394.

Sham surgery is controversial. For discussions of it, see Macklin, R. 1999. "The ethical problems with sham surgery in clinical research." New England Journal of Medicine 341: 992-996; and Johnson, A. G. 1994. "Surgery as a placebo." The Lancet 344: 1140-1142. For evidence of its power, see McRae, C. et al. 2004. "Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial." Archives of General Psychiatry 61: 412-420; and Goetz, C. G. et al. 2008. "Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions." Movement Disorders 23: 690-699.

Doctors' belief in the treatment can manifest itself in a variety of ways: if a doctor thinks the patient may have received a powerful painkiller, patients report less pain than if the doctor knows they have not. Similarly, a doctor's enthusiasm for a procedure often enhances its effect — for further information on this, see the Moerman book mentioned above. For the experiment involving the infusion of saline solution masquerading as a powerful drug, see Pollo, A. et al. 2001. "Response expectancies in placebo analgesia and their clinical relevance." Pain 93: 77-84.

In general, prescribing placebo treatments is considered to be bad medicine (see a recent report by Britain's Parliament.) For an alternative view, see Foddy, B. 2009. "A duty to deceive: placebos in clinical practice." American Journal of Bioethics 9: 4-12. For ways in which the placebo effect may be harnessed by "alternative" medical practices, see Kaptchuk, T. J. 2002. "The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance." Annals of Internal Medicine 136: 817-825.

Many thanks to everyone who has listened to my musings on the placebo effect, and to Mike Eisen for pointing out the study of Brazilians versus Germans. But particular thanks are due to Sofia Castello y Tickell, Dan Haydon, and Jonathan Swire for insights, comments and suggestions.

Sloths' bizarre 'toilet habit'

By Matt Walker Editor, Earth News

Two-toed sloths have been recorded descending from the trees to feed out of a human toilet.

The extraordinary behaviour, recorded on at least 25 occasions in the Amazon rainforest of Peru, has stumped the biologists who witnessed it. The sloths either crawl into the latrine to feed from it or scoop out the excrement and waste within. The feeding habit is even more bizarre as wild sloths are plant eaters not known to feed on animal matter. Details of the behaviour are published in the journal Mammalian Biology

Researchers speculate the sloths must derive some nutritional benefit from their bizarre feeding habit, though it is unclear exactly what that might be.

Emerging from a human toilet

The behaviour was recorded over a number of years by biologists working at the Estacion Biologica Quebrada Blanco field research site located in the Amazon rainforest in northeastern Peru.

The biologists based there usually study the behaviour and ecology of New World monkeys, including moustached tamarins, saddle-back tamarins and red titi monkeys.

Their camp is a traditionally built hut, with latrines located 20 to 40m away in the forest.

On the first occasion, a researcher using the latrine saw a two-toed sloth (Choloepus didactylus) hanging upside down from the wooden bars that enclose the toilet. It was using one hand to scoop out handfuls of semi-liquid manure, comprising human faeces, urine and toilet paper, and then eating from the hand.

Since that occasion, the scientists have since recorded sloths visiting the latrine on at least 25 other occasions.

Sometimes the sloths entered the pit that formed the latrine, to feed directly from the waste inside, emerging covered in the liquid held within.

Professor Eckhard Heymann of the German Primate Centre based in Gottingen, Germany, who led the team of researchers, told the BBC that they were surprised and astonished by the behaviour.

"The sequence of events was always more or less then same: someone arriving at the latrine, seeing the sloth inside and the sloth feeling disturbed and coming out and moving away," says Prof Heymann.

The researchers suspect many individual sloths visited the latrines: on one occasion a mother and baby visited.

Why the sloths decided to visit and feed from the latrines remains a mystery. Sloths hardly ever come down from the trees in which they live.

Usually they only descend to the forest floor to change trees or once every three to seven days to defecate.

One idea put forward by Prof Heymann's team is that the human faeces may provide a direct source of nutrients, as faeces can contain variable amounts of fibre and energy in the form of proteins, sugars and fatty acids.

Another is that the sloths visit to acquire sodium or other minerals in the waste, in the same way that some animals visit salt licks.

The third proposal is that the sloths may be eating insect larvae that grow among the waste.

While wild sloths are plant eaters, captive sloths have been known to accept meat and fish in their food, suggesting the animals may seek out larvae as an additional source of protein.

The odd behaviour may also come at a cost to the sloths, however.

"While at first glance our observations may simply represent a bizarre contribution to the natural history of sloths, they also bear implications for the transmission of disease from humans to wildlife," the researchers write in the journal.

Two-toed sloths can survive in secondary or disturbed forest close to human settlements.

If other sloths have developed similar tastes for human waste, it could increase the possibility of them acquiring human diseases and parasites.

It Started More Than One Revolution

By GARDINER HARRIS

The birth control pill has been called the most important scientific advance of the 20th century, and no wonder. Fifty years after its approval by the Food and Drug Administration, it is still one of the leading methods of contraception, in the United States and around the world.

Much has been written about how it revolutionized sexual and social relationships, allowing women to defer pregnancy, enter the work force and make life choices their mothers could not - or, if you prefer, spawning promiscuity and undermining the foundations of marriage.

But the pill also led to profound changes in the F.D.A. itself - a revolution in what Dr. Margaret Hamburg, the current food and drug commissioner, calls regulatory science. Many of the steps that underlie modern drug approvals - extensive clinical trials, routine referrals to panels of outside experts, continuing assessments of a medicine’s safety, and direct communications between the F.D.A. and patients - were pioneered to deal with evolving concerns about the pill’s safety.

In regulatory terms, the pill brought about a kind of reformation: just as Martin Luther insisted that individual Christians could communicate directly with God without the mediation of priests, the pill eventually led the F.D.A. to communicate directly with patients without going through doctors.

That change, fiercely resisted by some physician groups, is now firmly entrenched; the F.D.A. now routinely requires that many medicines carry significant and sometimes complex warnings that patients are expected to read and understand. But the pill was the first.

“The F.D.A. had been battling with the American Medical Association for years about who would talk to patients,” said Daniel P. Carpenter, a professor of government at Harvard. “And with the pill, the F.D.A. clearly established the upper hand.”

The pill’s role in the maturing of the F.D.A. has often been overlooked because shortly after the agency’s approval of the contraceptive, news of the horrific effects of thalidomide swept the world. That drug had been introduced in Europe as a sedative but was withdrawn in 1961 after it was linked with profound birth defects.

Although thalidomide was never approved in the United States, the horror surrounding its effects led Congress to toughen the drug approval process by requiring manufacturers to prove their medicines were both safe and effective. It was a standard the F.D.A. had already been putting into effect, quietly if fitfully, in part because of the growing view that the safety of a medicine was inextricably linked with its efficacy.

Enovid, a pill combining the hormones estrogen and progestin, was already being prescribed for menstrual problems. But in approving it as a contraceptive, the agency's reviewers required Searle to prove that it was effective in preventing pregnancy. (If it worked, the pill would spare women the risks of pregnancy and childbirth, which dwarfed any known risks from the drug.)

So the company undertook one of the most extensive clinical trial programs to date, said Suzanne Junod, an F.D.A. historian. The pill was formally tested in 897 women, mostly in Puerto Rico and Haiti.

The trials were relatively brief and did not answer fundamental questions about risks of cancer, heart disease and other chronic diseases. Uncertain about the long-term effects of hormonal contraceptives, the F.D.A. mandated that doctors limit prescriptions to two years.

The pill's overwhelming popularity, however, soon rendered this limitation unenforceable. New versions were introduced, so women could simply switch brands - or find another doctor to prescribe the old one. And many doctors ignored the limit anyway.

Then in November 1961, a British physician reported in The Lancet that a young woman had developed a blood clot and died while taking the pill. Within months, two similar fatalities were reported in the United States, and by August 1962, the F.D.A. had received 26 reports of users' suffering blood clots.

By the end of 1964, more than four million women had used Searle's pill, and a blizzard of competitors had begun to blanket the market. With something so popular, the agency had no way of knowing if the problems experienced by users were related to the pill or would have happened anyway - the kind of mystery that has plagued drug regulators ever since.

So agency officials did two things for the first time that would eventually become routine. They asked a panel of outside experts to review the evidence on a continuing basis, and they and British regulators pressed for a large epidemiological investigation that would become a model for the future.

Even before the pill, the federal government had a long history of using advisory committees to assess specific subjects and issue reports. But in 1965, the F.D.A. established its first permanent advisory panel, the Obstetrics and Gynecology Advisory Committee, largely to track the safety of the pill. The agency now has 32 permanent advisory committees, one of them with 18 different panels. These committees provide crucial advice not only about whether to approve certain medicines and devices but also how to address safety concerns that arise after approval.

"What the pill does," said Dr. Carpenter, of Harvard, "is show the F.D.A. that postmarketing surveillance is a tough problem."

The challenge of communicating these risks to patients while still supporting the product's continued use bedeviled top agency officials. Protests by women's groups and hearings on Capitol Hill made clear that despite the agency's attempts, many women said they took the pill without being fully informed of its risks.

Frustrated that some doctors were not communicating adequately with their patients, the F.D.A. created a handout in 1975 that doctors could use in counseling patients. Many doctors, incensed at what they saw as the agency's intrusion into the doctor-patient relationship, either ignored the material or refused to give it out.

In 1978, faced with mounting complaints that women did not have the information they needed, the F.D.A. mandated that patients be given the handouts when they picked up their prescriptions at the drugstore.

"It was the first time that the agency had provided information directly to patients at the point of sale instead of relying on physicians," said Dr. Junod, the historian.

More recently, the Ortho Evra birth control patch has become a telling example of the continuing challenges that the F.D.A. faces in regulating a global, multibillion-dollar industry on which the agency depends for crucial information about drug safety.

Johnson & Johnson developed the patch in hopes of exposing women to even lower doses of estrogen than they got with the pill. But the company's own studies showed that the patch actually delivered far higher doses.

The finding was buried in a mathematical formula in a 435-page report filed with the F.D.A. The company said it acted responsibly, but after four years, the F.D.A. issued a warning about high estrogen doses, and sales plunged.

One last bit of lore about the pill: no one is even sure when to celebrate its birthday. Ten years ago, the agency honored the occasion on June 23, the date that the F.D.A. gave formal approval for Searle to market the product. This year, the agency is celebrating on May 9, which coincides with the period 50 years ago when it announced its intention to approve the pill when a few technical details were ironed out. That this happens to be Mother's

Day this year may have played a role in the decision. But whatever the date, it represents the F.D.A.'s first steps into adulthood.
"The pill was a landmark in the field of drug regulation," said Peter Barton Hutt, a former top agency lawyer. "This is the drug that started it all."

Fishing fleet working 17 times harder than in 1880s to make same catch

The UK trawl fishing fleet has to work 17 times harder to catch the same amount of fish today as it did when most of its boats were powered by sail, according to new research.

Researchers from the University of York and the Marine Conservation Society (MCS) used UK Government data on the amount of fish caught and the size and number of boats involved – the fleet's fishing power – to analyse the change in fish stocks since 1889.

They found that trawl fish landings peaked in 1937, 14 times higher than today, and the availability of bottom-living fish to the fleet fell by 94 per cent.

The findings are the result of a study using previously overlooked records and suggest the decline in stocks of popular fish such as cod, haddock and plaice is far more profound than previously thought. The research is published in Nature Communications, the new online science journal from the publishers of Nature.

Ruth Thurstan, lead author of the study from the University of York's Environment Department, said: "We were astonished to discover that we landed over four times more fish into England and Wales in 1889 than we do today. "For all its technological sophistication and raw power, today's trawl fishing fleet has far less success than its sail-powered equivalent of the late 19th century because of the sharp declines in fish abundance."

The findings suggest that the damage to fisheries is greater and has taken place over a much longer period than previously acknowledged, pre-dating developments such as the Common Fisheries Policy which are usually blamed for declining stocks.

Simon Brockington, Head of Conservation at the Marine Conservation Society and an author of the study, said: "Over a century of intensive trawl fishing has severely depleted UK seas of bottom living fish like halibut, turbot, haddock and plaice. "It is vital that governments recognise the changes that have taken place. The reform of the Common Fisheries Policy gives an opportunity to set stock protection and recovery targets that are reflective of the historical productivity of the sea."

The study calculated 'landings of fish per unit of fishing power' (LPUP) from 1889 to 2007 to give an indication of changes in the amount of fish available for capture by the fishing fleet. In that time, LPUP declined 500 times for halibut, more than 100 times for haddock and more than 20 times for plaice, wolffish, hake and ling. Cod has declined by 87 per cent.

Professor Callum Roberts, from the University of York's Environment Department, said: "This research makes clear that the state of UK bottom fisheries – and by implication European fisheries, since the fishing grounds are shared – is far worse than even the most pessimistic of assessments currently in circulation.

"European fish stock assessments, and the management targets based on them, go back only 20 to 40 years. These results should supply an important corrective to the short-termism inherent in fisheries management today."

By 2030, cardiovascular disease and death rates in China will surge

Study highlights:

**** By 2030, researchers project that aging and increases in risk factors will raise annual heart disease and stroke rates in China by up to 73 percent.***

**** This could translate into 21.3 million more cardiovascular disease events and 7.7 million related deaths between 2010 and 2030.***

**** If the population in China dramatically eliminates smoking in men, or lowers high blood pressure in men and women, it could reverse future cardiovascular disease.***

DALLAS, – Cardiovascular disease (CVD) and death rates will surge in China by up to 73 percent by 2030, due to aging, smoking, high blood pressure and other risk factors, according to research reported in Circulation: Cardiovascular Quality and Outcomes, an American Heart Association journal.

"China is a prime example of a middle income nation in transition. The country's standard of living and life expectancy have improved for many, but aging, dietary changes and less physical activity are leading to more heart disease and stroke," said lead author Andrew Moran, M.D., M.P.H., assistant professor at Columbia University Medical Center in New York City, N.Y. "Our study used a computer model to forecast future cardiovascular disease in Chinese adults, and is the first to project the individual and combined effects of major risk factor trends on a national scale."

Moran and colleagues reviewed risk factor surveys of Chinese adults, ages 35-84, since economic reforms in the 1980s, and used them to project future trends in blood pressure, cholesterol, smoking, diabetes and body

weight. Although smoking prevalence has declined in men by more than 10 percent since the mid 1980s, 62 percent of Chinese men still smoke, and 49 percent of nonsmokers, mostly women, are exposed to passive smoke, researchers said.

Demographic changes will be the main driver of the CVD epidemic in China in the next two decades, Moran said.

"We projected that yearly cardiovascular disease in China will increase by more than 50 percent due to aging and growth of the population alone between 2010 and 2030," he said. "Projected trends of increased blood pressure, cholesterol and diabetes may result in an additional 23 percent increase in cardiac events."

Together, these percentages may translate into 21.3 million more CVD events and 7.7 million related deaths between 2010 to 2030, researchers said.

Dramatically reducing smoking to 20 percent of the male population by 2020 and 10 percent by 2030, or lowering average systolic blood pressure four points in men and women, would counteract adverse trends in other risk factors and prevent between 2.9 and 5.7 million deaths by 2030, Moran said.

Aggressive anti-tobacco policy and control of elevated blood pressure are two promising policy directions that need to be studied in more detail, he said.

Study co-author Dongfeng Gu, M.D., M.Sc., vice president of the Chinese Academy of Medical Sciences in Beijing, China, said that the demographic changes stand to increase the burden of CVD as well as that of cancer and other non-communicable diseases and disabilities.

"In China, as in many other parts of the world, the government has mainly focused on infectious diseases; however, China now has a 'double burden' of disease," Gu said. "If no massive preventative measures are taken, the burden of cardiovascular disease will inevitably continue to rise in China. The priority for prevention and control of cardiovascular diseases should be adequately addressed by the government and the Chinese public."

"China now finds itself facing a major crisis with the predicted increase in mortality and morbidity from cardiovascular disease," said Sidney C. Smith, Jr., M.D., professor of medicine at the University of North Carolina School of Medicine in Chapel Hill, N.C., and Zhi-Jie Zheng, M.D., Ph.D., senior medical epidemiologist and program director of the division for the Application of Research Discoveries at the National Heart, Lung, and Blood Institute, National Institutes of Health in Bethesda, Md., co-authors of an accompanying editorial. "However, China is moving in the right direction by implementing major prevention programs. If they succeed, they will serve as an example for other countries now facing the pandemic of CVD."

Study co-authors are Dong Zhao, M.D., Ph.D.; Pamela Coxson, Ph.D.; Y. Claire Wang, M.D., M.Sc.; Chung-Shiuan Chen, M.S.; Jing Liu, M.D.; Jun Cheng, M.D.; Kirsten Bibbins-Domingo, M.D., Ph.D.; Yu-Ming Shen, Ph.D.; Jiang He, M.D., Ph.D.; and Lee Goldman, M.D., M.P.H.

Author disclosures are on the manuscript.

The study was funded by an award from the National Heart, Lung, and Blood Institute and a grant from the William J. Matheson Foundation to Columbia University; and grants from the Flight Attendants Medical Research Institute and Swanson Family Fund to the University of California - San Francisco.

Rocks record early magnetic field

By Jonathan Amos Science correspondent, BBC News, Vienna

Scientists have managed to push back the date for the earliest known presence of a magnetic field on Earth by about 250 million years. The evidence is seen in tiny iron minerals that are aligned inside ancient dacite rocks from the Barberton mountains in South Africa.

Analysis of the 3.45-billion-year-old minerals indicates the strength the field was much weaker than today.

Earth's magnetic field protects all life on the planet. It forms a shield that deflects harmful particles from the Sun around our world, and limits the ability of this "solar wind" to erode our atmosphere.

The new work by Professor John Tarduno, from the University of Rochester, US, and colleagues has been discussed at a major Earth sciences meeting in Vienna, Austria.

"Earth's magnetic field is important to us," Professor Tarduno told the European Geosciences Union meeting.

"[3.45 billion years ago] is a really critical time because it's when we start seeing the first tentative signs of life, so perhaps these two things are linked together."

The Rochester team has developed techniques for studying tiny magnetite minerals trapped inside the crystals of volcanic rock. These minerals orientate themselves with respect to the Earth's magnetic field in a cooling magma and lock their positions once the temperature in the host rock dips below 580C.

The Barberton samples indicate the nascent field was considerably weaker than today's protective shield.

Whereas the modern boundary between our planet's magnetosphere and the solar wind might be located ordinarily at about 10 Earth radii, the ancient boundary would have been much closer - perhaps three to five Earth radii, said Professor Tarduno.

He explained that one likely effect of this would have been the production of polar lights, or auroras, at much lower latitudes as many more solar particles breached the shield to collide with atmospheric molecules.

It probably also meant the atmosphere lost more of its lighter elements, like hydrogen, faster than had previously been supposed, argued Professor Tarduno.

"What that means in an evolutionary sense to us - and this is just speculation but something we want to follow it up - is that perhaps this is suggesting the Earth was much more water-rich very early on," he said.

"If, even with this magnetic field, we are losing hydrogen and water, that would suggest the palaeo-Earth in its infant state must have had more water than we think about today."

Professor Tarduno's team is now looking back still deeper into the past for evidence of a global magnetic field.

The field is generated by convection currents in the molten-iron outer-core of the planet, and finding evidence of an even more ancient field would say much about the interior state of the young Earth.

There are volcanic rocks in Africa, India and Australia that possibly retain a record that is 3.6bn years old.

"To go back even further in time, however, we don't have the rocks available. But what we do have is certain younger sedimentary rocks that record minerals which were eroded from more ancient rocks - as old as four billion years old," Professor Tarduno told BBC News.

"We are developing techniques and we believe we can actually record the Earth's magnetic field in these minerals also."

Trauma-induced changes to genes may lead to PTSD

A study by researchers at Columbia University's Mailman School of Public Health suggests that traumatic experiences "biologically embed" themselves in select genes, altering their functions and leading to the development of post-traumatic stress disorder (PTSD).

"Our findings suggest a new biological model of PTSD in which alteration of genes, induced by a traumatic event, changes a person's stress response and leads to the disorder," said Sandro Galea, MD, professor and chair of the Department of Epidemiology at the Mailman School of Public Health, and principal investigator.

"Identification of the biologic underpinnings of PTSD will be crucial for developing appropriate psychological and/or pharmacological interventions, particularly in the wake of an increasing number of military veterans returning home following recent wars worldwide."

The findings are published today online in Proceedings of the National Academy of Sciences (PNAS).

Previous studies have found that lifetime experiences may alter the activity of specific genes by changing their methylation patterns. Methylated genes are generally inactive, while unmethylated genes are generally active.

The new study is the first large scale investigation to search for trauma-induced changes in the genes of people with PTSD. DNA samples were obtained from participants in the Detroit Neighborhood Health Study (DNHS), a longitudinal epidemiologic study investigating PTSD and other mental disorders in the city of Detroit. The researchers analyzed the methylation patterns of over 14,000 genes from blood samples taken from 100 Detroit residents, 23 of whom suffer from PTSD.

The analysis found that participants with PTSD had six to seven times more unmethylated genes than unaffected participants, and most of the unmethylated genes were involved in the immune system.

The observed methylation changes in the immune system genes were reflected in the PTSD participants' immune systems: levels of antibodies to a herpes virus were high in PTSD patients, indicative of a compromised immune system.

While people who experience severe trauma will exhibit a normal stress response, in PTSD, the stress response system becomes deregulated and chronically overactive causing compromised immune functioning. PTSD has long been linked to increased risk of numerous physical health problems – including diabetes and cardiovascular disease. This paper suggests why PTSD is so strongly associated with physical health problems – trauma exposure causes epigenetic changes in immune system genes and thus, compromised immune functioning putting individuals at risk for a host of disorders.

"Our findings show that PTSD may be associated with epigenetic changes in immune-system genes. If this is the case, these clusters could provide clues to our understanding of how a traumatic event changes gene expression, thus altering immune function and resulting in other possible physiologic alterations," says Dr. Galea.

The study was funded by grants from the NIH, with additional support provided by the Robert Wood Johnson Health and Society Scholars Program.

A new biological explanation for sadness in early postpartum

Toronto – Greater levels of a brain protein called monoamine oxidase A (MAO-A) – may explain why postpartum blues and clinical depression are so common after childbirth according to an important study published today in the Archives of General Psychiatry.

Using an advanced brain imaging method, researchers at the Centre for Addiction and Mental Health discovered that levels of brain MAO-A in healthy women four to six days after delivery were 43% greater as compared to women not recently pregnant. The findings were strongest on day 5, the day when postpartum blues is usually the most severe.

MAO-A removes chemicals like serotonin that help maintain a normal mood. Greater MAO-A levels mean that this removal process is overly active making people feel sad.

"Understanding the biology of postpartum blues is important because when it is severe it leads to clinical level postpartum depression, the most common complication of childbearing affecting 13% of mothers, and one that can have a devastating impact. We hope this information may be used in the future to create dietary supplements that could provide the nutrients removed by high MAO-A and lower the risk for postpartum depression," according to Dr. Jeffrey Meyer, principal investigator for the study.

The brain imaging technique is called positron emission tomography (PET). VP of Research Dr. Bruce Pollock explains, "CAMH has the only PET centre in the world dedicated solely to mental health and addiction research. As a result we were able to apply this high level technology to better understand postpartum depression, an important research direction in mood disorders."

The study (Elevated Brain Monoamine Oxidase A Binding in the Early Postpartum Period) was funded by the Canadian Institutes of Health Research, the Ontario Mental Health Foundation, the National Alliance for Research in Depression and Schizophrenia, and the Canadian Foundation for Innovation. Dr. Meyer holds a Canada Research Chair in the Neurochemistry of Major Depression.

U of T researchers crack 'splicing code,' solve a mystery underlying biological complexity

Toronto, On – Researchers at the University of Toronto have discovered a fundamentally new view of how living cells use a limited number of genes to generate enormously complex organs such as the brain.

In a paper published on May 6 in the journal Nature entitled "Deciphering the Splicing Code," a research team led by Professors Brendan Frey and Benjamin Blencowe of the University of Toronto describes how a hidden code within DNA explains one of the central mysteries of genetic research – namely how a limited number of human genes can produce a vastly greater number of genetic messages. The discovery bridges a decade-old gap between our understanding of the genome and the activity of complex processes within cells, and could one day help predict or prevent diseases such as cancers and neurodegenerative disorders.

When the human genome was fully sequenced in 2004, approximately 20,000 genes were found. However, it was discovered that living cells use those genes to generate a much richer and more dynamic source of instructions, consisting of hundreds of thousands of genetic messages that direct most cellular activities. Frey, who has appointments in Engineering and Medicine, likens this discovery to "hearing a full orchestra playing behind a locked door, and then when you pry the door open, you discover only three or four musicians generating all that music."

To figure out how living cells generate vast diversity in their genetic information, Frey and postdoctoral fellow Yoseph Barash developed a new computer-assisted biological analysis method that finds 'codewords' hidden within the genome that constitute what is referred to as a 'splicing code'. This code contains the biological rules that are used to govern how separate parts of a genetic message copied from a gene can be spliced together in different ways to produce different genetic messages (messenger RNAs). "For example, three neurexin genes can generate over 3,000 genetic messages that help control the wiring of the brain," says Frey.

"Previously, researchers couldn't predict how the genetic messages would be rearranged, or spliced, within a living cell," Frey said. "The splicing code that we discovered has been successfully used to predict how thousands of genetic messages are rearranged differently in many different tissues." Blencowe's group, including graduate student John Calarco, generated experimental data used to derive and test predictions from the code. "That the splicing code can make accurate predictions on such a large scale is a major step forward for the field," says Blencowe.

Frey and Blencowe attribute the success of their project to the close collaboration between their team of talented computational and experimental biologists. "Understanding a complex biological system is like understanding a complex electronic circuit. Our team 'reverse-engineered' the splicing code using large-scale experimental data generated by the group," Frey said.

Prescription drug could boost effects of vaccines for HIV and other diseases

A prescription drug already approved to treat genital warts and skin cancer may have a new use in boosting the effectiveness of future vaccines for bacterial and viral diseases, such as hepatitis C and HIV (the AIDS virus). These findings appear in ACS' Molecular Pharmaceutics, a bi-monthly journal.

John Pesce and colleagues at the Naval Medical Research Center and UC-Berkeley note that vaccines prepared from weakened or inactivated viruses or bacteria have had enormous success in preventing polio, influenza, and other diseases. However, vaccines containing living or weakened viruses cannot be used for HIV, hepatitis C, and other devastating diseases due to safety concerns. Scientists are instead trying to develop a new generation of vaccines, made with DNA or proteins from infectious agents that can prevent illness without carrying a risk of causing the diseases. These vaccines will be weaker than conventional vaccines and require a new generation of "adjuvants," ingredients that boost a vaccine's immunogenicity.

The report identifies a promising candidate in the form of imiquimod, an immune-boosting drug already in general use. The scientists coated imiquimod with dextran-based microparticles in hopes of increasing the efficiency of cellular uptake by cells associated with immune response initiation. Sure enough, the coated drug significantly boosted levels of inflammatory cytokines in laboratory cultures of immune cells from mice. The findings have "broad significance" and open the door to more extensive testing of the approach, they indicate.
ARTICLE FOR IMMEDIATE RELEASE *"In Vitro Analysis of Acetalated Dextran Microparticles as a Potent Delivery Platform for Vaccine Adjuvants"*

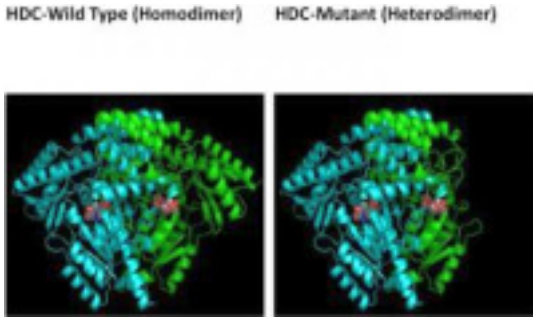
Discovery of rare genetic mutation could help battle Tourette syndrome

A single, very unusual family with Tourette syndrome (TS) has led Yale School of Medicine researchers to identify a rare mutation in a gene that is required to produce histamine. The finding provides a new framework to understand many years of data on the role of histamine function in the brain and points to a potentially novel approach to treatment of tics and Tourette.

The study is published online May 5 in the New England Journal of Medicine by a team led by Matthew State, M.D., the Donald J. Cohen Associate Professor in the Yale Child Study Center and in the Departments of Psychiatry and Genetics, and co-director of the Yale Program on Neurogenetics.

TS is a relatively common neurological disorder characterized by tics—involuntary, rapid, sudden movements or vocalizations that occur repeatedly in the same way. It affects as many as one of 100 school-age children. Tics begin in mid-childhood and peak at the start of adolescence. TS is not life threatening, but can be disabling. Affected children and adults commonly have other neuropsychiatric disorders including ADHD, obsessive-compulsive disorder or depression.

Based on strong evidence that genes contribute to TS, the State lab has been searching for rare genetic mutations causing TS for over a decade, in the hopes of gaining a better understanding of the cause of the disorder, and finding opportunities to develop more effective treatments. "Rare families have been used in a variety of other common conditions to help identify underlying mechanisms of disease and find new approaches to treatment," said first author and Yale post-doctoral fellow Adife Gulhan Ercan-Sencicek. "We thought we could use the same approach in Tourette syndrome."



These images shows the mutation in HDC genes. **Yale University, Matthew State**

State and his team found a family with TS with a rare mutation in a gene called 1-histidine de carboxylase (HDC). This gene makes a protein that is required for the production of histamine. Histamine is known more often for its role in allergic response, but it is an important neurotransmitter that influences a variety of brain functions.

The father and all eight offspring were diagnosed with TS. The mother and her family did not have the disorder. Two children and the father also had obsessive-compulsive disorder. The State lab took DNA samples from all family members, found the one region of the genome that all affected individuals shared, and then identified a rare mutation in HDC within this region, which resulted in the mutated protein losing its function.

State said past work on brain histamine by other labs shows that mice with low levels are more prone to repetitive behaviors that are similar to human tics, and that increasing brain histamine reverses this problem.

"The opportunity to go directly from a rare genetic finding to a trial of a new approach to treatment in a neuropsychiatric disorder is very unusual," said State. "We were lucky to happen across a gene pointing to a well-studied area in neuroscience. There are several new medications in development that increase the release of brain histamine. Based on this genetic finding, these compounds would be good candidates for new treatments for Tourette."

Other Yale authors on the study included Althea Stillman, Ananda Ghosh, Kaya Bilguvar, M.D, Thomas Abbott, Abha Gupta, M.D., Robert King, M.D., Erin Loring, Katsuhito Yasuno, Thomas Fernandez, M.D., Stephan Sanders, M.D., Angeliki Louvi, Judy Cho, M.D., Shrikant Mane, Christopher Colangelo, Thomas Biederer, Richard Lifton, M.D., and Murat Gunel, M.D.
***Citation**: N Engl J Med 2010. DOI: 10.1056/NEJMoa0907006 (Online May 5, 2010, In print May 20, 2010)*

Brain May Use Clot-Busting Drug Naturally as Protection Against Stroke

New research on the properties of the clot-busting stroke drug tPA (tissue-type plasminogen activator) suggests that tPA can act as a neuroprotectant and may form the keystone of an adaptive response to a reduction in blood flow. Scientists from Emory University School of Medicine have shown that certain parts of the brains of mice lacking the gene for tPA are more vulnerable to stroke. In addition, tPA can protect neurons in the same part of the brain from the stress of hypoxia (low oxygen).The results are published online this week in the Journal of Clinical Investigation.

tPA was introduced as a treatment for acute stroke in the 1990s. Physicians have debated its safety and effectiveness ever since then, because it can increase the likelihood of hemorrhage. Previous research has shown that in some situations, tPA can be seen as a neurotoxin. In addition to dissolving clots, tPA can increase the permeability of the blood-brain barrier, and it can cross from the blood vessels into the brain tissue, generating inflammation.

"tPA is not only a drug, it is a natural protein produced in response to hypoxia," says senior author Manuel Yepes, MD, associate professor of neurology at Emory University School of Medicine. "If you look at the parts of brain where the gene for tPA is turned on the most, one of these is the hippocampus. It is well known that the hippocampus is especially vulnerable to hypoxia compared with other regions of the brain. We believe there is a reason for this overlap."

The hippocampus is a structure in the middle of the brain thought to be responsible for memory formation. In mice lacking the gene for tPA, neurons in the hippocampus are more vulnerable to dying after a short simulated stroke lasting 20 minutes, Yepes and his colleagues found. In the laboratory, pre-treatment with tPA protects hippocampal neurons in culture from hypoxia. In contrast, tPA has the opposite effect on neurons from the cortex.

tPA's protective properties suggest that it may be playing a role in a process called "ischemic preconditioning," where a less-than-lethal stroke can protect the brain against a later repeat, Yepes says. tPA's effects on the blood-brain barrier can be seen as a way to get more blood to a deprived part of the brain.

In most people who experience a stroke, atherosclerosis has gradually restricted blood flow over a long time period, provoking attempts by the brain to work around the obstacle.

"Many individuals who have a transient ischemic attack, which is a non-lethal mini-stroke, go on to have a more serious and debilitating stroke," Yepes says. "This means we should be thinking about tPA less as a way of treating ischemic stroke but more as a way to prevent it."

One way to use tPA preventively could be to prolong the effects of tPA produced naturally in the brain, a strategy Yepes and his colleagues are investigating now. They are also probing which molecules in neurons are necessary for the protective effects of tPA. tPA appears to be acting on a class of neurotransmitter receptors known as NMDA receptors, they show in the paper.

The research was supported by the National Institutes of Health.
***Reference:** Tissue-type plasminogen activator is a neuroprotectant in the murine hippocampus. R. Echeverry, J. Wu, W.B. Haile, J. Guzman and M. Yepes. J. Clin. Invest. (2010)*

Mammoth Hemoglobin Offers More Clues to Its Arctic Evolution

By NICHOLAS WADE

The mammoth, seen here in a museum diorama, originated in the tropics, where they split from elephants some seven million years ago. **Jonathan S. Blair/National Geographic, via Getty Images**

For the first time in 43,000 years, a woolly mammoth has breathed again on earth.

Well, not the mammoth itself but its hemoglobin, the stuff in red blood cells that takes on oxygen in the lungs and offloads it in the tissues.

By reconstructing the mammoth's hemoglobin, a team led by Kevin L. Campbell of the University of Manitoba in Canada has discovered how the once-tropical species adapted to living in arctic temperatures.

Dr. Campbell's work raises a somewhat astonishing possibility: that much of the physiology of extinct animals may one day be recoverable from the DNA extracted from their remains.

“It is a very exciting result and opens a new chapter in paleontology, a subject usually constrained to examining old bones and teeth,” said Adrian Lister, an expert on mammoth evolution at the Natural History Museum in London.

Mammoths, despite their association with the frozen north, originated in the tropics when they split apart from elephants some seven million years ago. To adapt to the cold of northern latitudes, they developed smaller ears, a thick fur coat and glands in their skin to keep the fur well oiled.

So much is clear from their remains. But other kinds of adaptation, which have not survived, would also have been necessary. Most arctic animals arrange their blood vessels so that the arteries going down a leg can transfer heat to the veins coming up. The blood reaching the toes is thus quite cold, and the animal conserves lots of heat while it stands on frozen ground.

But this arrangement raises a problem for the hemoglobin, the protein of red blood cells that takes on oxygen in the lungs and delivers it in the tissues. The offloading process becomes much less efficient at low temperatures. So animals like the arctic fox, whose foot temperature is just a degree or so above freezing, have changes in their hemoglobin genes that enable the protein to release oxygen more easily at very low temperatures.

Dr. Campbell set out nine years ago to see if the same was true of mammoths. His first problem was to figure out which of several globin genes were active in the species. Globin genes make the four globin chains from which the hemoglobin molecule is assembled. Humans have at least four globin genes — alpha, beta, gamma and delta. Most hemoglobin molecules in human blood consist of two alpha chains and two beta chains, but in 10 percent of the blood, delta chains substitute for the betas. The gamma globin gene is active only in the fetus.

Dr. Campbell figured that the hemoglobin system of living elephants would offer the best guide to how mammoth globin genes operate. After a frustrating effort to get permits to take samples from wild elephants, he acquired blood from an Asian elephant called Caesar at the Bowmanville Zoo in Ontario.

It turned out that way back in the elephant lineage, the beta and delta globin genes had swapped DNA to create a hybrid beta-delta chain. Elephant hemoglobin molecules are composed of two chains from the alpha globin gene and two from the fused beta-delta gene, and it is reasonable to assume mammoths had the same system.

With this knowledge, Dr. Campbell and his colleagues could construct the tools to fish out the alpha and beta-delta globin genes from the ancient DNA of three permafrost-preserved Siberian mammoths that lived between 25,000 and 43,000 years ago. They found the alpha chain differed in one of its amino acid units from that of Asian elephants, and the beta-delta chain differed in three units from its counterpart, they report in Nature Genetics.

The team’s next step was to synthesize copies of the mammoth’s two globin genes. Instead of doing that from scratch, Dr. Campbell used a technique for altering DNA units one by one and simply converted the Asian elephant’s two globin genes at the four differing sites to the mammoth version. The mammoth genes were then inserted into bacteria, which synthesized the two mammoth globin chains, inserted the required iron atoms, and assembled the chains into working hemoglobin molecules. With the mammoth hemoglobin in hand, Dr. Campbell could at last address the question of whether its genetic changes had been shaped by natural selection to help mammoths survive in the cold.

“It’s the same as if I went back 43,000 years in a time machine and took blood from a mammoth,” he said.

The answer was yes: In a chemical environment like that in red blood cells, the reconstructed mammoth hemoglobin let go of its oxygen much more readily at cold temperatures than did that of Asian elephants.

The DNA changes in the mammoth hemoglobin genes differ from those in other arctic animals, an instance of convergent evolution or attaining the same end by a different genetic route.

One species that did not modify its hemoglobin genes to cope with arctic temperatures is that of humans. “With our ability to make mitts and hats, we’ve not needed these sorts of changes,” Dr. Campbell said.

He is now reconstructing important proteins of other extinct species such as the mastodon, the woolly rhinoceros and the Steller’s sea cow, a huge dugong that lived in the arctic.

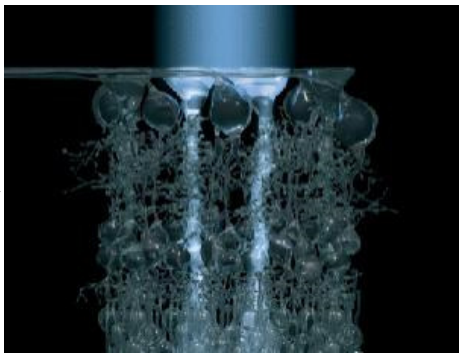
Two years ago, scientists at Penn State University sequenced a large part of the mammoth’s genome from a clump of hair. They published the sequence along with the arresting suggestion that for just $10 million it might be possible to complete the sequence and use it to generate a living mammoth.

The suggestion was not as wild as it might seem, given that the idea came from George Church, a leading genome technologist at the Harvard Medical School. The mammoth’s genome differs at about 400,000 sites from that of the African elephant. Dr. Church has been developing a method for altering 50,000 sites at a time, though he is not at present applying it to mammoths. In converting four sites on the elephant genome to the mammoth version, Dr. Campbell has resurrected at least one tiny part of the mammoth.

Reconstructing the whole animal will take a little longer. “I’m 42 years old,” he said, “but I doubt I’ll ever see a living mammoth.”

Evolution gave flawed eye better vision

* 06 May 2010 **by Kate McAlpine**



IT LOOKS wrong, but the strange, "backwards" structure of the vertebrate retina actually improves vision.

Certain cells act as optical fibres, and rather than being just a workaround to make up for the eye's peculiarities, they help filter and focus light, making images clearer and keeping colours sharp.

Although rods and cones are responsible for capturing light, they are in a curious position. Hidden at the base of the retina, they are covered by several layers of cells as well as the bed of nerves that carries visual information to the brain. One result is a blind spot in our visual field, leading the vertebrate retina to be listed among evolution's biggest "mistakes".

Müller cells refocus the red and blue light, delivering them directly to the same cone cell **Image: Jens Grosche**

Light clearly gets through, however, and in 2007 researchers analysing the retinas of guinea pigs reported that the glial cells which nourish and physically support the bed of neurons also act as optical fibres for the rods and cones. These Müller cells are funnel-shaped, with wide tops that cover the surface of the retina and a long slender body that guides light to the receptors below.

Now Amichai Labin and Erez Ribak of the Technion-Israel Institute of Technology in Haifa have used data from human eye cells to model the workings of the retina. Their findings suggest that sending light via the Müller cells offers several advantages.

At least two types of light get inside the eye: light carrying image information, which comes directly through the pupil, and "noise" that has already been reflected multiple times within the eye. The simulations showed that the Müller cells transmit a greater proportion of the former to the rods and cones below, while the latter tends to leak out. This suggests the cells act as light filters, keeping images clear.

The researchers also found that light that had leaked out of one Müller cell was unlikely to be taken up by a neighbour, because the surrounding nerve cells help disperse it. What's more, the intrinsic optical properties of Müller cells seemed to be tuned to visible light, leaking wavelengths outside and on the edges of the visible spectrum to a greater extent.

The cells also seem to help keep colours in focus. Just as light separates in a prism, the lenses in our eyes separate different colours, causing some frequencies to be out of focus at the retina. The simulations showed that Müller cells' wide tops allow them to "collect" any separated colours and refocus them onto the same cone cell, ensuring that all the colours from an image are in focus (see diagram).

"It suggests that light-coupling by Müller cells is a crucial event that contributes to vision as we know it," says Kristian Franze, a neurophysicist at the University of Cambridge and co-author of the 2007 study. "This work nicely complements our experimental data."

However, Kenneth Miller, a biologist at Brown University in Providence, Rhode Island cautions that this doesn't mean that the backwards retina itself helps us to see. Rather, it emphasises the extent to which evolution has coped with the flawed layout. "The shape, orientation and structure of the Müller cells help the retina to overcome one of the principal shortcomings of its inside-out wiring," says Miller.

The new understanding of the role of Müller cells might find applications in more successful eye transplants and better camera designs, says Ribak. *Journal reference: Physical Review Letters, DOI: 10.1103/physrevlett.104.158102*

The eye was evolution's great invention

THE eye has long been an evolutionary battleground. Ever since William Paley came up with the watchmaker analogy in 1802 - that something as complex as a watch must have a maker - creationists have used it to make the "argument from design". Eyes are so intricate, they say, that it strains belief to suggest they evolved through the selection and accumulation of random mutations.

Recently, evolutionary biologists have turned this argument on its head. They say that the "inside out" vertebrate retina - curiously structured so that its wiring obscures the light sensors and leaves us with a blind spot - can be described as one of evolution's "greatest mistakes".

The anatomy of the retina is indeed good evidence that eyes were cobbled together bit by bit. Surely a creator would never have chosen to construct an eye in this way. In return, creationists have argued that the backwards retina clearly has no problems providing vertebrates with excellent vision - and even that its structure enhances vision.

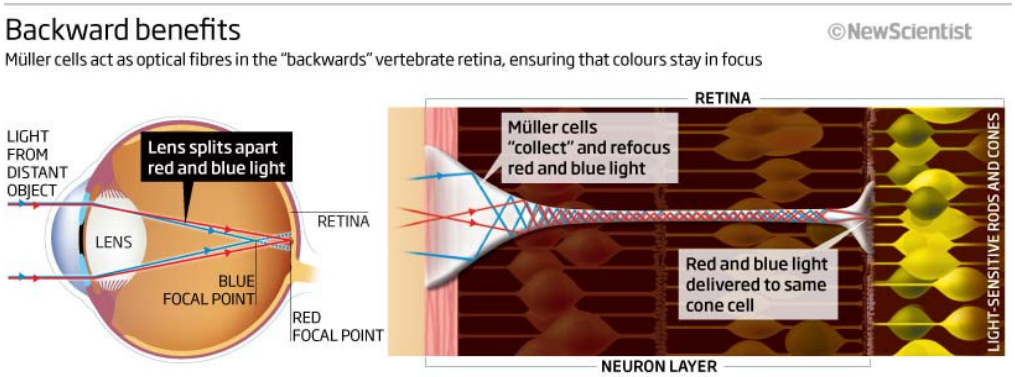
This week, a study by (non-creationist) neurophysicists in Israel has found just that (see "Optical fibre cells transform our weird, 'backward' retinas"). Their simulations showed that Müller cells, which support and

nourish the neurons overlying the retina's light-sensitive layer, also collect, filter and refocus light, before delivering it to the light sensors to make images clearer.

Of course, findings that coincide with the claims of creationists do not mean they have a point - although they may well quote this study. Intelligent design proponents have shown themselves to be adept at speciously quoting peer-reviewed studies that appear to support their claims.

Sure, sending light through Müller cells enhances vision, but that is not an argument for choosing to put the wiring in front of the sensors. It still creates a blind spot, where the nerves dive through the light-sensitive cells on their way to the brain.

It would make much more sense to put Müller-like cells in front of the sensors, with the wiring behind. Rather than provide evidence in support of intelligent design, the new work is actually yet another example of evolution's extraordinary ability to create workaround solutions to problems arising from earlier iterations.



Kenneth Miller, a biologist at Brown University in Providence, Rhode Island, and an untiring veteran of the creation-evolution wars, calls the Müller cells "a retrofit: a successful and highly functional adaptation made necessary by the original architecture of the retina, but a retrofit". The eye's structure, and the blind spot in particular, bears the unmistakable fingerprints of Darwinian evolution.

First cancer vaccine approved for use in people

THE latest weapon in the war on cancer is a patient's own cells. A prostate cancer vaccine that the US Food and Drug Administration rejected in 2007 has now won the regulator's approval, making it the first cancer vaccine to do so.

Provenge, made by Dendreon of Seattle, does not prevent or cure prostate cancer, which killed 27,000 men in the US last year and more than 10,000 in the UK in 2008. Rather, in its largest study yet, the therapy extended the lives of 512 people with aggressive prostate tumours by four months, compared with patients who did not receive it.

Administering Provenge involves harvesting a patient's immune cells and exposing them to a protein produced by prostate tumours. These "primed" cells are then re-injected into the patient, where they attack tumours.

Though modest, the latest result shows that harnessing the immune system is a viable way to fight cancer. Oncologist Philip Kantoff at the Dana-Farber Cancer Institute in Boston led the trial. He expects similar approaches to other cancers, such as melanoma, kidney cancer and lymphoma, to be approved in five to 10 years and that tweaks to Provenge will see it further extend people's lives.

How dark chocolate may guard against brain injury from stroke

Johns Hopkins researchers discover pathway in mice for epicatechin's apparent protective effect

Researchers at Johns Hopkins have discovered that a compound in dark chocolate may protect the brain after a stroke by increasing cellular signals already known to shield nerve cells from damage.

Ninety minutes after feeding mice a single modest dose of epicatechin, a compound found naturally in dark chocolate, the scientists induced an ischemic stroke by essentially cutting off blood supply to the animals' brains. They found that the animals that had preventively ingested the epicatechin suffered significantly less brain damage than the ones that had not been given the compound.

While most treatments against stroke in humans have to be given within a two- to three-hour time window to be effective, epicatechin appeared to limit further neuronal damage when given to mice 3.5 hours after a stroke. Given six hours after a stroke, however, the compound offered no protection to brain cells.

Sylvain Doré, Ph.D., associate professor of anesthesiology and critical care medicine and pharmacology and molecular sciences at the Johns Hopkins University School of Medicine, says his study suggests that epicatechin stimulates two previously well-established pathways known to shield nerve cells in the brain from damage. When the stroke hits, the brain is ready to protect itself because these pathways — Nrf2 and heme oxygenase 1 — are activated. In mice that selectively lacked activity in those pathways, the study found, epicatechin had no significant protective effect and their brain cells died after a stroke.

The study now appears online in the Journal of Cerebral Blood Flow and Metabolism.

Eventually, Doré says, he hopes his research into these pathways could lead to insights into limiting acute stroke damage and possibly protecting against chronic neurological degenerative conditions, such as Alzheimer's disease and other age-related cognitive disorders.

The amount of dark chocolate people would need to consume to benefit from its protective effects remains unclear, since Doré has not studied it in clinical trials. People shouldn't take this research as a free pass to go out and consume large amounts of chocolate, which is high in calories and fat. In fact, people should be reminded to eat a healthy diet with a variety of fruits and vegetables.

Scientists have been intrigued by the potential health benefits of epicatechin by studying the Kuna Indians, a remote population living on islands off the coast of Panama. The islands' residents had a low incidence of cardiovascular disease. Scientists who studied them found nothing striking in the genes and realized that when they moved away from Kuna, they were no longer protected from heart problems. Researchers soon discovered the reason was likely environmental: The residents of Kuna regularly drank a very bitter cocoa drink, with a consistency like molasses, instead of coffee or soda. The drink was high in the compound epicatechin, which is a flavanol, a flavanoid-related compound.

But Doré says his research suggests the amount needed could end up being quite small because the suspected beneficial mechanism is indirect. "Epicatechin itself may not be shielding brain cells from free radical damage directly, but instead, epicatechin, and its metabolites, may be prompting the cells to defend themselves," he suggests. The epicatechin is needed to jump-start the protective pathway that is already present within the cells. "Even a small amount may be sufficient," Doré says.

Not all dark chocolates are created equally, he cautions. Some have more bioactive epicatechin than others.

"The epicatechin found in dark chocolate is extremely sensitive to changes in heat and light" he says. "In the process of making chocolate, you have to make sure you don't destroy it. Only few chocolates have the active ingredient. The fact that it says 'dark chocolate' is not sufficient."

The new study was supported by grants from the National Institutes of Health and the American Heart and Stroke Association. Other Johns Hopkins researchers on the study include Zahoor A. Shah, Ph.D.; Rung-chi Li, Ph.D.; Abdullah S. Ahmad, Ph.D.; Thomas W. Kensler, Ph.D.; and Shyam Biswal, Ph.D.

Neanderthal genome reveals interbreeding with humans

* 19:00 06 May 2010 **by Ewen Callaway**

How closely are Neanderthals related to us?

They are so closely related that some researchers group them and us as a single species. "I would see them as a form of humans that are bit more different than humans are today, but not much," says Svante Pääbo, a palaeogeneticist at the Max Planck Institute in Leipzig, Germany, whose team sequenced the Neanderthal genome.

The common ancestor of humans and Neanderthals lived in Africa around half a million years ago. After that, the ancestors of Neanderthals moved north and eventually made it to Europe and Asia. Our ancestors, meanwhile, stuck around Africa until about 100,000 years ago before eventually conquering the globe. Neanderthals died out around 28,000 years ago.

How did they sequence the Neanderthal genome?

Bone contains DNA that survives long after an animal dies. Over time, though, strands of DNA break up, and microbes with their own DNA invade the bone. Pääbo's team found ways around both problems with 38,000 and 44,000-year-old bones recovered in Croatia: they used a DNA sequencing machine that rapidly decodes short strands and came up with ways to get rid of the microbial contamination.

They ended up with short stretches of DNA code that computers stitched into a more complete sequence. This process isn't perfect: Pääbo's team decoded about 5.3 billion letters of Neanderthal DNA, but much of this is duplicates, because - assuming it's the same size as the human genome - the actual Neanderthal genome is only about 3 billion letters long. More than a third of the genome remains unsequenced. "It's pretty darn good for something that's 38,000 years old," says Edward Green, a team member now at the University of California, Santa Cruz.

What did they find?

Any human whose ancestral group developed outside Africa has a little Neanderthal in them – between 1 and 4 per cent of their genome, Pääbo's team estimates. In other words, humans and Neanderthals had sex and had hybrid offspring. A small amount of that genetic mingling survives in "non-Africans" today: Neanderthals didn't live in Africa, which is why sub-Saharan African populations have no trace of Neanderthal DNA.

It's impossible to know how often humans invited Neanderthals back to their cave (and vice versa), but the genome data offers some intriguing details.

"It must have been at least 45,000 years ago," says David Reich, a geneticist at Harvard Medical School who was involved in the project. That's because all non-Africans – be they from France, China or Papua New Guinea – share the same amount of Neanderthal DNA, suggesting that interbreeding occurred before those populations split. The timing makes the Middle East the likeliest place where humans leaving Africa and resident Neanderthals did the deed.

Does this mean that Neanderthals didn't interbreed with Europeans more recently?

Not necessarily – it's just that earlier interbreeding is more likely to leave a mark on our genomes than more recent trysts, largely because of population expansion. With a more complete Neanderthal genome and DNA from other Neanderthals, it will be possible to find out if Europeans and Asians interbred with Neanderthals after those groups went their separate ways.

Archaeological evidence suggests that humans and Neanderthals overlapped for about 10,000 years in Europe and some fossils have even been interpreted as Neanderthal-human hybrids, though not all palaeoanthropologists agree on this.

Can we trace any human traits back to Neanderthals?

Probably not. Some researchers had hypothesised that some human genes, including one involved in brain development, originated from interbreeding with Neanderthals, but Pääbo's team found no evidence for this. In fact, no Neanderthal DNA sequences are consistently found in humans. "Each person has a different bit of Neanderthal in them," says Reich.

However, Sarah Tishkoff, a geneticist at the University of Pennsylvania in Philadelphia not involved in the project, says it is possible that interbreeding introduced traits into a few human populations. "It will be interesting to look at other ethnic groups and other Neanderthals," she says.

Does the Neanderthal genome explain what makes us different from them?

That is the hope, though this first scan emphasises the overwhelming similarity between humans and Neanderthals. Pääbo's team found just 78 amino acid peculiarities – differences that change the shape and potentially the function of a protein – which all humans have in their genes but Neanderthals didn't. To put that in context, the genome encodes about 10 million amino acids. They also identified more than 200 regions of the human genome that look like they have evolved since we split from Neanderthals.

These changes occurred in genes linked to cognition, skin and bone development, and reproduction, but they don't explain what makes us human, because they occurred after humans split from Neanderthals 500,000 years ago. "There is no compelling story where you say, 'Ah, ah, this difference means this,'" Green says. "'It let us write poetry instead of making stone tools' – there's nothing that jumps out like that."

That means a lot of hard work for researchers, examining the genetic differences between humans and Neanderthals one by one, and in some cases genetically engineering bacteria, mice and other organisms with these genes. "This is really a gold mine for finding recent changes in human evolution," Green says.

Does this mean we could clone a Neanderthal?

No. "Resurrecting" a Neanderthal based on its genome sequence poses a number of scientific and technological problems, not to mention ethical dilemmas. The most straightforward way to bring Neanderthals back to life would be to alter the DNA of a human cell to match that of Neanderthals and then transplant its nucleus into an unfertilised egg and implant it into a surrogate mother, a process called somatic cell nuclear transfer (SCNT). No one has accomplished this feat for humans, and it may not be possible.

Even if we could clone humans, another challenge would be introducing the millions of genetic differences that exist between humans and Neanderthals into a human cell. As it stands, the Neanderthal genome is incomplete and riddled with errors.

More problematic, though, is making many genetic mutations at once instead of one at a time, as is conventionally done. A technology exists to introduce dozens of mutations at a time into bacteria but this doesn't come close to the complexity required to make a Neanderthal.

Journal reference: Science, DOI: 10.1126/science/1188021

Neandertal Genome Study Reveals That We Have a Little Caveman in Us

The sequence shows that Neandertals and modern humans interbred, and that their DNA persists in us

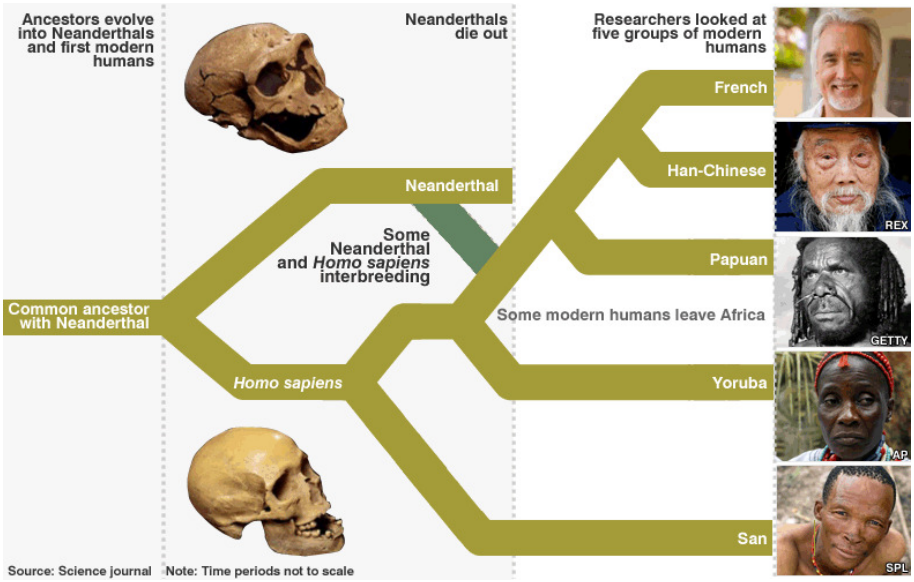
By Kate Wong

Researchers sequencing Neandertal DNA have concluded that between 1 and 4 percent of the DNA of people today who live outside Africa came from Neandertals, the result of interbreeding between Neandertals and early modern humans.

A team of scientists led by Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Leipzig pieced together the first draft of the sequence—which represents about 60 percent of the entire genome—using DNA obtained from three Neandertal bones that come from Vindija cave in Croatia and are more than 38,000 years old. The researchers detail their analysis of the sequence in the May 7 Science.

The evidence that Neandertals contributed DNA to modern humans came as a shock to the investigators. "First I thought it was some kind of statistical fluke," Pääbo remarked during a press teleconference on May 5. "We as a consortium came into this with a very, very strong bias against gene flow," added team member David Reich of Harvard University. But when the researchers conducted additional analyses, the results all pointed to the same conclusion.

Rethinking the Gene Pool



The finding contrasts sharply with Pääbo's previous work. In 1997 he and his colleagues sequenced the first Neandertal mitochondrial DNA . Mitochondria are the cell's energy-generating organelles, and they have their own DNA, which is distinct from the much longer DNA sequence that resides in the cell's nucleus. Their analysis revealed that Neandertals had not made any contributions to modern mitochondrial DNA. Yet because mitochondrial DNA represents only a tiny fraction of an individual's genetic makeup, the possibility remained that Neandertal nuclear DNA might tell a different story. Still, additional genetic analyses have typically led researchers to conclude that Homo sapiens arose in Africa and replaced the archaic humans it encountered as it spread out from its birthplace without mingling with them.

But mingle they apparently did, according to the new study. When Pääbo's team looked at patterns of nuclear genome variation in present-day humans, it identified 12 genome regions where non-Africans exhibited variants that were not seen in Africans and that were thus candidates for being derived from the Neandertals, who lived not in Africa but Eurasia. Comparing those regions with the same regions in the newly assembled Neandertal sequence, the researchers found 10 matches, meaning 10 of these 12 variants in non-Africans came from Neandertals. (Where the other two segments came from remains unknown.)

Intriguingly, the researchers failed to detect a special affinity to Europeans—a link that might have been expected given that Neandertals seem to have persisted in Europe longer than anywhere else before disappearing around 28,000 years ago. Rather, the Neandertal sequence was equally close to sequences from present-day people from France, Papua New Guinea and China, even though no Neandertal specimens have turned up in the latter two parts of the world. By way of explanation, the investigators suggest that the interbreeding occurred in the Middle East between 45,000 and 80,000 years ago, before moderns fanned out to other parts of the Old World and split into different groups.

Bolstering Multiregional Theory?

Intermixing does not surprise paleoanthropologists who have long argued on the basis of fossils that archaic humans, such as the Neandertals in Eurasia and Homo erectus in East Asia, mated with early moderns and can be counted among our ancestors—the so-called multiregional evolution theory of modern human origins. The detection of Neandertal DNA in present-day people thus comes as welcome news to these scientists. "It is important evidence for multiregional evolution," comments Milford H. Wolpoff of the University of Michigan, the leading proponent of the theory.

The new finding shows that "gene flow across taxonomic boundaries happens," observes geneticist Michael F. Hammer of the University of Arizona. Hammer is among the minority of geneticists who have espoused the idea of gene flow between archaic and modern populations. His own studies of the DNA of people living today have uncovered, for example, a stretch of DNA that seems to have come from encounters between moderns and H. erectus.

Some experts suspect that the estimate for the amount of Neandertal DNA people carry today could rise with further studies - if a Neandertal from the Middle East were sequenced, for instance. In addition, says paleoanthropologist John Hawks of the University of Wisconsin, the current study might be obscuring a

contribution of Neandertal genes to the African gene pool, because the team specifically looked to explain genetic diversity in non-Africans compared with Africans. He and his colleagues are currently working on a way to assess that possibility.

Many researchers concur that the results disprove the strict Out of Africa replacement model of modern human origins. In a prepared statement Out of Africa theorist Christopher B. Stringer of the Natural History Museum in London said "although I have never ruled out the possibility of interbreeding, I have considered this to have been small and insignificant in the bigger picture of our evolution— for example, the results of isolated interbreeding events could easily have been lost in the intervening millennia. Now, the Neanderthal genome strongly suggests those genes were not lost, and that many of us outside of Africa have some Neanderthal inheritance." But Stringer maintains that the origin of our species is mostly an Out of Africa story.

Population geneticist Laurent Excoffier of the University of Bern in Switzerland agrees that Out of Africa is still the most plausible model of modern human origins, noting that the alleged admixture did not continue as moderns moved into Europe. "In all scenarios of speciation, there is a time during which two diverging species remain interfertile," he explains.

Other Forebears as Well?

Pääbo, for his part, says that now that his team has shown that early modern humans interbred with one archaic group, he thinks other archaic humans might have passed along genes to us through interbreeding. Whether such contributions might have been beneficial remains unknown, however, although the Neandertal DNA in non-Africans does not seem to encode anything particularly important from a functional standpoint.

In addition to illuminating how Neandertals and moderns interacted, the Neandertal genome is helping researchers to figure out which parts of the modern human genome separate us from all other creatures. "Many traits that distinguish humans from chimps are believed to have evolved more recently than the human–Neanderthal split," observes biostatistician Katherine S. Pollard of the Gladstone Institutes at the University of California, San Francisco. "A Neanderthal genome is a very important step towards determining the genetic basis for these characteristics that define the modern human species."

Thus far, Pääbo's group has identified a number of modern human genome regions containing sequence variation that is not seen in Neandertals and that may have helped modern humans adapt. Some of these regions play a role in cognitive development, sperm movement and the physiology of the skin.

But exactly how these slight changes to the modern human sequence affected the functioning of these genome regions remains to be determined. "A complete understanding of this is really a stepwise process," team member Richard E. Green of the University of California, Santa Cruz, remarked at the press teleconference. "What we have done here is take a really important step forward. We can say exactly what changes happened recently with very high resolution." Says Pääbo: "This is just the beginning of the exploration of human uniqueness that is now possible."

New genes involved in human eye color identified

Three new genetic loci have been identified with involvement in subtle and quantitative variation of human eye colour. The study, led by Manfred Kayser of the Erasmus University Medical Center Rotterdam, The Netherlands, is published May 6 in the open-access journal PLoS Genetics.

Previous studies on the genetics of human eye colour used broadly-categorized trait information such as 'blue', 'green', and 'brown'; however, variation in eye colour exists in a continuous grading from the lightest blue to the darkest brown. In this genome-wide association study, the eye colour of about 6000 Dutch Europeans from the Rotterdam Study was digitally quantified using high-resolution full-eye photographs. This quantitative approach, which is cost-effective, portable, and time efficient, revealed that human eye colour varies along more dimensions than are represented by the colour categories used previously.

The researchers identified three new loci significantly associated with quantitative eye colour. One of these, the LYST gene, was previously considered a pigmentation gene in mice and cattle, whereas the other two had no previous association with pigmentation.

These three genes, together with previously identified ones, explained over 50% of eye colour variance, representing the highest accuracy achieved so far in genomic prediction of complex and quantitative human traits.

"These findings are also of relevance for future forensic applications", said Kayser, "where appearance prediction from biological material found at crime scenes may provide investigative leads to trace unknown persons".

***CITATION**: Liu F, Wollstein A, Hysi PG, Ankra-Badu GA, Spector TD, et al. (2010) Digital Quantification of Human Eye Color Highlights Genetic Association of Three New Loci. PLoS Genet 6(5): e1000934. doi:10.1371/journal.pgen.1000934*

Hand-washing wipes emotional baggage from decisions

* 13:32 07 May 2010 **by Wendy Zukerman**

Long a metaphor for the desire to distance oneself from immoral acts, hand washing doesn't just wipe the conscience clean – it also changes how an individual regards a decision they have just made.

Lady Macbeth notwithstanding, the physical act of washing one's hands is known to ease the guilt we feel about past unethical deeds. Now it seems that the act also removes our natural inclination to validate even trivial past decisions.

It is known that after people have made a decision – be it a big one such as choosing which politician to vote for or a trivial one such as which CD to buy – they tend to exaggerate its benefits. They also overplay the potential downsides of options they rejected.

"People focus on the positive features of their choice and the negative features of the rejected option," says Spike Lee at the University of Michigan, Ann Arbor. "As a consequence, they come to like the choice they made better."

Soap test

To see whether hand-washing affects this justification process, Lee first asked 40 students to rank 10 CDs by how much they liked them. He then asked them to choose between owning either their fifth or sixth-ranked CD.

Next he asked half the volunteers to evaluate the quality of a liquid soap by washing their hands and the other half to examine the soap by observation only. Then, all students ranked the original 10 CDs again.

Lee's team found that, in the second CD ranking, those who had not washed their hands increased the ranking of the CD they had chosen to keep – which had originally been either their fifth or sixth choice – by two places compared with its original ranking, and pushed the rejected CD down by two places, on average.

This was a sign that they were justifying their choice of which CD to keep, says Lee; the expected pattern of behaviour.

But for those who washed their hands before ranking the CDs for a second time, the order tended not to change. In other words, their choice of which CD to keep did not change the way that they went on to rank that CD, when given a second chance to do so.

Washing away enjoyment

When the researchers repeated the same experiment using choices of jam instead of CDs, and antiseptic wipes instead of soap, the results were the same. They conclude that the hand washing removes the usual tendency to justify a decision that has already been made.

On one hand, Lee says, this is a more rational way of thinking. But there's also a catch. "Justification has a purpose, it makes people feel good. Washing away the need to justify past decisions also washes away the cognitive good." It's possible that those who washed their hands won't enjoy the CD or jam as much as their unwashed counterparts will, he says.

Katie Liljenquist of Brigham Young University in Provo, Utah, who first demonstrated that hand-washing changes psychological behaviour, calls this "exciting work".

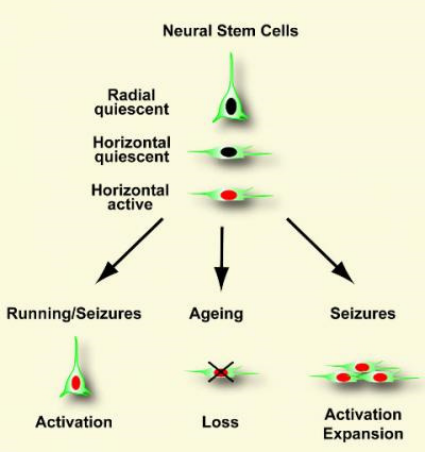
It shows that daily tasks can have profound effects on our psychology in more ways than we knew, she says. "And it's fun to see how metaphors in daily life, such as wiping the slate clean, can typify human behaviour."

Journal reference: Science, DOI: 10.1126/science.1186799

New nerve cells -- even in old age

After birth the brain looses many nerve cells and this continues throughout life – most neurons are formed before birth, after which many excess neurons degenerate. However, there are some cells that are still capable of division in old age – in the brains of mice, at least. According to scientists from the Max Planck Institute of Immunobiology in Freiburg, different types of neuronal stem cells exist that can create new neurons. While they divide continuously and create new neurons in young animals, a large proportion of the cells in older animals persist in a state of dormancy.

However, the production of new cells can be reactivated, for example, through physical activity or epileptic seizures. What happens in mice could also be applicable to humans as neurons that are capable of dividing also occur in the human brain into adulthood. *(Cell Stem Cell, May 7th 2010)*



This illustration shows different types of stem cells in the brains of mature mice. **Verdon Taylor, Max Planck Institute of Immunobiology**

You can't teach an old dog new tricks. The corresponding view that the brain loses learning and memory capacity with advancing age prevailed for a long time. However, neuronal stem cells exist in the hippocampus –

a region of the brain that plays a central role in learning and memory functions – that can produce new nerve cells throughout life. It is known from tests on mice that the newly formed cells are integrated into the existing networks and play an important role in the learning capacity of animals. Nonetheless, the formation of new cells declines with age and the reasons for this were unknown up to now.

Together with colleagues from Dresden and Munich, the Freiburg researchers have now succeeded in explaining for the first time why fewer new neurons are formed in the adult mouse brain. They managed to identify different populations of neuronal stem cells, thereby demonstrating that the hippocampus has active and dormant or inactive neuronal stem cells. "In young mice, the stem cells divide four times more frequently than in older animals. However, the number of cells in older animals is only slightly lower. Therefore, neuronal stem cells do not disappear with age but are kept in reserve," explains Verdon Taylor from the Max Planck Institute of Immunobiology.

The precise factors that influence the reactivation of dormant stem cells are not yet clear. The cells can, however, be stimulated to divide again. The scientists observed more newborn hippocampal neurons in physically active mice than in their inactive counterparts. "Consequently, running promotes the formation of new neurons," says Verdon Taylor. Pathological brain activity, for example that which occurs during epileptic seizures, also triggers the division of the neuronal stem cells.

Horizontal and radial stem cells

The different stem cell populations are easy to distinguish under the microscope. The first group comprises cells which lie perpendicular to the surface of the hippocampus. Most of these radial stem cells are dormant. As opposed to this, over 80% of the cells in the group of horizontal stem cells - cells whose orientation runs parallel to the hippocampus surface - continuously form new cells; the remaining 20% are dormant but sporadically become activated. The activity of genes such as Notch, RBP-J and Sox2 is common to all of the cells.

Radial and horizontal stem cells differ not only in their arrangement, apparently they also react to different stimuli. When the animals are physically active, some radial stem cells abandon their dormant state and begin to divide, while this has little influence on the horizontal stem cells. The result is that more radial stem cells divide in active mice. The horizontal stem cells, in contrast, are also influenced by epileptic seizures.

It would appear that neuronal stem cells are not only found in the brains of mice. The presence of neurons that are formed over the course of life has also been demonstrated in the human hippocampus. Therefore, scientists suspect that different types of active and inactive stem cells also arise in the human brain. It is possible that inactive stem cells in humans can also be activated in a similar way to inactive stem cells in mice. "There are indicators that the excessive formation of new neurons plays a role in epilepsy. The use of neuronal brain stem cells in the treatment of brain injuries or degenerative diseases like Alzheimers may also be possible one day," hopes Verdon Taylor.

Quiescent and active hippocampal neural stem cells with distinct morphologies respond selectively to physiological and pathological stimuli and ageing *Sebastian Lugert, Onur Basak, Philip Knuckles, Ute Haussler, Klaus Fabel, Magdalena Götz, Carola A. Haas, Gerd Kempermann, Verdon Taylor, Claudio Giachino Cell Stem Cell, May 7th 2010*

New atherosclerosis vaccine gives promising results

A new study by researchers at the Swedish medical university Karolinska Institutet shows that the immune defence's T cells can attack the "bad" LDL cholesterol and thereby cause an inflammation that leads to atherosclerosis. By producing a vaccine against the T cell receptors, the researchers have managed to inhibit the development of atherosclerosis in animals. The study is presented online in the distinguished periodical Journal of Experimental Medicine and is expected to be of considerable significance to the future treatment of atherosclerosis, heart attack and stroke.

Cholesterol is transported in the blood in LDL particles, which are a kind of fat drops that can accumulate in the walls of blood vessels. LDL activates the immune defence and triggers an inflammation in the blood vessels that leads to atherosclerosis (also known as arteriosclerosis). When the atherosclerotic plaque finally ruptures, a blood clot is formed that in turn can cause a heart attack or stroke.

It was previously thought that the inflammation in the blood vessels arises when the T cells react to oxidised LDL particles located in the atherosclerotic plaque. Now, however, the team at Karolinska Institutet has found that the opposite is true, namely that the T cells react to components in the normal LDL particles, and that they no longer recognise LDL once it has been oxidised.

"Since reactions to LDL can be dangerous, T cells are normally held in check by inhibitory signals," says Professor Göran K Hansson, who led the study. "The body's own control works well as long as the LDL keeps to the blood, liver and lymph glands. But when it accumulates in the artery wall, this inhibition is no longer enough, the T cells are activated and an inflammation arises."

Together with his research group at Karolinska Institutet he now presents a new principle for inhibiting atherosclerosis. Vaccination against the receptor that the T cells use to recognise LDL can block the immune reaction and reduce the disease by between 60 and 70 per cent. The vaccine has been successfully tested on animals and the researchers are now hoping to see if it can be developed into a treatment for patients with a high risk of myocardial infarction and stroke.

The researchers also now believe that their results explain why antioxidants are ineffective against cardiovascular disease when they have been tested in large clinical studies.

"If one takes antioxidants, one simply prevents the oxidation of LDL," says Professor Hansson. "It retains its ability to activate the T cells, and so the inflammation in the blood vessels can increase. This could give the opposite results to what one was hoping for."

Göran K Hansson is professor of experimental cardiovascular science at the Department of Medicine, Solna, Karolinska Institutet. He and his group work at the Center for Molecular Medicine at Karolinska University Hospital, Solna.
Publication: "Inhibition of T cell response to native low-density lipoprotein reduces atherosclerosis", Andreas Hermansson, Daniel F.J. Ketelhuth, Daniela Strodthoff, Marion Wurm, Emil M. Hansson, Antonino Nicoletti, Gabrielle Paulsson-Berne & Göran K. Hansson, Journal of Experimental Medicine, online 3 May 2010, doi: 10.1084/jem.20092243.
Read the abstract: http://jem.rupress.org/content/early/2010/04/28/jem.20092243

Shape up the quick way

Lose weight fast for lasting results suggests new study

If you thought the best way to lose and maintain weight was the slow and steady approach, think again. A new study by Lisa Nackers and colleagues, from the University of Florida in the US, suggests that the key to long-term weight loss and maintenance is to lose weight quickly, not gradually, in the initial stages of obesity treatment. Their findings1 are published online in Springer's International Journal of Behavioral Medicine.

Successful weight loss in obese individuals is defined as a reduction of 10 percent or more of initial body weight maintained for at least a year. The jury is still out, however, as to whether fast or slow initial weight loss is the best approach for long-term weight control in obese patients. On the one hand, there is evidence that losing weight slowly initially results in continued weight loss, reduced risk of weight regain, and successful long-term weight loss maintenance. On the other hand, it has also been shown that the greater the initial weight loss in obese patients, the larger the total weight loss observed longer term.

Nackers and team's study examines the association between rate of initial weight loss and long-term maintenance of lost weight, by looking specifically at whether losing weight at a slow initial rate results in larger long-term weight reduction and less weight regain than losing weight at a fast initial rate.

The authors analyzed data for 262 middle-aged obese women who took part in the Treatment of Obesity in Underserved Rural Settings (TOURS) trial. These women followed a six-month lifestyle program encouraging them to reduce their calorie intake and increase their moderate intensity physical activity to achieve an average weight loss of 0.45kg per week. They were then supported for a further year with an extended care program involving contact twice a month in the form of group sessions, telephone contact or newsletters.

Nackers and team split the women into three groups according to how much weight they lost in the first month of the intervention. Women in the FAST group lost over 0.68kg per week; those in the MODERATE group lost between 0.23 and 0.68kg per week; women in the SLOW group lost less than 0.23kg per week in that first month. The authors then looked at the womens' weight loss at 6 and 18 months, as well as any weight regain.

They found that there were long-term advantages to fast initial weight loss. Fast weight losers lost more weight overall, maintained their weight loss for longer and were not more likely to put weight back on than the more gradual weight losers. In particular, women in the FAST group were five times more likely to achieve the clinically significant 10 percent weight loss at 18 months than those in the SLOW group and those in the MODERATE group were nearly three times more likely to achieve this milestone than women in the SLOW group.

The authors conclude: "Our study provides further evidence that, within the context of lifestyle treatment, losing weight at a fast initial rate leads to greater short-term weight reductions, does not result in increased susceptibility to weight regain, and is associated with larger weight losses and overall long-term success in weight management. We suggest that, within lifestyle weight control programs, substantial efforts should be focused on promoting large rather than small behavioral changes during the initial weeks of treatment."

Reference: *1. Nackers LM et al (2010). The association between rate of initial weight loss and long-term success in obesity treatment: does slow and steady win the race? International Journal of Behavioral Medicine, DOI 10.1007/s12529-010-9092-y*

Cosmic 'dandruff' may have brought carbon to Earth

* 19:00 06 May 2010 **by David Shiga**

Fluffy specks of carbon-rich dust found in Antarctic snow seem to be relics from the dawn of the solar system, when the planets were still forming. The cosmic dandruff could help explain how the carbon needed for life wound up on Earth.

Researchers led by Jean Duprat of the University of Paris-South in Orsay, France, melted Antarctic snow and filtered particles from the resulting water, turning up two extraterrestrial dust particles.

The particles are relatively large, at 80 and 275 micrometres across. They also carry a lot of deuterium, a heavy isotope of hydrogen: they have 10 to 30 times as much as typical terrestrial materials. At cold temperatures, deuterium atoms are incorporated into solid materials more readily than hydrogen atoms are, suggesting the particles formed in the frigid outer reaches of the cloud of gas and dust that gave rise to our solar system.

Carbon snow

The fluff-balls are also extremely rich in carbon. In one of the dust grains, carbonaceous material accounts for 48 per cent of the area analysed so far, while it makes up 85 per cent of the area studied in the other dust grain – an amount as high as any particle of interplanetary dust studied before.

Carbon is a crucial element for the development of life as we know it, and Earth's supply of it must have had an extraterrestrial source. That's because temperatures at Earth's orbital distance from the sun were too warm for solid carbon to condense out of the solar system's natal cloud.

Some of the carbon may have rained down from space in particles like those found in Antarctica, says Donald Brownlee of the University of Washington in Seattle, who was not involved in the study. The particles were likely sloughed off by comets that wandered into the inner solar system.

Comets probably delivered a "significant fraction" of Earth's carbon, Brownlee told New Scientist.

Mix and match

Fragments of the fluffy particles may have come from asteroids, too. That could explain micrometre-sized grains rich in deuterium that had previously been found in some meteorites, Duprat and his colleagues say.

The particles also provide new evidence that material in the inner and outer regions of the solar system's birth cloud mixed together early on. That's because some minerals inside the particles had to be forged at high temperatures. They probably formed near the sun before migrating outwards to be incorporated into the dust grains, the team says. High-temperature minerals were previously found in comet material collected by NASA's Stardust mission. *Journal reference: Science (vol 328, p 742-745)*

Lack of sleep 'poses death risk'

Getting less than six hours sleep a night can lead to an early grave, UK and Italian researchers have warned.

They said people regularly having such little sleep were 12% more likely to die over a 25-year period than those who got an "ideal" six to eight hours. They also found an association between sleeping for more than nine hours and early death, although that much sleep may merely be a marker of ill health.

Sleep journal reports the findings, based on 1.5m people in 16 studies. The study looked at the relationship between sleep and mortality by reviewing earlier studies from the UK, US and European and East Asian countries. Premature death from all causes was linked to getting either too little or too much sleep outside of the "ideal" six to eight hours per night. But while a lack of sleep may be a direct cause of ill health, ultimately leading to an earlier death, too much sleep may merely be a marker of ill health already, the UK and Italian researchers believe.

Time pressures

Professor Francesco Cappuccio, leader of the Sleep, Health and Society Programme at the UK's University of Warwick, said: "Modern society has seen a gradual reduction in the average amount of sleep people take and this pattern is more common amongst full-time workers, suggesting that it may be due to societal pressures for longer working hours and more shift-work. "On the other hand, the deterioration of our health status is often accompanied by an extension of our sleeping time."

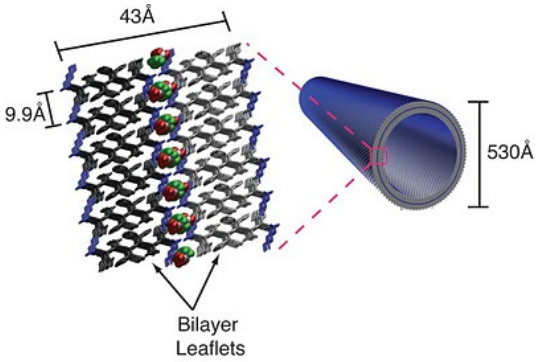
If the link between a lack of sleep and death is truly causal, it would equate to over 6.3 million attributable deaths in the UK in people over 16 years of age.

Prof Cappuccio said more work was needed to understand exactly why sleep seemed to be so important for good health.

Professor Jim Horne, of the Loughborough Sleep Research Centre, said other factors may be involved rather than sleep per se. "Sleep is just a litmus paper to physical and mental health. Sleep is affected by many diseases and conditions, including depression," he said. And getting improved sleep may not make someone better or live longer, he said. "But having less than five hours a night suggests something is probably not right.

"Five hours is insufficient for most people and being drowsy in the day increases your risk of having an accident if driving or operating dangerous machinery."

Peptides may hold 'missing link' to life



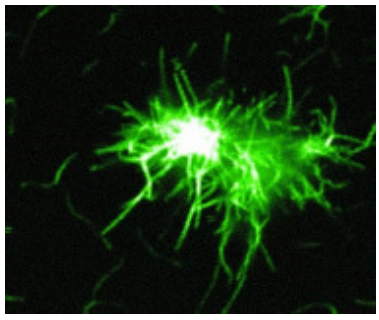
Emory scientists have discovered that simple peptides can organize into bi-layer membranes. The finding suggests a "missing link" between the pre-biotic Earth's chemical inventory and the organizational scaffolding essential to life.

"We've shown that peptides can form the kind of membranes needed to create long-range order," says chemistry graduate student Seth Childers, lead author of the paper recently published by the German Chemical Society's Angewandte Chemie. "What's also interesting is that these peptide membranes may have the potential to function in a complex way, like a protein."

Chemistry graduate student Yan Liang captured images of the peptides as they aggregated into molten globular structures, and self-assembled into bi-layer membranes. The results of that experiment were recently published by the Journal of the American Chemical Society.

"In order to form nuclei, which become the templates for growth, the peptides first repel water," says Liang, who is now an Emory post-doctoral fellow in neuroscience. "Once the peptides form the template, we can now see how they assemble from the outer edges."

In addition to providing clues to the origins of life, the findings may shed light on protein assemblies related to Alzheimer's disease, Type 2 diabetes, and dozens of other serious ailments.

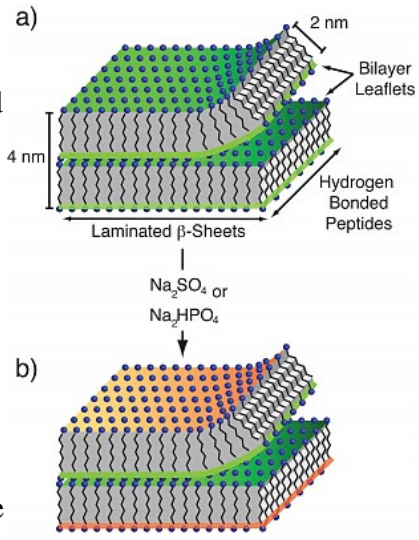


"This is a boon to our understanding of large, structural assemblies of molecules," says Chemistry Chair David Lynn, who helped lead the effort behind both papers, which were collaborations of the departments of chemistry, biology and physics. "We've proved that peptides can organize as bi-layers, and we've generated the first, real-time imaging of the self-assembly process. We can actually watch in real-time as these nano-machines make themselves."

Click here to watch the movies.

The ability to organize things within compartments and along surfaces underpins all of biology. From the bi-layer phospholipids of cell membranes to information-rich DNA helices, self-assembling arrays define the architecture of life. But while phospholipids and DNA are complicated molecules, peptides are composed of the simple amino acids that make up proteins. The Miller-Urey experiment demonstrated in 1953 that amino acids were likely to be present on the pre-biotic Earth, opening the question of whether simple peptides could achieve supra-molecular order.

To test how the hollow, tubular structure of peptides is organized, the researchers used specialized solid-state nuclear magnetic resonance (NMR) methods that have been developed at Emory during the past decade.



Working with Anil Mehta, a chemistry post-doctoral fellow, Childers tagged one end of peptide chains with an NMR label, and then allowed them to assemble to see if the ends would interact. The result was a bi-layer membrane with inner and outer faces and an additional, buried layer that localized functionality within the interior.

"The peptide membranes combine the long-range structure of cell membranes with the local order of enzymes," Childers said. "Now that we understand that peptide membranes are organized locally like a protein, we want to investigate whether they can function like a protein."

The goal is to direct molecules to perform as catalysts and create long-range order. "We'd really like to understand how to build something from the bottom up," Childers says. "How can we take atoms and make molecules? How can we get molecules that stick together to make nano-machines that will perform specific tasks?"

The research is part of "The Center for Chemical Evolution," a center based at Emory and Georgia Tech, for integrated research, education and public outreach focused on the chemistry that may have led to the origin of life. The National Science Foundation and the U.S. Department of Energy have funded the research.

Many groups studying the origins of life have focused on RNA, which is believed to have pre-dated living cells. But RNA is a much more complicated molecule than a peptide. “Our studies have now shown that, if you just add water, simple peptides access both the physical properties and the long-range molecular order that is critical to the origins of chemical evolution,” Childers says.

Endometrial stem cells restore brain dopamine levels

Mouse study may lead to new therapies for Parkinson's Disease

Endometrial stem cells injected into the brains of mice with a laboratory-induced form of Parkinson's disease appeared to take over the functioning of brain cells eradicated by the disease.

The finding raises the possibility that women with Parkinson's disease could serve as their own stem cell donors. Similarly, because endometrial stem cells are readily available and easy to collect, banks of endometrial stem cells could be stored for men and women with Parkinson's disease.

"These early results are encouraging," said Alan E. Guttmacher, M.D., acting director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the NIH Institute that funded the study. "Endometrial stem cells are widely available, easy to access and appear to take on the characteristics of nervous system tissue readily."

Parkinson's disease results from a loss of brain cells that produce the chemical messenger dopamine, which aids the transmission of brain signals that coordinate movement.

This is the first time that researchers have successfully transplanted stem cells derived from the endometrium, or the lining of the uterus, into another kind of tissue (the brain) and shown that these cells can develop into cells with the properties of that tissue. The findings appear online in the Journal of Cellular and Molecular Medicine. The study's authors were Erin F. Wolff, Xiao-Bing Gao, Katherine V. Yao, Zane B. Andrews, Hongling Du, John D. Elsworth and Hugh S. Taylor, all of Yale University School of Medicine.

Stem cells retain the capacity to develop into a range of cell types with specific functions. They have been derived from umbilical cord blood, bone marrow, embryonic tissue, and from other tissues with an inherent capacity to develop into specialized cells. Because of their ability to divide into new cells and to develop into a variety of cell types, stem cells are considered promising for the treatment of many diseases in which the body's own cells are damaged or depleted.

In the current study, the researchers generated stem cells using endometrial tissue obtained from nine women who did not have Parkinson's disease and verified that, in laboratory cultures, the unspecialized endometrial stem cells could be transformed into dopamine-producing nerve cells like those in the brain.

The researchers also demonstrated that, when injected directly into the brains of mice with a Parkinson's-like condition, endometrial stem cells would develop into dopamine-producing cells.

Unspecialized stem cells from the endometrial tissue were injected into mouse striatum, a structure deep in the brain that plays a vital role in coordinating balance and movement. When the researchers examined the animals' striata five weeks later, they found that the stem cells had populated the striatum and an adjacent brain region, the substantia nigra. The substantia nigra produces abnormally low levels of dopamine in human Parkinson's disease and the mouse version of the disorder. The researchers confirmed that the stem cells that had migrated to the substantia nigra became dopamine-producing nerve cells and that the animals' dopamine levels were partially restored.

The study did not examine the longer-term effects of the stem cell transplants or evaluate any changes in the ability of the mice to move. The researchers noted that additional research would need to be conducted to evaluate the safety and efficacy of the technique before it could be approved for human use.

According to the researchers, stem cells derived from endometrial tissue appear to be less likely to be rejected than are stem cells from other sources. As expected, the stem cells generated dopamine producing cells when transplanted into the brains of mice with compromised immune systems. However, the transplants also successfully gave rise to dopamine producing cells in the brains of mice with normal immune systems.

According to Dr. Taylor, because women could provide their own donor tissue, there would be no concern that their bodies would reject the implants. Moreover, because endometrial tissue is widely available, banks of stem cells could be established. The stem cells could be matched by tissue type to male recipients with Parkinson's to minimize the chances of rejection.

In addition, Dr. Taylor added that endometrial stem cells might prove to be easier to obtain and easier to use than many other types of stem cells. With each menstrual cycle, women generate new endometrial tissue every month, so the stem cells are readily available. Even after menopause, women taking estrogen supplements are capable of generating new endometrial tissue. Because doctors can gather samples of the endometrial lining in a simple office procedure, it is also easier to collect than other types of adult stem cells, such as those from bone marrow, which must be collected surgically.

"Endometrial tissue is probably the most readily available, safest, most easily attainable source of stem cells that is currently available. We hope the cells we derived are the first of many types that will be used to treat a variety of diseases," said senior author Hugh S. Taylor, M.D., of Yale University. "I think this is just the tip of the iceberg for what we will be able to do with these cells."

Unlike CT, standard X-rays don't detect the majority of pelvic injuries, study suggests

Computed tomography (CT) scans are superior to standard radiography (X-rays) for the detection of pelvic fractures, according to a study to be presented at the ARRS 2010 Annual Meeting in San Diego, CA. CT scanning combines special X-ray equipment with sophisticated computers to produce multiple images of pictures of the inside of the body.

The study, performed at Allegheny General Hospital in Pittsburgh, PA, included 132 patients with pelvic fractures who were evaluated using standard X-rays (with special views to detect pelvic fractures) and CT. "Based on the results of our retrospective study, pelvic X-rays, especially special views, failed to identify 48 percent of pelvic injuries and also failed to add any significant value to patient care," said Zulfiqar Ali, MD, lead author of the study.

"Most orthopedic surgeons order special, additional X-ray views after a CT scan has been performed and a diagnosis confirmed. We recommend that these additional views be eliminated since pelvic CT, with multi-planar and three dimensional reconstructed images, is sufficient for complete evaluation of suspected pelvic injuries," said Ali.

"Eliminating these extra pelvic X-rays altogether in cases of suspected pelvic injury can reduce the overall radiation dose to patients; reduce patient discomfort and pain by eliminating unnecessary movements in an injured patient; reduce cost; and ultimately provide faster service to patients," he said.

This study will be presented on Friday, May 7 at 11:40 a.m. Pacific Time. For a copy of the abstract or to schedule an interview with Dr. Strickland, please contact Heather Curry via E-MAIL at hcurry@acr-arrs.org.

Gender-specific disease risks start in the womb

Disease risk in later life differs for women and men -- scientists at the Power of Programming Conference present evidence to demonstrate this may start in the womb

Pregnancy places competing demands on a mother's physiology: Her body wants to produce a strong healthy baby but not at the expense of her own health. Some of the genes that she passes on to her child therefore try to protect her own body from excessive demands from her child. These so-called "imprinted genes" inherited from the father however do not show the same restraint – their goal is to get as many resources for the fetus as possible. Evidence that this battle of the imprinted genes might be at the root of later life disease processes will be presented at the International Conference The Power of Programming in Munich on 6 to 8 May, organised by the EC-funded Early Nutrition Programming Project (EARNEST).

"The imprinted genes derived from the father are greedy whilst those from the mother are conservative in their needs to ensure future reproductive success", said Dr. Miguel Constancia from the University of Cambridge, England. "We have found evidence that imprinted genes play important roles in the control of endocrine functions of the placenta. These placental adaptations have marked effects on nutrient delivery to the fetus, resulting in the programming of homeostatic mechanisms with metabolic consequences extending to adulthood, for example for type 2 diabetes susceptibility."

There is evidence that some programming effects are different in male and female offspring. Dr. Rachel Dakin from the University of Edinburgh, Scotland, shows how maternal obesity is associated with sex-specific programming effects in young adult mice. Female offspring of obese mothers had raised blood insulin levels, whilst male offspring did not. Male offspring did have alterations in the expression of liver genes important in lipid and glucocorticoid metabolism.

Professor Claudine Junien from the Institut National de Recherche Agronomique (INRA) in France says: "For me a gene, a cell and even a sex does not think and has no intelligent design. Instead it reacts to diverse environments and situations according to what its build-up can afford, pushing in one direction or another (or several at a time). The limits to which it can go without going awry or dying have been established progressively throughout the slow and long process of evolution, with different genetic backgrounds throughout the world depending on the diversity of experiences over the ages.

We have data showing that gene expression and DNA methylation are sexually dimorphic in male and female placentae under normal/control conditions. Surprisingly, in stressful conditions, such as a high fat diet or low calorie diet, or maternal overweight/obesity - the male and female placentae do not use the same strategies: they use different gene pathways and networks to cope with the stress.

Does this directly lead to different outcomes? It may lead to sex-dependent differences in the outcome of programming with long lasting effects. Alternatively, it may be that metaphorically speaking males climb the

mountain taking the north face while females take the south face - but they ultimately reach the same peak after using these different paths."

Professor Ricardo Closa Monasterolo from the University Rovira I Virgili of Tarragona, Italy, presents work that suggested that infant boys and girls might have different responses to lower or higher protein diets. Females given higher protein formula milk had higher IGF-1 levels than males, whilst males showed higher C-peptide/creatinine levels compared to females. The significance of lower or higher protein diets has also been examined in the EU Childhood Obesity Project (CHOP) co-ordinated by Professor Berthold Koletzko of Ludwig-Maximilians-Universität (LMU) in Munich. Starting in 1990, over 1,000 infants were followed. The first results show that, after 2 years, the infants fed a formula milk with a lower protein content – closer to the composition of breast milk - weighed significantly less than those on higher protein formula, with their weights being more similar to those of breast fed infants. These differences emerged by 6 months of age and persisted, even after the intervention ceased and the children went onto similar diets. The researchers predict that these low protein induced differences in early growth would reduce obesity at 14 to 16 years of age by 13%.

Koletzko, who is also the Co-ordinator of the EARNEST project said, "This is a new and exciting area of research which suggests that some of the differences in disease risk seen in men and women in later life might be explained by different responses to programming effects in early life."

UT Southwestern researchers uncover Fragile X syndrome gene's role in shaping brain

DALLAS - Researchers at UT Southwestern Medical Center have discovered how the genetic mutation that causes Fragile X syndrome, the most common form of inherited mental retardation, interferes with the "pruning" of nerve connections in the brain. Their findings appear in the April 29 issue of Neuron.

Soon after birth, the still-developing brain of a mammal produces too many nerve connections that create "noise" in the nervous system. The brain finds it hard to process these signals, like a person trying to have a conversation at a loud party. But as the brain matures and learning takes place, some nerve connections naturally become stronger while others weaken and die, leading to an adult with a properly wired brain.

Fragile X is caused by a mutation in a single gene, Fmr1, on the X chromosome. The gene codes for a protein called FMRP, which plays a role in learning and memory but whose full function is unknown. The protein's role in pruning nerve connections had been unclear.

"I think we've uncovered a core function for the gene involved in this disease, and if we can find other biochemical methods involved in nerve pruning, we might be able to help correct this," said Dr. Kimberly Huber, associate professor of neuroscience at UT Southwestern and senior author of the study.

In the current study, Dr. Huber and her colleagues examined nerve cells isolated from mice that had been engineered to lack the Fmr1 gene and, therefore, did not produce FMRP protein. They then tested whether the lack of FMRP affected the functions of another protein called MEF2, which is known to be involved in pruning nerve connections. The researchers found that nerve cells lacking FMRP were unable to respond to MEF2. Adding FMRP to the cells restored MEF2's normal function.

"We were massively activating the MEF2 gene in the cell, and it did absolutely nothing without FMRP," Dr. Huber said. Such an all-or-nothing requirement in a biochemical relationship is rare, she said.

The findings also raise questions about how the two proteins interact physically. MEF2 works in the nucleus of a cell, where it controls whether other genes are turned on or off. FMRP shuttles in and out of the cell's nucleus and into its main body.

"This opens up new ideas about how processes in the cell's nucleus, near its DNA, can affect the nerve connections, which are very far away at the other end of the cell," Dr. Huber said. "We think MEF2 is making messenger RNA [ribonucleic acid], which translates the genetic code of the DNA, and FMRP is binding to the RNA and either transporting it to the nerve connections and/or controlling how the RNA makes protein."

Further research will focus on the relationship between the proteins. For instance, one might directly control the other, or they might work together on a common target, Dr. Huber said.

"This work might not have clinical implications for quite a while," she said. "The goal for us as scientists is to understand how these genes relate to mechanisms that control the development of nerve connections."

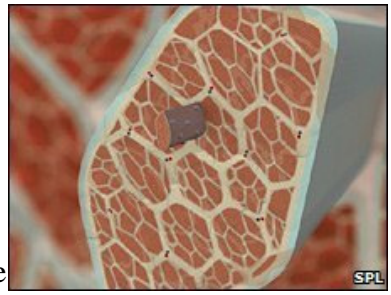
Like other genetic diseases carried on the X chromosome, Fragile X syndrome strikes boys more often and more severely than girls. Girls have two X chromosomes, so a normal gene on one chromosome can mitigate the effects of the disease if the gene on the other X chromosome is abnormal. Boys, however, have only one X chromosome, so if they inherit an abnormal gene on the X chromosome, they have no protection.

Other UT Southwestern researchers involved in the study were lead author and former graduate student Brad Pfeiffer; Dr. Tong Zang, postdoctoral researcher in neuroscience; Dr. Julia Wilkerson, postdoctoral researcher in neuroscience; Dr. Makoto Taniguchi, postdoctoral researcher in psychiatry; Marina Maksimova, research assistant in neuroscience; Dr. Laura Smith, postdoctoral researcher in psychiatry; and Dr. Christopher Cowan, assistant professor of psychiatry.

The study was funded by the National Institutes of Health, Autism Speaks, the Whitehall Foundation and Simons Foundation.
This news release is available on our World Wide Web home page at http://www.utsouthwestern.edu/home/news/index.html

Novel material 'mimics muscles'

Scientists have created an artificial material that mimics the tough, stretchy properties of muscle.



The material mimics the elastic properties of muscle

The material could find a potential application as a "scaffold" to aid muscle regeneration.

Researchers engineered a polymer to reproduce the properties of titin - a protein which largely determines the elastic properties of muscle. The work, by a US-Canadian team of researchers, is reported in the latest issue of the journal Nature

"A hallmark of titin-like proteins is that they unfold under a stretching force to dissipate energy and prevent damage to tissues by over-stretching," said co-author John Gosline from the University of British Columbia in Canada. "We've been able to replicate one of the more unique characteristics exhibited by muscle tissues, but not all of them."

Scientists cross-linked the polymers to form a solid, rubber-like material.

The authors suggest that the properties of this material could even be fine-tuned to resemble specific types of muscle by adjusting the compositions of the proteins.

Initially, the discovery could assist in the healing of tissue tears, acting as a tough stretchy scaffold that allows new tissue to grow across the wound. But scientists will have to test whether the material is compatible with human tissue.

Even silent videos excite the listening brain

IS A sound only a sound if someone hears it? Apparently not. Silent videos that merely imply sound - such as of someone playing a musical instrument - still get processed by auditory regions of the brain.

Kaspar Meyer at the University of Southern California in Los Angeles and colleagues showed eight volunteers nine silent video clips that implied sound, including people playing violins, a dog howling and chainsaws cutting into trees. As they watched, their brains were scanned using functional MRI.

Each type of implied sound created a unique pattern of brain activity in the "early auditory cortices" - regions thought to be devoted to the initial processing of sounds. After noting these patterns in a several of the volunteers, the researchers were able to predict which type of video other volunteers had watched, just from the activity in the auditory cortices (Nature Neuroscience, DOI: 10.1038/nn.2533). The volunteers also reported imagining the sounds as they watched the videos.

The results broaden the role of regions previously thought only to be involved in initial sensory processing.