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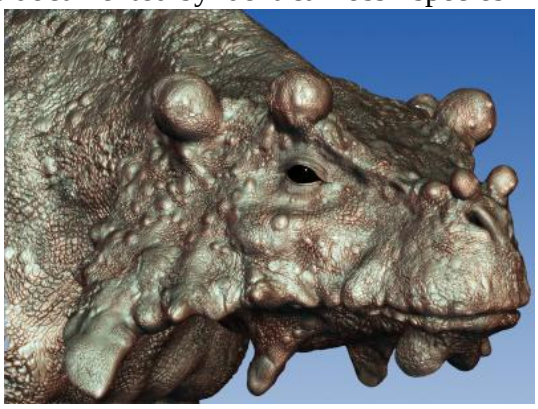
Bumpy beast was a desert dweller

Roaming the desert in what is now northern Niger was a very distinctive creature known as a pareiasaur.

DEERFIELD, IL—During the Permian era, the Earth was dominated by a single supercontinent called Pangea – "All-Earth". Animal and plant life dispersed broadly across this land, as documented by identical fossil species found on multiple modern continents. But a new study published in the Journal of Vertebrate Paleontology supports the idea that there was an isolated desert in the middle of Pangea with a fauna all its own. Roaming this desert in what is now northern Niger was a very distinctive creature known as a pareiasaur. Pareiasaurs were large, herbivorous reptiles that were common across Pangea during the Middle and Late Permian, about 266-252 million years ago. "Imagine a cow-sized, plant-eating reptile with a knobby skull and bony armor down its back," said lead author Linda Tsuji. The newly discovered fossils belong to the aptly-named genus Bunostegos, which means "knobby [skull] roof."



Artist's rendering of the pareiasaur Bunostegos, a cow-sized, plant-eating reptile that roamed the ancient central desert of Pangea over 250 million years ago. Illustration by Marc Boulay.

Most pareiasaurs had bony knobs on their skulls, but Bunostegos sported the largest, most bulbous ones ever discovered. In life, these were probably skin-covered horns like those on the heads of modern giraffes. Although at first blush these features seem to suggest that Bunostegos was an evolutionarily advanced pareiasaur, it also had many primitive characteristics. Tsuji's analysis showed that Bunostegos was actually more closely related to older and more primitive pareiasaurs, leading to two conclusions: first, that its knobby noggin was the result of convergent evolution, and second, that its genealogical lineage had been isolated for millions of years.

So how do you isolate a population of cow-sized reptiles? Though there were no fences in the Permian, climatic conditions conspired to corral Bunostegos – along with several other reptiles, amphibians, and plants – and keep them constrained to the central area of the supercontinent. "Our work supports the theory that central Pangea was climatically isolated, allowing a unique relict fauna to persist into the Late Permian," said Christian Sidor, another author of the paper. This is surprising because areas outside this central region show fossil evidence of regular faunal interchange.

Geological data also show that central Pangea was hyperarid (extremely dry), effectively discouraging some animals from passing through, while keeping those within from venturing out. The long period of isolation under these parched conditions gave Bunostegos lineage time to evolve its unique anatomical features. Paleontologist Gabe Bever, who was not involved with the study, said "Research in these lesser-known basins is critically important for meaningful interpretation of the Permian fossil record. Our understanding of the Permian and the mass extinction that ended it depends on discovery of more fossils like the beautifully bizarre Bunostegos."

Much of what was once central Pangea remains to be explored by paleontologists. "It is important to continue research in these under-explored areas," said Tsuji. "The study of fossils from places like northern Niger paints a more comprehensive picture of the ecosystem during the Permian era."

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2 mutations triggered an evolutionary leap 500 million years ago

Resurrecting ancient proteins in the lab, researchers discover just 2 mutations set the stage for the evolution of modern hormone signaling

Evolution, it seems, sometimes jumps instead of crawls. A research team led by a University of Chicago scientist has discovered two key mutations that sparked a hormonal revolution 500 million years ago.

In a feat of "molecular time travel," the researchers resurrected and analyzed the functions of the ancestors of genes that play key roles in modern human reproduction, development, immunity and cancer. By re-creating the same DNA changes that occurred during those genes' ancient history, the team showed that two mutations set the stage for hormones like estrogen, testosterone and cortisol to take on their crucial present-day roles.

"Changes in just two letters of the genetic code in our deep evolutionary past caused a massive shift in the function of one protein and set in motion the evolution of our present-day hormonal and reproductive systems," said Joe Thornton, PhD, professor of human genetics and ecology & evolution at the University of Chicago, who led the study. "If those two mutations had not happened, our bodies today would have to use different

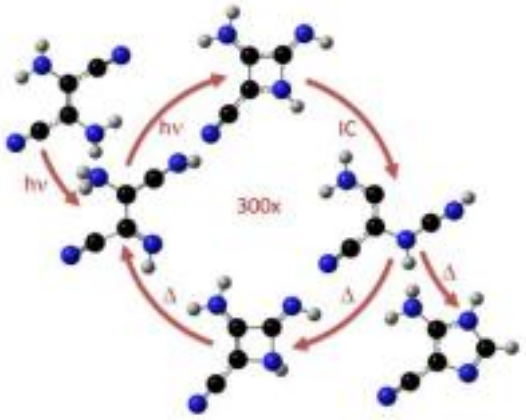
mechanisms to regulate pregnancy, libido, the response to stress, kidney function, inflammation, and the development of male and female characteristics at puberty," Thornton said.
The findings were published online June 24 in the Proceedings of the National Academy of Sciences.
Understanding how the genetic code of a protein determines its functions would allow biochemists to better design drugs and predict the effects of mutations on disease. Thornton said the discovery shows how evolutionary analysis of proteins' histories can advance this goal, Before the group's work, it was not previously known how the various steroid receptors in modern species distinguish estrogens from other hormones.
The team, which included researchers from the University of Oregon, Emory University and the Scripps Research Institute, studied the evolution of a family of proteins called steroid hormone receptors, which mediate the effects of hormones on reproduction, development and physiology. Without receptor proteins, these hormones cannot affect the body's cells.
Thornton's group traced how the ancestor of the entire receptor family - which recognized only estrogens - evolved into descendant proteins capable of recognizing other steroid hormones, such as testosterone, progesterone and the stress hormone cortisol.
To do so, the group used a gene "resurrection" strategy. They first inferred the genetic sequences of ancient receptor proteins, using computational methods to work their way back up the tree of life from a database of hundreds of present-day receptor sequences. They then biochemically synthesized these ancient DNA sequences and used molecular assays to determine the receptors' sensitivity to various hormones.
Thornton's team narrowed down the time range during which the capacity to recognize non-estrogen steroids evolved, to a period about 500 million years ago, before the dawn of vertebrate animals on Earth. They then identified the most important mutations that occurred during that interval by introducing them into the reconstructed ancestral proteins. By measuring how the mutations affected the receptor's structure and function, the team could re-create ancient molecular evolution in the laboratory.
They found that just two changes in the ancient receptor's gene sequence caused a 70,000-fold shift in preference away from estrogens toward other steroid hormones. The researchers also used biophysical techniques to identify the precise atomic-level mechanisms by which the mutations affected the protein's functions. Although only a few atoms in the protein were changed, this radically rewired the network of interactions between the receptor and the hormone, leading to a massive change in function.
"Our findings show that new molecular functions can evolve by sudden large leaps due to a few tiny changes in the genetic code," Thornton said. He pointed out that, along with the two key changes in the receptor, additional mutations, the precise effects of which are not yet known, were necessary for the full effects of hormone signaling on the body to evolve.
This work was supported by grants from the National Institutes of Health, National Science Foundation and the Howard Hughes Medical Institute.

http://www.sciencedaily.com/releases/2013/06/130624104213.htm

Excited, but Cold: Scientists Unveil the Secret of a Reaction for Prebiotic Synthesis of Organic Matter

How is it that a complex organism evolves from a pile of dead matter? How can lifeless materials become organic molecules that are the bricks of animals and plants?

Scientists have been trying to answer these questions for ages. Researchers at the Max Planck Institut für Kohlenforschung have now disclosed the secret of a reaction that has to do with the synthesis of complex organic matter before the origin of life. Since the 1960's it has been well known that when concentrated hydrogen cyanide (HCN) is irradiated by UV light, it forms an imidazole intermediate that is a key substance for synthesis of nucleobases and nucleotides in abiotic environment. The way how UV radiation acts in this reaction to produce complex organic matter was, however, never clarified. Dr. Mario Barbatti and his colleagues in Germany, India and Czech Republic have now shown how this process occurs via computer simulations.



Each reactant molecule absorbs hundreds of UV photons before it finally gets converted into the imidazole intermediate. **Image courtesy of Max-Planck-Institut für Kohlenforschung**

Using diverse computational-chemistry methods, the team has arrived at astonishing conclusions: For example that the reaction does not take place in the hot spot created by the solar radiation. "This has nothing to do with heat, but with electrons," says Mario Barbatti.

The reaction proceeds through a series of electronically excited intermediates. The molecules get into the "electronic excited state" because of the UV radiation, which means that their electrons are distributed in a much different way than the usual. That changes the molecule's attitudes. "But this takes some time," says Mario Barbatti. They showed that the radiation energy is dissipated too fast, and because of that each reactant molecule absorbs hundreds of UV photons before it finally gets converted into the imidazole intermediate.
"This is very inefficient -- and quite extraordinary," says Mario Barbatti. That is why it was quite challenging to comprehend the reaction, explains the physicist from Brazil. He and his colleagues have calculated a lot of possible intermediates, tried -- and discarded most of them. Finally they found out that there is only one single pathway that is consistent with the fast energy dissipation and previous experimental observations.
But why did they work on the computer? Isn't it the case that chemical reactions are worked on in laboratories? "Some intermediates are too elusive to analyze them in the laboratory -- they disappear before we may see them," Barbatti explains. Computational Chemistry allows the scientists to comprehend the reactions in a theoretical way.
"As I said before, this reaction has nothing to do with heat," says Barbatti. The transformation works in a cold environment, as in comets and in terrestrial ices, where spontaneous HCN polymerization is most expected to occur. The team has published their results, which help to understand the role of solar radiation on the origin of life, in the recent issue of Angewandte Chemie.

Eliot Boulanger, Anakuthil Anoop, Dana Nachtigallova, Walter Thiel, Mario Barbatti. Photochemical Steps in the Prebiotic Synthesis of Purine Precursors from HCN. Angewandte Chemie International Edition, 2013; DOI: 10.1002/anie.201303246

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Rubella Epidemics in Japan and Poland

Japan and Poland are both experiencing epidemics of rubella, and the Centers for Disease Control and Prevention has issued travel warnings suggesting that women who are pregnant or might be consult their doctors before visiting either country.

By DONALD G. McNEIL Jr.

The disease, also known as German measles, usually causes only mild fever and rash in adults and children, but can be devastating to a fetus, causing stillbirth or a host of birth defects, including developmental disabilities, deafness, heart problems and cataracts. Rubella cases in Japan have shot up to over 10,000 and are still increasing. Because of peculiarities in Japan's vaccination history, nearly 75 percent of the cases are in men ages 20 to 40. Poland has had more than 26,000 cases this year.
Japan normally gets more than twice as many American visitors as Poland - about 750,000 a year, compared with 350,000. And Japan's outbreak is concentrated in cities like Tokyo and Osaka that are frequented by tourists and business executives, while Poland's is not.
Japan began vaccinating schoolgirls - but not schoolboys - against rubella in 1976, then in 1989 switched to vaccinating infants of both sexes against rubella, measles and mumps with one shot. Then problems with the mumps component caused a switch to individual shots, rendering coverage less uniform.
Most Japanese over age 50 had rubella in their youth and are immune, so the most vulnerable group is young men, and many outbreaks are in workplaces.
Although at least five babies have been born with rubella-related birth defects, Japan's Health Ministry has resisted calls for a nationwide immunization campaign. Local governments have subsidized shots for those who seek them from doctors. Rubella vaccine is available to Americans only in the triple measles/mumps/rubella formula, which is not recommended for pregnant women.

http://www.eurekalert.org/pub_releases/2013-06/sfn-ttp061013.php

Technique to promote nerve regeneration after spinal cord injury restores bladder function in rats

Findings suggest similar strategies may one day be useful for human patients

Washington, DC — Using a novel technique to promote the regeneration of nerve cells across the site of severe spinal cord injury, researchers have restored bladder function in paralyzed adult rats, according to a study in the June 26 issue of The Journal of Neuroscience. The findings may guide future efforts to restore other functions lost after spinal cord injury. It also raises hope that similar strategies could one day be used to restore bladder function in people with severe spinal cord injuries.
For decades, scientists have experimented with using nerve grafts as a way of bridging the spinal cord injury site in an attempt to recover lost function following spinal cord injury. However, coaxing these cells to grow and form connections capable of relaying nerve signals has been elusive. In the current study, Yu-Shang Lee, PhD, of the Cleveland Clinic, together with Jerry Silver, PhD, of Case Western Reserve Medical School, and

others, used a chemical that promotes cell growth along with a scar-busting enzyme to create a more hospitable environment for the nerve graft at the injury site.
"Although animals did not regain the ability to walk, they did recover a remarkable measure of urinary control," Silver explained. This basic function is one that many spinal cord injury patients rank as one of the most important to regain following injury. "This is the first time that significant bladder function has been restored via nerve regeneration after a devastating cord injury," Lee added.
When a spinal cord injury takes place, extensions of nerve cells from the brainstem — the region of the brain where the command and coordination for urination takes place — become disconnected from cells in the spinal cord that control the muscles that squeeze or relax the bladder and open and close the urethra. The body's natural response to form a scar at the injury site reduces the spread of inflammation but deters the growth of severed nerve fibers. With no way for the cells between the brain stem and spinal cord to regenerate or reconnect, the injury often results in the permanent inability to empty the bladder.
The team of researchers delivered an enzyme called chondroitinase to disrupt scar formation in tandem with a chemical called fibroblast growth factor used to promote cell survival as they performed nerve graft surgery at the site of the injury. After three and six months, the scientists discovered that the rats that received this combination of treatment saw a significant return of bladder function, as indicated by measurements of urine output. Researchers also saw the regrowth of some brainstem cells across the injury site.
"What was especially surprising and exciting was that a subset of nerve cells situated largely in the brainstem could slowly re-grow far down the spinal cord once a permissive environment that allowed them past the site of the scar was provided," Silver said. "What endows these particular neurons with such an innately high re-growth capacity is unknown but will be an extremely important area of research in the future."
Elizabeth Bradbury, PhD, a spinal cord injury researcher at King's College London who was not involved with this study, cautioned that several challenges must be overcome before this type of therapy could be tested in people. "Nevertheless, this remarkable advance offers great hope for the future of restoring bladder function to spinal cord injury patients," she said.
The research was supported by the National Institute of Neurological Disorders and Stroke and the Cleveland Clinic Foundation.

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Three Planets in Habitable Zone of Nearby Star: Gliese 667c Reexamined

A record-breaking three planets in this system are super-Earths lying in the zone around a star where liquid water could exist, making them possible candidates for the presence of life. This is the first system found with a fully packed habitable zone.

A team of astronomers has combined new observations of Gliese 667C with existing data from HARPS at ESO's 3.6-metre telescope in Chile, to reveal a system with at least six planets. A record-breaking three of these planets are super-Earths lying in the zone around the star where liquid water could exist, making them possible candidates for the presence of life. This is the first system found with a fully packed habitable zone.
Gliese 667C is a very well-studied star. Just over one third of the mass of the Sun, it is part of a triple star system known as Gliese 667 (also referred to as GJ 667), 22 light-years away in the constellation of Scorpius (The Scorpion). This is quite close to us -- within the Sun's neighbourhood -- and much closer than the star systems investigated using telescopes such as the planet-hunting Kepler space telescope.
Previous studies of Gliese 667C had found that the star hosts three planets with one of them in the habitable zone. Now, a team of astronomers led by Guillem Anglada-Escudé of the University of Göttingen, Germany and Mikko Tuomi of the University of Hertfordshire, UK, has reexamined the system. They have added new HARPS observations, along with data from ESO's Very Large Telescope, the W.M. Keck Observatory and the Magellan Telescopes, to the already existing picture [1]. The team has found evidence for up to seven planets around the star [2].
These planets orbit the third fainter star of a triple star system. Viewed from one of these newly found planets the two other suns would look like a pair of very bright stars visible in the daytime and at night they would provide as much illumination as the full Moon. The new planets completely fill up the habitable zone of Gliese 667C, as there are no more stable orbits in which a planet could exist at the right distance to it.
"We knew that the star had three planets from previous studies, so we wanted to see whether there were any more," says Tuomi. "By adding some new observations and revisiting existing data we were able to confirm these three and confidently reveal several more. Finding three low-mass planets in the star's habitable zone is very exciting!"
Three of these planets are confirmed to be super-Earths -- planets more massive than Earth, but less massive than planets like Uranus or Neptune -- that are within their star's habitable zone, a thin shell around a star in

which water may be present in liquid form if conditions are right. This is the first time that three such planets have been spotted orbiting in this zone in the same system [3].
"The number of potentially habitable planets in our galaxy is much greater if we can expect to find several of them around each low-mass star -- instead of looking at ten stars to look for a single potentially habitable planet, we now know we can look at just one star and find several of them," adds co-author Rory Barnes (University of Washington, USA).
Compact systems around Sun-like stars have been found to be abundant in the Milky Way. Around such stars, planets orbiting close to the parent star are very hot and are unlikely to be habitable. But this is not true for cooler and dimmer stars such as Gliese 667C. In this case the habitable zone lies entirely within an orbit the size of Mercury's, much closer in than for our Sun. The Gliese 667C system is the first example of a system where such a low-mass star is seen to host several potentially rocky planets in the habitable zone.
The ESO scientist responsible for HARPS, Gaspare Lo Curto, remarks: "This exciting result was largely made possible by the power of HARPS and its associated software and it also underlines the value of the ESO archive. It is very good to also see several independent research groups exploiting this unique instrument and achieving the ultimate precision."
And Anglada-Escudé concludes: "These new results highlight how valuable it can be to re-analyse data in this way and combine results from different teams on different telescopes."
[1] The team used data from the UVES spectrograph on ESO's Very Large Telescope in Chile (to determine the properties of the star accurately), the Carnegie Planet Finder Spectrograph (PFS) at the 6.5-metre Magellan II Telescope at the Las Campanas Observatory in Chile, the HIRES spectrograph mounted on the Keck 10-metre telescope on Mauna Kea, Hawaii as well as extensive previous data from HARPS (the High Accuracy Radial velocity Planet Searcher) at ESO's 3.6-metre telescope in Chile (gathered through the M dwarf programme led by X. Bonfils and M. Mayor 2003-2010.
[2] The team looked at radial velocity data of Gliese 667C, a method often used to hunt for exoplanets. They performed a robust Bayesian statistical analysis to spot the signals of the planets. The first five signals are very confident, while the sixth is tentative, and seventh more tentative still. This system consists of three habitable-zone super-Earths, two hot planets further in, and two cooler planets further out. The planets in the habitable zone and those closer to the star are expected to always have the same side facing the star, so that their day and year will be the same lengths, with one side in perpetual sunshine and the other always night.
[3] In the Solar System Venus orbits close to the inner edge of the habitable zone and Mars close to the outer edge. The precise extent of the habitable zone depends on many factors.
Guillem Anglada-Escudé, Mikko Tuomi, Enrico Gerlach, Rory Barnes, Reńe Heller, James S. Jenkins, Sebastian Wende, Steven S. Vogt, R. Paul Butler, Ansgar Reiners, and Hugh R. A. Jones. A dynamically-packed planetary system around GJ 667C with three super-Earths in its habitable zone. Astronomy & Astrophysics, 2013

http://www.eurekalert.org/pub_releases/2013-06/uu-och062413.php

Overweight causes heart failure -- large study with new method clarifies the association

An international research team led by Swedish scientists has used a new method to investigate obesity and overweight as a cause of cardiovascular disease.

Strong association have been found previously, but it has not been clear whether it was overweight as such that was the cause, or if the overweight was just a marker of another underlying cause, as clinical trials with long-term follow-ups are difficult to implement.
A total of nearly 200,000 subjects were included in the researchers' study of the causality between obesity/overweight and diseases related to cardiovascular conditions and metabolism, which is being published for the first time in PLOS Medicine. The goal was to determine whether obesity as such is the actual cause of these diseases or whether obesity is simply a marker of something else in the subject's lifestyle that causes the disease.
"We knew already that obesity and cardiovascular disease often occur together. However, it has been hard to determine whether increased BMI as such is dangerous. In this study we found that individuals with gene variants that lead to increased body-mass index (BMI) also had an increased risk of heart failure and diabetes. The risk of developing diabetes was greater than was previously thought," says Tove Fall, a researcher at the Department of Medical Sciences and the Science for Life Laboratory, Uppsala University, who coordinated the study together with researchers from the Karolinska Institutet and Oxford University.
These scientists studied whether a gene variant in the FTO gene, which regulates the appetite and thereby increases the individual's BMI, is also linked to a series of cardiovascular diseases and metabolism. The risk variant is common in the population, and each copy of the risk variant increases BMI by an average of 0.3-0.4 units. Since an individual's genome is not affected by lifestyle and social factors, but rather is established at conception, when the embryo randomly receives half of each parent's genome, the method is thus called

"Mendelian randomization". To achieve reliable results a large study material was needed, and nearly 200,000 individuals from Europe and Australia participated.
"Epidemiological studies look for associations in large populations, but it is usually difficult to reliably determine cause and effect – what we call causality. By using this new genetic method, Mendelian randomization, in our research, we can now confirm what many people have long believed, that increased BMI contributes to the development of heart failure. We also found that overweight causes increases in liver enzymes . This knowledge is important, as it strengthens the evidence that forceful societal measures need to be taken to counteract the epidemic of obesity and its consequences," says Erik Ingelsson, professor at the Department of Medical Sciences and the Science for Life Laboratory, Uppsala University.
The results show that an increase of one unit of BMI increases the risk of developing heart failure by an average of 20 per cent. Further, the study also confirms that obesity leads to higher insulin values, higher blood pressure, worse cholesterol values, increased inflammation markers, and increased risk of diabetes.
The present study was carried out within the framework of the major research consortium ENGAGE, which brings together more than 35 studies and more than 130 co-authors. The study was coordinated by Erik Ingelsson's research group in collaboration with the Karolinska Institutet and Oxford University.
Publication: "The Role of Adiposity in Cardiometabolic Traits: A Mendelian Randomization Analysis". Tove Fall, Sara Hägg, Reedik Mägi, [more than 125 additional authors], Nancy L. Pedersen, Mark I. McCarthy, Erik Ingelsson, Inga Prokopenko for the European Network for Genetic and Genomic Epidemiology (ENGAGE) consortium. PLOS Medicine. In press.
The study was funded by, among others, the European Union's Seventh Framework Programme (ENGAGE), the Swedish Research Council, the Swedish Foundation for Strategic Research, and the Swedish Heart-Lung Foundation.

http://www.sciencedaily.com/releases/2013/06/130625120933.htm

Protein That Contributes to Cognitive Decline in Alzheimer's Identified

Researchers at Columbia University Medical Center (CUMC) have demonstrated that a protein called caspase-2 is a key regulator of a signaling pathway that leads to cognitive decline in Alzheimer's disease.

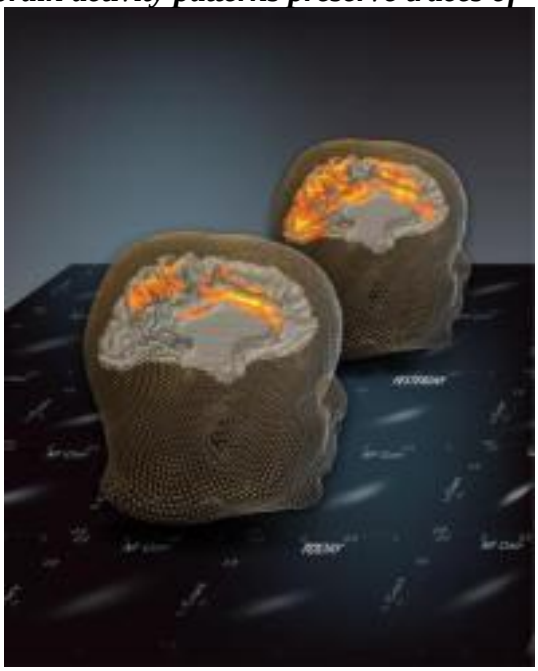
The findings, made in a mouse model of Alzheimer's, suggest that inhibiting this protein could prevent the neuronal damage and subsequent cognitive decline associated with the disease. The study was published this month in the online journal Nature Communications.
One of the earliest events in Alzheimer's is disruption of the brain's synapses (the small gaps across which nerve impulses are passed), which can lead to neuronal death. Although what drives this process has not been clear, studies have indicated that caspace-2 might be involved, according to senior author Michael Shelanski, MD, PhD, the Delafield Professor of Pathology & Cell Biology, chair of the Department of Pathology & Cell Biology, and co-director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at CUMC.
Several years ago, in tissue culture studies of mouse neurons, Dr. Shelanski found that caspace-2 plays a critical role in the death of neurons in the presence of amyloid beta, the protein that accumulates in the neurons of people with Alzheimer's. Other researchers have shown that caspase-2 also contributes to the maintenance of normal synaptic functions.
Dr. Shelanski and his team hypothesized that aberrant activation of caspase-2 may cause synaptic changes in Alzheimer's disease. To test this hypothesis, the researchers crossed J20 transgenic mice (a common mouse model of Alzheimer's) with caspase-2 null mice (mice that lack caspase-2). They compared the animals' ability to negotiate a radial-arm water maze, a standard test of cognitive ability, with that of regular J20 mice and of normal mice at 4, 9, and 14 months of age.
The results for the three groups of mice were similar at the first two intervals. At 14 months, however, the J20/caspase-2 null mice did significantly better in the water maze test than the J20 mice and similarly to the normal mice. "We showed that removing caspase-2 from J20 mice prevented memory impairment -- without significant changes in the level of soluble amyloid beta," said co-lead author Roger Lefort, PhD, associate research scientist at CUMC.
Analysis of the neurons showed that the J20/caspase-2 null mice had a higher density of dendritic spines than the J20 mice. The more spines a neuron has, the more impulses it can transmit.
"The J20/caspase-2 null mice showed the same dendritic spine density and morphology as the normal mice -- as opposed to the deficits in the J20 mice," said co-lead author Julio Pozueta, PhD. "This strongly suggests that caspase-2 is a critical regulator in the memory decline associated with beta-amyloid in Alzheimer's disease."
The researchers further validated the results in studies of rat neurons in tissue culture.
Finally, the researchers found that caspase-2 interacts with RhoA, a critical regulator of the morphology (form and structure) of dendritic spines. "It appears that in normal neurons, caspase-2 and RhoA form an inactive complex outside the dendritic spines," said Dr. Lefort. "When the complex is exposed to amyloid beta, it breaks

apart, activating the two components." Once activated, caspase-2 and RhoA enter the dendritic spines and contribute to their demise, possibly by interacting with a third molecule, the enzyme ROCK-II.
"This raises the possibility that if you can inhibit one or all of these molecules, especially early in the course of Alzheimer's, you might be able to protect neurons and slow down the cognitive effects of the disease," said Dr. Lefort.
The paper is titled, "Caspase-2 is required for dendritic spine and behavioural alterations in J20 APP transgenic mice." The other contributors are Julio Pozueta, PhD (co-lead author), Elena M. Ribe, Carol M. Troy, and Ottavio Arancio, all based at CUMC at the time of the study.
Dr. Pozueta was an associate research scientist at CUMC at the time of this research and is currently a senior analyst at Prescient Life Sciences. The remaining authors declare no financial or other conflicts of interests.
The study was supported by grants from the National Institutes of Health (NIHAG08702 and NS15076), the Wallace Foundation for Research, and the Taub Foundation.
Julio Pozueta, Roger Lefort, Elena M. Ribe, Carol M. Troy, Ottavio Arancio, Michael Shelanski. Caspase-2 is required for dendritic spine and behavioural alterations in J20 APP transgenic mice. Nature Communications, 2013; 4 DOI: 10.1038/ncomms2927

http://www.eurekalert.org/pub_releases/2013-06/wios-pba062513.php

Past brain activation revealed in scans

Weizmann Institute scientists discover that spontaneously emerging brain activity patterns preserve traces of previous cognitive activity



What if experts could dig into the brain, like archaeologists, and uncover the history of past experiences? This ability might reveal what makes each of us a unique individual, and it could enable the objective diagnosis of a wide range of neuropsychological diseases. New research at the Weizmann Institute hints that such a scenario is within the realm of possibility: It shows that spontaneous waves of neuronal activity in the brain bear the imprints of earlier events for at least 24 hours after the experience has taken place.
The new research stems from earlier findings in the lab of Prof. Rafi Malach of the Institute's Neurobiology Department and others that the brain never rests, even when its owner is resting. When a person is resting with closed eyes – that is, no visual stimulus is entering the brain – the normal bursts of nerve cell activity associated with incoming information are replaced by ultra- slow patterns of neuronal activity. Such spontaneous or "resting" waves travel in a highly organized and reproducible manner through the brain's outer layer – the cortex – and the patterns they create are complex, yet periodic and symmetrical.

The brain image at the back presents spontaneous (resting state) patterns before a fMRI-based neurofeedback training session. The front brain image presents spontaneous (resting state) patterns a day after the training session, illustrating the long term trace of the training. The two brains are overlaid above scatter plots of individual subjects that demonstrate the "Hebbian-like" learning rule: Cortical sites that were co-activated during training increased their resting state connectivity, while those that were de-correlated during training decreased it. For more information, see the article by Harmelech et al. Journal of Neuroscience, 33(22):9488-97 2013. **Weizmann Institute of Science**

Like hieroglyphics, it seemed that these patterns might have some meaning, and research student Tal Harmelech, under the guidance of Malach and Dr. Son Preminger, set out to uncover their significance. Their idea was that the patterns of resting brain waves may constitute "archives" for earlier experiences. As we add new experiences, the activation of our brain's networks lead to long-term changes in the links between brain cells, a facility referred to as plasticity. As our experiences become embedded in these connections, they create "expectations" that come into play before we perform any type of mental task, enabling us to anticipate the result. The researchers hypothesized that information about earlier experiences would thus be incorporated into the links between networks of nerve cells in the cortex, and these would show up in the brain's spontaneously emerging wave patterns.
In the experiment, the researchers had volunteers undertake a training exercise that would strongly activate a well-defined network of nerve cells in the frontal lobes. While undergoing scans of their brain activity in the Institute's functional magnetic resonance imaging (fMRI) scanner, the subjects were asked to imagine a situation in which they had to make rapid decisions. The subjects received auditory feedback in real time, based on the information obtained directly from their frontal lobe, which indicated the level of neuronal activity in the

trained network. This "neurofeedback" strategy proved highly successful in activating the frontal network – a part of the brain that is notoriously difficult to activate under controlled conditions.
To test whether the connections created in the brain during this exercise would leave their traces in the patterns formed by the resting brain waves, the researchers performed fMRI scans on the resting subjects before the exercise, immediately afterward, and 24 hours later. Their findings, which appeared in the Journal of Neuroscience, showed that the activation of the specific areas in the cortex did indeed remodel the resting brain wave patterns. Surprisingly, the new patterns not only remained the next day, they were significantly strengthened. These observations fit in with the classic learning principles proposed by Donald Hebb in the mid-20th century, in which the co-activation of two linked nerve cells leads to long term strengthening of their link, while activity that is not coordinated weakens this link. The fMRI images of the resting brain waves showed that brain areas that were activated together during the training sessions exhibited an increase in their functional link a day after the training, while those areas that were de-activated by the training showed a weakened functional connectivity.
This research suggests a number of future possibilities for exploring the brain. For example, spontaneously emerging brain patterns could be used as a "mapping tool" for unearthing cognitive events from an individual's recent past. Or, on a wider scale, each person's unique spontaneously emerging activity patterns might eventually reveal a sort of personal profile – highlighting each individual's abilities, shortcomings, biases, learning skills, etc. "Today, we are discovering more and more of the common principles of brain activity, but we have not been able to account for the differences between individuals," says Malach. "In the future, spontaneous brain patterns could be the key to obtaining unbiased individual profiles." Such profiles could be especially useful in diagnosing or learning the brain pathologies associated with a wide array of cognitive disabilities.
Prof. Rafi Malach's research is supported by the Nella and Leon Benoziyo Center for Neurosciences; the Nella and Leon Benoziyo Center for Neurological Diseases; the Carl and Micaela Einhorn-Dominic Brain Research Institute; the Norman and Helen Asher Center for Human Brain Imaging; the Murray H. and Meyer Grodetsky Center for Research of Higher Brain Functions; the Kahn Family Research Center for Systems Biology of the Human Cell; the Friends of Dr. Lou Siminovitch; the Adelis Foundation; and the Mike and Valeria Rosenbloom through the Mike Rosenbloom Foundation. Prof. Malach is the recipient of the Helen and Martin Kimmel Award for Innovative Investigation; and he is the incumbent of the Barbara and Morris L. Levinson Professorial Chair in Brain Research.

http://www.medscape.com/viewarticle/805478?src=rss

Organs Donated by Prisoners? No, No, No! (Video)

First statute of its kind in the United States allows prisoners to donate their organs

Arthur L. Caplan, PhD

Hi. I am Art Caplan, and I am at the Division of Medical Ethics at the New York University (NYU) Langone Medical Center in New York City.
Today I want to talk about a law that was just passed in the State of Utah that allows prisoners to donate their organs. This is the first statute of its kind in the United States. The statute says that if a prisoner wants to donate a kidney, the prisoner can do so. It does not say that they are supposed to be rewarded or get time off for that, but it does not prohibit that kind of an incentive, and it suggests that before prisoners are executed, they could say that they want to be organ donors.
I am sure everyone watching this understands that we face a tremendous shortage of organs every day, and many, many people are dying while on waiting lists for kidneys, livers, hearts, and other vital organs. So far, we have found no other way to get more organs.
Certainly we want to encourage our patients to sign their donor cards or drivers licenses. It is very important to encourage the public to support organ donation. That ought to be part of almost every interview one has with a patient, as part of a good medical history, asking, "Have you thought about organ donation?"

This Will Not Solve the Problem

Are prisoners really the population to turn to for organ donations? Is that going to solve the shortage problem? It certainly will not help with hearts and livers. We do not execute that many people in the United States. We only have a few states still doing executions. Those kinds of organs are only available when the donor dies, and we have no more than about 40 or 50 executions in a year. That will not put much of a dent in the overall demand.
Moreover, after their multiple appeals, the people who are executed have been on Death Row for 10, 15, 20 years. They are older and sicker. Their diets are not good; they have been exposed to many infectious diseases in prison. The executed prisoner is not the best candidate for harvesting healthy organs.

Most modes of execution would not be consistent with getting a healthy organ. You would almost have to remove it at the moment the person is executed in order to have a viable heart and other organs. What we typically see with an execution is a relatively long wait to make sure the person is dead. This is not consistent with organ donation practice; most donors of vital organs are on life support, and executed prisoners would not be on life support. I do not see capital punishment doing much good as a source of organs from the prisoner population.

What happens in countries such as China that do not have any type of cadaver organ recovery system in place? These countries get all their organs for transplant by execution on demand. This means that when a transplant tourist comes to these countries needing a liver, the government says, "We will have a liver for you in 2 weeks." They choose someone from the prison population, execute them, remove organs on the spot, and that is how they supply their systems. When we say that it is tolerable to use prisoners, the message to the rest of the world is that we are okay with the way prisoners are used in other countries. That kind of endorsement absolutely should not be the case.

What About the Inmate Who Just Wants to Do Good?

What about the donation from a living prisoner? Again, prisons are not the healthiest of places to be, even though in the movies it looks like every prisoner is a physical fitness paragon. In reality, most prisons are not great places to exercise or eat well, and there is a high prevalence of drugs and infectious diseases, so most of these prisoners will not be good sources of kidneys, which is the primary organ we are talking about.

In addition, prisoners may feel coerced, as if the only way to be paroled or released is to agree to give a kidney. We have tried to prevent people from selling their organs in this country, but trying to bargain a kidney donation for early release may seem coercive in terms of what the prisoner faces.

I am not utterly against kidney or bone marrow donation from a prisoner, but I think it has to be reviewed carefully on a case-by-case basis, probably by some sort of independent group or committee that is not representing the person who needs the kidney, not representing the prison authorities, and not representing the transplant center that might want access to that donor kidney. That may be a place where careful procedures, oversight, and review may be appropriate to make sure the prisoner really is not being pressured and is healthy enough to do it.

I hope that sheds some light on a very difficult question, a close moral call. Thanks for watching. This is Art Caplan from the NYU Langone Medical Center.

http://www.sciencedaily.com/releases/2013/06/130625120937.htm

First-Ever Therapeutic Offers Hope for Improving Blood Transfusions

Researchers from Case Western Reserve University School of Medicine have developed an unprecedented approach to restore nitric oxide (NO) to donated blood, a breakthrough that could dramatically reduce harmful effects from transfusions.

Jonathan Stamler, MD, and colleagues from Case Western Reserve School of Medicine and from Duke University Medical Center describe their findings in the June 24 issue of the Proceedings of the National Academy of Sciences. Stamler and his colleagues report that restoring blood levels of NO in animals prior to transfusion improved their tissue blood flow, oxygen delivery, and kidney function.

Patients in the U.S. receive approximately 15 million blood transfusions a year. The procedure is often used to replace blood lost through trauma, but also can supplement shortages in a patient's own ability to produce blood due to cancer and other diseases. Increasingly, medical research publications associate transfusions with harmful consequences including heart attacks, renal failure, and death. A compelling explanation put forward in the literature is that the quantity of NO declines rapidly after donation because it has a short lifespan. Normally, NO dilates blood vessels and allows red blood cells to access tissue and deliver oxygen.

In the blood, NO exists in a bioactive form called S-nitrosohemoglobin (SNO-Hb). The unique process Stamler and team developed to restore SNO-Hb -- so-called renitrosylation therapy -- could have significant benefits for millions of patients.

"Inasmuch of the world's supply of banked blood is deficient in SNO-Hb, efforts to restore its levels may hold great therapeutic promise," said Stamler, director, Institute for Transformative Molecular Medicine and the Robert S. and Sylvia K. Reitman Family Foundation Distinguished Chair in Cardiovascular Innovation, Case Western Reserve School of Medicine and University Hospitals (UH) Case Medical Center, and director, Harrington Discovery Institute, UH Case Medical Center. "One important aspect of our study is the insight that knowledge of banked blood's SNO-Hb status may be used to judge the efficacy of a transfusion," Stamler said. This information would allow physicians to discriminate between blood donations that may cause harm versus those that will have restorative effects following transfusion.

The research team hypothesized that the loss of NO compromises the ability to dilate blood vessels and thereby deliver oxygen to tissues, which is critical for survival. Red blood cells lacking NO instead would plug small blood vessels and cause heart attacks and kidney failure. In contrast, restoration of NO would ensure oxygen delivery.
The study, funded by the National Heart Lung and Blood Institute (NHLBI), found that mice, rats and sheep transfused with untreated banked blood had decreased oxygen levels in skeletal muscle and other tissues -- exactly the opposite of what would have been predicted. By contrast, in animals transfused with renitrosylated (NO repleted) red blood cells, tissue oxygenation improved. In addition, researchers applied the same treatment to anemic animals and found improved blood flow, tissue oxygenation, and kidney function.
Stamler explained that these results demonstrate that restoration of blood NO levels may be useful in treating and preventing a wide variety of conditions, including heart attacks and strokes, and kidney damage following surgery. The findings also may offer new promise for patients with sickle disease, malaria and other blood disorders. In addition, the data suggest that Stamler's therapeutic is a simple way to reverse the potential toxicity of regular blood transfusions.
The Food and Drug Administration considers a transfusion successful if 75 percent of the banked red blood cells are circulating in the body of the recipient 24 hours after administration. "Based on our findings, the criteria might need to be revised to include measures of red blood cell function -- namely the ability of banked blood to deliver oxygen," Stamler added.
Motivated by these promising findings, Stamler has secured a grant from the NHLBI of the National Institutes of Health (NIH) to begin a clinical trial to evaluate the oxygen delivery function of banked blood. In addition, the team has applied for NHLBI funding of a Phase I clinical trial to study the use of renitrosylation in patient transfusions. If funded, the trial would be based at University Hospitals Case Medical Center and would enroll approximately 30 healthy volunteers.
The original work was sponsored in part by NIH grants HL91876 and HL095463, DARPA Contract N66001-10-C-2015, a grant from the Clinical and Translational Science Collaborative at Case Western Reserve (UL1RR024989), the Coulter-Case Translational Research Partnership, the Duke-Coulter Translational Partnership Grant Program, and by the Institute for Transformative Molecular Medicine at Case Western Reserve.
J. D. Reynolds, K. M. Bennett, A. J. Cina, D. L. Diesen, M. B. Henderson, F. Matto, A. Plante, R. A. Williamson, K. Zandinejad, I. T. Demchenko, D. T. Hess, C. A. Piantadosi, J. S. Stamler. S-nitrosylation therapy to improve oxygen delivery of banked blood. Proceedings of the National Academy of Sciences, 2013; DOI: 10.1073/pnas.1306489110

http://phys.org/news/2013-06-komodo-dragon-bacteria-myth.html

Fear of Komodo dragon bacteria wrapped in myth

A team led by a University of Queensland researcher has proven that the fearsome Komodo dragon is a victim of bad press.

Phys.org – It has long been believed that Komodo dragon bites were fatal because of toxic bacteria in the reptiles' mouths. But ground-breaking research by The University of Queensland's Associate Professor Bryan Fry and colleagues in the United States has found that the mouths of Komodo dragons are surprisingly ordinary and the levels and types of bacteria do not differ from any other carnivore.
This presents a powerful challenge to how most scientists and zookeepers have viewed the Komodo dragon.
"Komodo dragons are actually very clean animals," Associate Professor Fry said.
"After they are done feeding, they will spend 10 to 15 minutes lip-licking and rubbing their head in the leaves to clean their mouth. "The inside of their mouth is also kept extremely clean by the tongue. "Unlike people have been led to believe, they do not have chunks of rotting flesh from their meals on their teeth, cultivating bacteria." In fact it seems the poor hygiene of water buffalo is responsible for perceptions about deadly toxic bacteria in the dragons.
Komodo dragons evolved in Australia and preyed upon young megafauna. They now populate the islands of Indonesia where they prey on the introduced water buffalo, and on pigs and deer.
Professor Fry said attacks on pigs and deer were extremely successful, with about 75 per cent bleeding out within 30 minutes and a further 15 per cent dying within three to four hours from venom in the salivary glands of the Komodo dragons.
"In contrast, water buffalo always get away but with deep wounds to the legs," he said.
"The water buffalo follow their instincts and seek shelter in warm water that is usually stagnant, filled with water buffalo faeces and flourishing with bacteria, particularly nasty anaerobic types."
Pathogenic bacteria found in komodo mouths were simply the remnants from when the dragons drank from sewage filled watering holes. The dragons do not have enough bacteria in their mouths to infect an injured water buffalo.

"It is when the water buffalo go stand in the toxic water with gaping wounds that they get infected," Professor Fry said. "It really has been that simple all along. "If water buffalo had never been introduced onto the islands, then this enchanting fairy tale never would have come into existence.
"The water buffalo are not living in their native habitat of large fresh marshes but rather on islands with the only water source being tiny water holes. "So they are basically going to the bathroom directly onto their wounds. This is an ideal scenario for infection, but a situation that is man-made and thus entirely artificial."
Professor Fry says the next step is to conduct tests on the watering holes to prove that they are the true source of any infection to water buffalo and to characterise what sorts of pathogens are responsible for the sickness to the water buffaloes.

http://nyti.ms/16zPMIK

DNA Buried 7,000 Centuries Is Retrieved

Researchers have recovered an ancient genome from a 700,000-year-old horse fossil in Canada. They are also analyzing the genomes of many members of the horse evolutionary tree, including the Przewalski horse, a species thought to represent the last living wild horse population.

By NICHOLAS WADE

Researchers have reconstructed an ancient genome that is 10 times as old as any retrieved so far, and they now say that DNA should be recoverable from animals that lived one million years ago. This would greatly extend biologists' ability to understand the evolutionary past.
Two pieces of bone from a hind toe of a horse that lived some 700,000 years ago in what is now the Yukon Territory in Canada. The ancient genome recovered from the sample is 10 times as old as any retrieved so far from a fossil. The genome was that of a horse that lived about 700,000 years ago in what is now the Yukon Territory in Canada, and its reconstruction has already led to new insights. The researchers who sequenced it then analyzed DNA from a less ancient horse, one that lived 43,000 years ago, as well as five contemporary horse breeds and a donkey named Willy that resides in the Copenhagen Zoo. They concluded that the genus that gave rise to modern horses, zebras and donkeys - Equus - arose about four million years ago, twice as far back as had been thought.

A late Pleistocene horse skull, found in the Yukon Territory. D.J. Froese

Before this work, the oldest genome that had been recovered was that of a Denisovan human who lived 70,000 years ago. The new finding, if accepted, would extend by tenfold the reach of paleogenomics, the study of ancient genomes reconstructed from fossil bones. Within the last few decades this young science has become a powerful complement to paleontology, the study of fossils, as a way of reconstructing evolutionary history.
"I think the field has now in many respects matured," said Svante Paabo of the Max Planck Institute for Evolutionary Anthropology, who solved many of the early problems and went on to reconstruct the genome of Neanderthals and more recently of the Denisovan human. "It is clear that with frozen material one can go far back in time, approaching a million years," he said, but the challenge now was to retrieve ancient genomes from temperate zones, where important fossil bones are more plentiful.
The horse DNA was extracted from a hind toe bone found in the Thistle Creek region of the Yukon's Klondike gold mines. It owes its remarkable longevity to the bone having been buried in permafrost, which kept the DNA both very cold and very dry.
The researchers who discovered the bone, Duane Froese of the University of Alberta and Eske Willerslev, an expert on ancient DNA at the University of Copenhagen, first estimated its date from the layers of volcanic ash where it was found. They also conducted tests that showed that the horse bone, despite its age, was likely to contain DNA, even though the chemical starts to degrade as soon as an animal dies.
To help establish that the DNA from the horse bone was really 700,000 years old, Dr. Willerslev and Ludovic Orlando, a colleague at the University of Copenhagen, started an ambitious project to analyze the genomes of many other members of the horse evolutionary tree. These include the horse that lived 43,000 years ago, before horses were domesticated; a Przewalski's horse, a species thought to represent the last living wild horse population; five domestic horse breeds (Arabian, Icelandic, Norwegian fjord, Standardbred and Thoroughbred); and Willy the donkey.
Dr. Orlando said the range of genetic variation in the Thistle Creek bone lay outside that of all the other horses, showing it could not have been contaminated by modern horse DNA. Also, the DNA in the bone was much

more fragmented than that of late ice age horse bones from the same region, indicating it was older. The geological evidence for the bone's age is "very secure," Dr. Orlando said. With this and other data he is confident that the Thistle Creek horse and its genome are indeed 700,000 years old.
In a report published in the journal Nature on Wednesday, he and colleagues say that they have identified 29 regions in the genome of domestic horses where the DNA shows statistical evidence of selection, meaning that variant genes in these regions were favored as horses became domesticated. But each of the regions is about 200,000 DNA units in length and contains many genes, so the researchers do not yet know which of these genes was the target of selection, Dr. Orlando said.
Another finding from the new collection of horse genome data is that the Przewalski's horse shows no signs of having interbred with domestic horses, as some researchers had assumed was likely. Since the horse is threatened in the wild, this gives added reason for protecting it.
The rich genomic data on the horse family tree has enabled the Danish team to make statistical estimates of the size of the horse population through the ages. In the last two million years, horses have gone through three cycles of a population increase followed by a crash. The most recent peak was during the last glacial maximum, a cold period 25,000 years ago that preceded the end of the last ice age. The reason seems to be that during cold periods there are extensive grasslands, but these revert to forest in warmer times. "When it's fairly cold it's good to be a horse, but when it's warm it's pretty bad," Dr. Willerslev said Tuesday at news conference in Helsinki, Finland.
The most distant ancestor of the horse, Eohippus, was a cat-size animal that lived in forests 50 million years ago. Its descendants learned to feed on grass, but life in the open plains required larger size and speed to escape predators. The Thistle Creek horse, a male, would have been of modern size.
Bruce MacFadden, an expert on fossil horses at the University of Florida, said the Danish team's findings were reasonable in light of the fossil data. "It's always wonderful when the fossil and molecular evidence coincide," he said. But the influence of climate on horse demography is more complicated than the genomic data suggests, he said.
The horse's genome consists of 2.7 billion units of DNA. The DNA extracted from the Thistle Creek bone was fragmented into minute pieces about 25 to 75 DNA units in length. The Danish team calculates that pieces only 25 units long could survive for a million years, which they see as the theoretical limit for reconstructing ancient genomes.

http://www.eurekalert.org/pub_releases/2013-06/smh-nrf062513.php

New research finds flu shot effective regardless of circulating flu strain

New research out of St. Michael's Hospital has found that despite popular belief, the flu shot is effective in preventing the flu, even if the virus going around does not match the vaccine.

"It's quite common for people to say they are not going to get the flu shot this year because they've heard it does not match the strain of flu going around," said Dr. Andrea Tricco, the lead author of the paper and a scientist at the Li Ka Shing Knowledge Institute of St. Michael's Hospital. "However, we've found that individuals will be protected regardless of whether the flu strain is a match or not."
The review of the literature analyzed more than 40 years of data, from 1971 to 2011, and included 47 influenza seasons and almost 95,000 healthy people.
Dr. Tricco and colleagues were particularly interested in flu seasons when the flu vaccines were not matched well to circulating strains. They wanted to understand whether the flu vaccines would still be effective when the strains were not a match.
Vaccines work by giving the body an inactive, or non-infective, form of the flu virus so that the body can produce antibodies. When an individual comes into contact with the virus in the future, the body can use the natural antibodies it has created to fight it off.
The study looked at the two most popular vaccine formulations in Canada – Trivalent inactive vaccine for adults and live-attenuated influenza vaccine for children. They found that both vaccines provided significant protection against matched (ranging from 65 per cent to 83 per cent effectiveness) and mismatched (ranging from 52 per cent to 54 per cent effectiveness) flu strains.
"Looking at matches and mismatches can be a difficult process because it's not a yes or no variable," Dr. Tricco said. "Often we're looking at the degree of match between a flu strain and what's included in a vaccine because strains drift from year to year."
Dr. Tricco said that the study's results are mainly applicable to the seasonal flu in otherwise healthy children and adults.

http://phys.org/news/2013-06-chimps-humans-baseball-pitcher.html

Researchers say ability to throw played a key role in human evolution

It's easy to marvel at the athleticism required to throw a 90-mile-per-hour fastball, but when Neil Roach watches baseball, he sees something else at work – evolution.

That ability – to throw an object with great speed and accuracy – is a uniquely human adaptation, one that Roach believes was crucial in our evolutionary past. How, when and why humans evolved the ability to throw so well is the subject of a study published today (June 26) in the journal Nature. The study was led by Roach, who recently received his Ph.D. from Harvard's Graduate School of Arts and Sciences and is now a postdoctoral researcher at George Washington University, with Madhusudhan Venkadesan of NCBS at the Tata Institute of Fundamental Research, Michael Rainbow of the Spaulding National Running Center, and Daniel Lieberman, the Edwin M. Lerner II Professor of Biological Sciences at Harvard. They found that a suite of changes to our shoulders and arms allowed early humans to more efficiently hunt by throwing projectiles, helping our ancestors become part-time carnivores and paving the way for a host of later adaptations, including increases in brain size and migration out of Africa.

"When we started this research, there were essentially two questions we asked – one of them was why are humans so uniquely good at throwing, while all other creatures including our chimpanzee cousins are not," said Roach. "The other question was: How do we do it? What is it about our body that enables this behavior, and can we identify those changes in the fossil record?" What they found, Roach said, were a suite of physical changes - such as the lowering and widening of the shoulders, an expansion of the waist, and a twisting of the humerus – that make humans especially good at throwing.

While some of those changes occurred earlier during human evolution, Lieberman said it wasn't until the appearance of Homo erectus, approximately 2 million years ago, that they all appeared together. The same period is also marked by some of the earliest signs of effective hunting, suggesting that the ability to throw an object very fast and very accurately played a critical role in human's ability to rise to the top of the food chain.

"The ability to throw was one of a handful of changes that enabled us to become carnivores, which then triggered a host of changes that occurred later in our evolution," Lieberman said. "If we were not good at throwing and running and a few other things, we would not have been able to evolve our large brains, and all the cognitive abilities such as language that come with it. If it were not for our ability to throw, we would not be who we are today."

To start unpacking the evolutionary origins of throwing, Roach began not by studying how humans throw, but how our closest relatives – chimpanzees – do. Though they're known to throw objects (often feces) underhand, chimps, on rare occasions, do throw overhand, but those throws are far less accurate and powerful than those of the average Little League pitcher, Roach said. Additionally, chimps throw as a part of display behavior and never when hunting.

Part of the reason for chimpanzee's poor throwing performance, Lieberman said, is tied to their technique, which in turn is limited by their anatomy. "Chimps throw overhand using either a dart throwing motion, where the elbow is extended, or much like a cricket bowler, where their elbow is kept straight and they generate force by swinging their shoulder", Lieberman said.

The ability to throw an object with great speed and accuracy is a uniquely human adaptation, one that Harvard researchers say played a key role in our evolution. In a paper published June 26 in Nature, a research team led by Neil Roach, who recently received his Ph.D. from Harvard, and Daniel Lieberman, the Edwin M. Lerner II Professor of Biological Sciences find that a suite of changes to the human body enabled early humans to throw -- a skill that became critical to hunting, and helped our ancestors become part-time carnivores, and which later paved the way for a host of later adaptations, including increases in brain size and migration out of Africa. **VIDEO**

"That led us to studying cricket bowlers and trying to understand what happens when you keep your arm straight, and why that diminishes your throwing ability," Roach said. "Eventually, we began to think that changes in the way the shoulder is oriented with regards to the rest of the body could change the way you generate force when you're throwing."

To explore those physical changes, Roach and colleagues began by creating a complex model that incorporated current research about the biomechanics of throwing. Using that model, they were able to explore how morphological changes to the body – wider shoulders, arms that are higher or lower on the body, the ability to twist the upper body independently of the hips and legs, and the anatomy of the humerus – effect throwing performance.

In addition to the modeling, Roach performed a series of real-world experiments in Lieberman's Skeletal Biology Lab using members of the Harvard Baseball team and a host of braces designed to limit their movements.The idea, Roach explained, was that by restricting certain motions, the players would be forced into a more primitive condition, giving him the opportunity to see how different anatomical shifts contribute to the mechanics of modern throwing. Armed with a method known as inverse dynamics, Roach and colleagues were able to not only quantify how much restricting certain types of movements affected throwing performance, but were able to trace the effect to specific changes in the mechanics of each player.

"We try to push these bits of anatomy back in time, if you will, to see how that affects performance," Roach said. "The important thing about our experiments is that they went beyond just being able to measure how the restriction affects someone's ability to throw fast and accurately – they allowed us to to figure out the underlying physics. For example, when a thrower's velocity dropped by 10 percent, we could trace that change back to where it occurred."

"In order to test our evolutionary hypotheses, we needed to link the changes we'd seen in the fossil record to performance in terms of throwing," he continued. "This type of analysis allowed us to do that."

What they found were three key physical changes that helped to make fast, accurate throwing possible. Evolutionary changes in the shoulder show that, as a pitcher cocks their arm back, "what they're doing is stretching the ligaments and tendons that run across their shoulder," Roach said. "Those tendons and ligaments get loaded up like the elastic bands on a slingshot, and late in the throw they release that energy rapidly and forcefully to rotate the upper arm with extraordinary speed and force." That rotation is the fastest motion the human body can produce. "The rotation of the humerus can reach up to 9,000 degrees-per-second, which generates an incredible amount of energy, causing you to rapidly extend your elbow, producing a very fast throw", Roach said.

Among the evolutionary changes that proved key to generating a powerful throwing motions, he said, was a twist in the bone of the upper arm and an expanded, mobile waist, which both gave early humans the ability to store up and then release more of this elastic energy

"The linchpin is really what's going on with the shoulder," Roach said. "When you see the shift from a chimpanzee shoulder to a more relaxed human-like shoulder, that enables this massive energy storage. Many of the evolutionary changes we studied, whether in the torso or the wrist, may predate Homo erectus, but when we see that final change in the shoulder, that's what brings it all together."

While the findings help shed light on a critical phase of human evolution, they also hint at a possible solution to a hotly debated question in sports: When it comes to young players, how much throwing is too much?

"It's a tough question to answer," Roach said. "The real difference, from an evolutionary perspective, is the frequency with which some folks throw now. To successfully learn to throw and use that ability to hunt, our ancestors would need to throw often, but nothing like the 100 or more high speed throws that some baseball pitchers throw now in the span of a couple of hours." "I think it's really a case of what we evolved to do being superseded by what we're now asking athletes to do," he continued. "Athletes are overusing this capability that gave early humans an evolutionary advantage, and they're overusing it to the point that injuries are common."

Ultimately, Lieberman said, the evidence points to one clear conclusion – the ability to throw with speed and accuracy is a uniquely human adaptation, one that played an immeasurably important role in human development. "Recent research indicates that stone points – the oldest kind of spear point – are about 500,000 years old," he said. "But people have been killing animals for at least 2 million years, and eating animals for about 2.6 million years."

"That means that for about 1.5 million years, when people hunted, they basically had nothing more lethal to throw than a pointed wooden stick," he continued. "If you want to kill something with that, you have to be able to throw that pretty hard, and you have to be accurate. Imagine how important it must have been to our ancestors to throw hard and fast."

More information: Paper: dx.doi.org/10.1038/nature12267

http://www.sciencedaily.com/releases/2013/06/130626113654

How Men and Women Cooperate

While men tend to match their partners' emotions during mutual cooperation, woman may have the opposite response, according to new research.

Cooperation is essential in any successful romantic relationship, but how men and women experience cooperation emotionally may be quite different, according to new research conducted at the University of Arizona. Ashley Randall, a post-doctoral research associate in the John & Doris Norton School of Family and Consumer Sciences in the UA's College of Agriculture and Life Sciences, has been interested for some time in how romantic partners' emotions become coordinated with one another. For example, if someone comes home

from work in a bad mood we know their partner's mood might plummet as well, but what are the long-term implications of this on their relationship?
Randall wondered how the act of cooperating, a beneficial relationship process, might impact emotional coordination between partners. "Cooperation -- having the ability to work things out with your partner, while achieving mutually beneficial outcomes -- is so important in relationships, and I wondered what kind of emotional connectivity comes from cooperating with your partner?" said Randall, who is also a research associate in the UA's department of psychiatry.
What she found in her recent study -- published in SAGE's Journal of Social and Personal Relationships -- were surprising gender differences. She and her colleagues found that during high mutual levels of cooperation with a romantic partner, men typically experience an "inphase" response to their significant other's emotions. That is, if the woman in the relationship is feeling more positive, the man will feel more positive. If she feels less positive, he will feel less positive.
On the contrary, it seems women experience more of an "antiphase" pattern during high mutual cooperation. If her partner is feeling more positive, she will tend to feel less positive, and vice versa.
Take, for example, the following familiar scenario: A woman emerges from a department store fitting room and asks her husband what he thinks of a potential new shirt. He likes it, he says, hoping his time at the mall is nearing an end. So does the woman head straight to the cash register and make the purchase? Probably not. Chances are, her husband's enthusiasm won't be enough; she'll want to try on a few more shirts first.
Social psychology literature on cooperation tells us that women generally tend to cooperate more, while men often try to avoid conflict. Thus, men might be subconsciously syncing their emotions with their partners' during cooperation in an effort to avoid conflict or reach a speedy resolution, Randall says.
If that's the case, it's possible, although Randall's study didn't test for it, that women may pick up on the fact that their partner's agreeability is not entirely authentic. If she suspects he's not really as positive as he seems, or that he has an ulterior motive, she may become less positive herself in an attempt to get at his real feelings and reach a more mutually satisfying resolution, Randall suggests.
"If you think about a couple that is trying to cooperate with one another, the man might go along and say, 'oh sure, honey, this is great, are we almost done?' whereas the women might say, 'I'm so glad that you're happy, but I just want to talk about this one other thing because I think we're really getting at a resolution,'" Randall said. In the end, Randall's results suggest that women may tend to serve as the emotional regulators during cooperation.
Randall based her findings on an analysis of 44 heterosexual couples who were videotaped having a conversation about their shared lifestyle related to diet and health. The couples were asked to watch the video back and, using a rating dial, provide momentary feedback about how they were feeling emotionally. Researchers analyzed the videos as well as the participants' responses to them.
Co-authored by the UA's Jesi Post, Rebecca Reed and Emily Butler, the study has implications for better understanding how romantic partners' emotions are connected.
"Cooperation is something that's invaluable and instrumental in a successful relationship but men and women experience it differently," Randall said. "This research provides another avenue to understanding how partners' emotions can become linked, but future research is needed on how these emotional patterns may ultimately contribute to the longevity, or demise, of the romantic relationship."
A. K. Randall, J. H. Post, R. G. Reed, E. A. Butler. Cooperating with your romantic partner: Associations with interpersonal emotion coordination. Journal of Social and Personal Relationships, 2013; DOI: 10.1177/0265407513481864

http://www.eurekalert.org/pub_releases/2013-06/nu-pa062413.php

Promising Alzheimer's 'drug' halts memory loss

'Drug' strikes newly identified target and could be used early in disease

CHICAGO --- A new class of experimental drug-like small molecules is showing great promise in targeting a brain enzyme to prevent early memory loss in Alzheimer's disease, according to Northwestern Medicine® research.
Developed in the laboratory of D. Martin Watterson, the molecules halted memory loss and fixed damaged communication among brain cells in a mouse model of Alzheimer's.
"This is the starting point for the development of a new class of drugs," said Watterson, lead author of a paper on the study and the John G. Searle Professor of Molecular Biology and Biochemistry at Northwestern University Feinberg School of Medicine. "It's possible someday this class of drugs could be given early on to people to arrest certain aspects of Alzheimer's."
Changes in the brain start to occur ten to 15 years before serious memory problems become apparent in Alzheimer's.

"This class of drugs could be beneficial when the nerve cells are just beginning to become impaired," said Linda Van Eldik, a senior author of the paper and director of the University of Kentucky Sanders-Brown Center on Aging.
The study is a collaboration between Northwestern's Feinberg School, Columbia University Medical Center and the University of Kentucky. It will be published June 26 in the journal PLOS ONE.
The novel drug-like molecule, called MW108, reduces the activity of an enzyme that is over-activated during Alzheimer's and is considered a contributor to brain inflammation and impaired neuron function. Strong communication between neurons in the brain is an essential process for memory formation.
"I'm not aware of any other drug that has this effect on the central nervous system," Watterson said.
"These exciting results provide new hope for developing drugs against an important molecular target in the brain," said Roderick Corriveau, program director at the National Institute of Neurological Disorders and Stroke, which helped support the research. "They also provide a promising strategy for identifying small molecule drugs designed to treat Alzheimer's disease and other neurological disorders."
Watterson and his collaborators have a new National Institutes of Health (NIH) award to further refine the compound so it is metabolically stable and safe for use in humans and develop it to the point of starting a phase 1 clinical trial.
Other senior authors on the paper are Wayne Anderson, professor of molecular pharmacology and biological chemistry at Feinberg, and Ottavio Arancio, M.D., associate professor of pathology and cell biology at Columbia.

Compound Strikes New Bull's Eye

The compound strikes at a new, single target that has long flown under the radar in Alzheimer 's drug development. The target is a stress-related protein kinase, p38alpha MAPK.
"We think this protein kinase target is one of the key players in the early to mid-stage of several diseases of the central nervous system and cancer," Watterson said. Recent neuroscience research has shown that the target is activated in neurological disorders such as Alzheimer's.
These other diseases include amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), Parkinson's and frontotemporal dementia. In cancer, the protein helps malignant tumors evade the immune system as they metastasize and alter their microenvironment in a stealth type of expansion. Scientists at the University of California at San Diego currently are studying MW108 in preclinical cancer immunology research.

"Drug" Prevents Alzheimer's-like Symptoms in Mice

In a key memory experiment in the study, mice brains were injected with beta-amyloid, whose increase is one hallmark of Alzheimer's in humans. One group of mice was then administered MW108 and another group was administered a placebo.
Next, each group of mice was taught environmental cues to learn how to swim through a water maze to find a resting platform. Then the mice were placed in a different arm of the maze and tested on their ability to remember the location of the platform based on the environmental cues.
The mice administered MW108 found the resting platform in the water maze as quickly as a control group of mice. The mice given the placebo made more mistakes and took longer to find the platform. They also had difficulty learning the location of the resting platform during the teaching phase.
"The results show the compound prevented the cognitive impairment," Van Eldik said.

Can You Hear Me Now?

Another experiment in the study directly tested the compound's effect on the synaptic signal, the strength of the electrical connection between brain cells. Like a signal on your cell phone, you can't hear what the caller is saying if you don't have a strong signal. The same goes for brain cell communication. "That's why we think people with Alzheimer's disease have trouble learning," said Columbia's Arancio, who performed the synaptic signal experiment. "If you can't transmit information from one cell to another, you can't learn."
Arancio's team took slices of a normal mouse brain and incubated them with beta-amyloid or a combination of beta-amyloid and the MW108 compound. Then they pulsed electrical current -- similar to the current in a brain – through each slice and measured the strength of the electrical signal in the synapses. The mouse brain treated with beta-amyloid had a lower signal that decayed more rapidly, indicating the synapse is impaired and not communicating well. The mouse brain treated with beta-amyloid and the MW108 had a strong signal that fired normally. The compound prevented the impairment of the synapse.

Damaging the Wiring

The over-activated protein kinase p38 MAPK damages the wiring of the communication network within the brain. Neurons communicate with other neurons at structures called synapses. Over activation of p38 MAPK damages the synapses and alters the normal functioning of neurons, impairing communication.

The p38 MAPK is also present in glial cells, which are critical to the brain's health and comprise 90 percent of brain cells. They control the strength and duration of the synaptic signal. Too much activation of p38 MAPK in glial cells impairs their supportive function and can result in the release of neurotoxic molecules further harming the synapse.
MW108 protects the brain in two different but complementary ways. By inhibiting p38 MAPK, it prevents both inflammation in the glial cells and disruption of the neuronal messages at the synapse. The result is a robust signal between neurons and within the larger communication network, which protects memory formation.

Designing the Right Puzzle Piece To Disable the Target

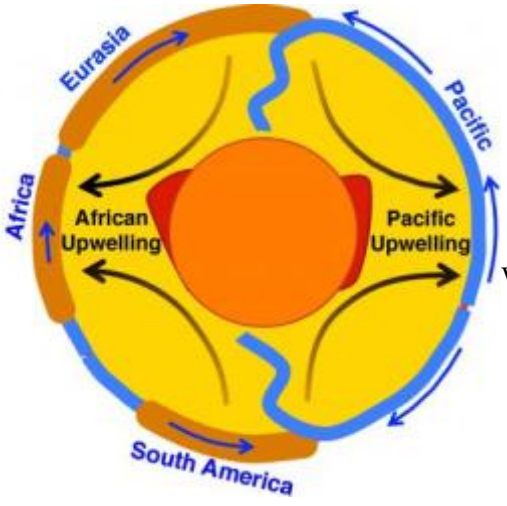
The new drug-like probe strikes a single bull's eye that selectively disables the lone protein kinase, whose over activation is a major contributor to the brain network dysfunction. The single target approach of MW108 is novel. The prevailing view has been that multiple kinases in a network had to be disabled in order to restore normal function. There are an estimated 400-500 kinases in the human genome, with literally dozens being activated during disease processes. The research of Watterson and collaborators shows that striking the right one can be highly effective.
Watterson envisions that an array of drugs eventually will be used to treat Alzheimer's and other complex neurological diseases. He said MW108 was designed to minimize drug interaction so it could be used in combination with other drugs.
Northwestern scientists were able to rapidly design the novel small molecule MW108 to selectively disable the protein kinase because of Northwestern's premier structural genomics programs, Watterson said.
Wayne Anderson is one of the leaders of Northwestern's structural genomics programs, which use state-of-the-art expertise and technology to map the three-dimensional atomic structure of proteins involved in human disease. Anderson and Valerie Grum-Tokars, a junior structural biologist on the team, developed a three-dimensional structure of human p38 MAPK, enabling the chemists to design and synthesize novel drug-like small molecules that would disable it. "We found the piece that fits precisely into the binding site of the protein kinase and prevents its operation," Anderson said.
The research was supported by the Thome Memorial Foundation, an Alzheimer's Association Zenith award and grants R01 NS064247, R01 NS056051 from the National Institute of Neurological Disorders and Stroke at NIH and grants R01 AG031311, F32 AG037280 and U01AG043415 from the National Institute on Aging at NIH.

http://www.eurekalert.org/pub_releases/2013-06/uoha-lou062513.php

Location of upwelling in Earth's mantle discovered to be stable

A study published in Nature today shares the discovery that large-scale upwelling within Earth's mantle mostly occurs in only two places: beneath Africa and the Central Pacific.

Honolulu, HI - More importantly, Clinton Conrad, Associate Professor of Geology at the University of Hawaii – Manoa's School of Ocean and Earth Science and Technology (SOEST) and colleagues revealed that these upwelling locations have remained remarkably stable over geologic time, despite dramatic reconfigurations of tectonic plate motions and continental locations on the Earth's surface. "For example," said Conrad, "the Pangaea supercontinent formed and broke apart at the surface, but we think that the upwelling locations in the mantle have remained relatively constant despite this activity."



Conrad has studied patterns of tectonic plates throughout his career, and has long noticed that the plates were, on average, moving northward. "Knowing this," explained Conrad, "I was curious if I could determine a single location in the Northern Hemisphere toward which all plates are converging, on average." After locating this point in eastern Asia, Conrad then wondered if other special points on Earth could characterize plate tectonics. "With some mathematical work, I described the plate tectonic 'quadrupole', which defines two points of 'net convergence' and two points of 'net divergence' of tectonic plate motions."

This is a diagram showing a slice through the Earth's mantle, cutting across major mantle upwelling locations beneath Africa and the Pacific. **C. Conrad (UH SOEST)**

When the researchers computed the plate tectonic quadruople locations for present-day plate motions, they found that the net divergence locations were consistent with the African and central Pacific locations where scientists think that mantle upwellings are occurring today. "This observation was interesting and important, and it made sense," said Conrad. "Next, we applied this formula to the time history of plate motions and plotted

the points - I was astonished to see that the points have not moved over geologic time!" Because plate motions are merely the surface expression of the underlying dynamics of the Earth's mantle, Conrad and his colleagues were able to infer that upwelling flow in the mantle must also remain stable over geologic time. "It was as if I was seeing the 'ghosts' of ancient mantle flow patterns, recorded in the geologic record of plate motions!"
Earth's mantle dynamics govern many aspects of geologic change on the Earth's surface. This recent discovery that mantle upwelling has remained stable and centered on two locations (beneath Africa and the Central Pacific) provides a framework for understanding how mantle dynamics can be linked to surface geology over geologic time. For example, the researchers can now estimate how individual continents have moved relative to these two upwelling locations. This allows them to tie specific events that are observed in the geologic record to the mantle forces that ultimately caused these events.
More broadly, this research opens up a big question for solid earth scientists: What processes cause these two mantle upwelling locations to remain stable within a complex and dynamically evolving system such as the mantle? One notable observation is that the lowermost mantle beneath Africa and the Central Pacific seems to be composed of rock assemblages that are different than the rest of the mantle. Is it possible that these two anomalous regions at the bottom of the mantle are somehow organizing flow patterns for the rest of the mantle? How?
"Answering such questions is important because geologic features such as ocean basins, mountains belts, earthquakes and volcanoes ultimately result from Earth's interior dynamics," Conrad described. "Thus, it is important to understand the time-dependent nature of our planet's interior dynamics in order to better understand the geological forces that affect the planetary surface that is our home."
The mantle flow framework that can be defined as a result of this study allows geophysicists to predict surface uplift and subsidence patterns as a function of time. These vertical motions of continents and seafloor cause both local and global changes in sea level. In the future, Conrad wants to use this new understanding of mantle flow patterns to predict changes in sea level over geologic time. By comparing these predictions to observations of sea level change, he hopes to develop new constraints on the influence of mantle dynamics on sea level.
This research was funded by the U.S. National Science Foundation and the Norwegian Centre for Advanced Study in Oslo, Norway.
C P Conrad, B Steinberger, T H Torsvik (2013) Stability of active mantle upwelling revealed by net characteristics of plate tectonics. Nature, doi:10.1038/nature12203

http://www.eurekalert.org/pub_releases/2013-06/ciot-asf062613.php

A stepping-stone for oxygen on Earth

Caltech researchers find evidence of an early manganese-oxidizing photosystem

For most terrestrial life on Earth, oxygen is necessary for survival. But the planet's atmosphere did not always contain this life-sustaining substance, and one of science's greatest mysteries is how and when oxygenic photosynthesis—the process responsible for producing oxygen on Earth through the splitting of water molecules—first began. Now, a team led by geobiologists at the California Institute of Technology (Caltech) has found evidence of a precursor photosystem involving manganese that predates cyanobacteria, the first group of organisms to release oxygen into the environment via photosynthesis.
The findings, outlined in the June 24 early edition of the Proceedings of the National Academy of Sciences (PNAS), strongly support the idea that manganese oxidation—which, despite the name, is a chemical reaction that does not have to involve oxygen—provided an evolutionary stepping-stone for the development of water-oxidizing photosynthesis in cyanobacteria.
"Water-oxidizing or water-splitting photosynthesis was invented by cyanobacteria approximately 2.4 billion years ago and then borrowed by other groups of organisms thereafter," explains Woodward Fischer, assistant professor of geobiology at Caltech and a coauthor of the study. "Algae borrowed this photosynthetic system from cyanobacteria, and plants are just a group of algae that took photosynthesis on land, so we think with this finding we're looking at the inception of the molecular machinery that would give rise to oxygen."
Photosynthesis is the process by which energy from the sun is used by plants and other organisms to split water and carbon dioxide molecules to make carbohydrates and oxygen. Manganese is required for water splitting to work, so when scientists began to wonder what evolutionary steps may have led up to an oxygenated atmosphere on Earth, they started to look for evidence of manganese-oxidizing photosynthesis prior to cyanobacteria. Since oxidation simply involves the transfer of electrons to increase the charge on an atom—and this can be accomplished using light or O2—it could have occurred before the rise of oxygen on this planet.
"Manganese plays an essential role in modern biological water splitting as a necessary catalyst in the process, so manganese-oxidizing photosynthesis makes sense as a potential transitional photosystem," says Jena Johnson, a graduate student in Fischer's laboratory at Caltech and lead author of the study.

To test the hypothesis that manganese-based photosynthesis occurred prior to the evolution of oxygenic cyanobacteria, the researchers examined drill cores (newly obtained by the Agouron Institute) from 2.415 billion-year-old South African marine sedimentary rocks with large deposits of manganese.

Manganese is soluble in seawater. Indeed, if there are no strong oxidants around to accept electrons from the manganese, it will remain aqueous, Fischer explains, but the second it is oxidized, or loses electrons, manganese precipitates, forming a solid that can become concentrated within seafloor sediments.

"Just the observation of these large enrichments—16 percent manganese in some samples—provided a strong implication that the manganese had been oxidized, but this required confirmation," he says.

To prove that the manganese was originally part of the South African rock and not deposited there later by hydrothermal fluids or some other phenomena, Johnson and colleagues developed and employed techniques that allowed the team to assess the abundance and oxidation state of manganese-bearing minerals at a very tiny scale of 2 microns.

"And it's warranted—these rocks are complicated at a micron scale!" Fischer says. "And yet, the rocks occupy hundreds of meters of stratigraphy across hundreds of square kilometers of ocean basin, so you need to be able to work between many scales—very detailed ones, but also across the whole deposit to understand the ancient environmental processes at work."

Using these multiscale approaches, Johnson and colleagues demonstrated that the manganese was original to the rocks and first deposited in sediments as manganese oxides, and that manganese oxidation occurred over a broad swath of the ancient marine basin during the entire timescale captured by the drill cores.

"It's really amazing to be able to use X-ray techniques to look back into the rock record and use the chemical observations on the microscale to shed light on some of the fundamental processes and mechanisms that occurred billions of years ago," says Samuel Webb, coauthor on the paper and beam line scientist at the SLAC National Accelerator Laboratory at Stanford University, where many of the study's experiments took place. "Questions regarding the evolution of the photosynthetic pathway and the subsequent rise of oxygen in the atmosphere are critical for understanding not only the history of our own planet, but also the basics of how biology has perfected the process of photosynthesis."

Once the team confirmed that the manganese had been deposited as an oxide phase when the rock was first forming, they checked to see if these manganese oxides were actually formed before water-splitting photosynthesis or if they formed after as a result of reactions with oxygen. They used two different techniques to check whether oxygen was present. It was not—proving that water-splitting photosynthesis had not yet evolved at that point in time. The manganese in the deposits had indeed been oxidized and deposited before the appearance of water-splitting cyanobacteria. This implies, the researchers say, that manganese-oxidizing photosynthesis was a stepping-stone for oxygen-producing, water-splitting photosynthesis.

"I think that there will be a number of additional experiments that people will now attempt to try and reverse engineer a manganese photosynthetic photosystem or cell," Fischer says. "Once you know that this happened, it all of a sudden gives you reason to take more seriously an experimental program aimed at asking, 'Can we make a photosystem that's able to oxidize manganese but doesn't then go on to split water? How does it behave, and what is its chemistry?' Even though we know what modern water splitting is and what it looks like, we still don't know exactly how it works. There is a still a major discovery to be made to find out exactly how the catalysis works, and now knowing where this machinery comes from may open new perspectives into its function—an understanding that could help target technologies for energy production from artificial photosynthesis. "

Next up in Fischer's lab, Johnson plans to work with others to try and mutate a cyanobacteria to "go backwards" and perform manganese-oxidizing photosynthesis. The team also plans to investigate a set of rocks from western Australia that are similar in age to the samples used in the current study and may also contain beds of manganese. If their current study results are truly an indication of manganese-oxidizing photosynthesis, they say, there should be evidence of the same processes in other parts of the world.

"Oxygen is the backdrop on which this story is playing out on, but really, this is a tale of the evolution of this very intense metabolism that happened once—an evolutionary singularity that transformed the planet," Fischer says. "We've provided insight into how the evolution of one of these remarkable molecular machines led up to the oxidation of our planet's atmosphere, and now we're going to follow up on all angles of our findings."

Funding for the research outlined in the PNAS paper, titled "Manganese-oxidizing photosynthesis before the rise of cyanobacteria," was provided by the Agouron Institute, NASA's Exobiology Branch, the David and Lucile Packard Foundation, and the National Science Foundation Graduate Research Fellowship program. Joseph Kirschvink, Nico and Marilyn Van Wingen Professor of Geobiology at Caltech, also contributed to the study along with Katherine Thomas and Shuhei Ono from the Massachusetts Institute of Technology.

http://www.eurekalert.org/pub_releases/2013-06/wsu-rcf062513.php

Researchers call for rethinking efforts to prevent interplanetary contamination

Sterilized Mars spacecraft largely a waste of money

PULLMAN, Wash.—Two university researchers say environmental restrictions have become unnecessarily restrictive and expensive—on Mars.

Writing in the journal Nature Geoscience, astrobiologists Alberto Fairén of Cornell University and Dirk Schulze-Makuch of Washington State University say the NASA Office of Planetary Protection's "detailed and expensive" efforts to keep Earth microorganisms off Mars are making missions to search for life on the red planet "unviable." The researchers claim "the protocols and policies of Planetary Protection are unnecessarily restricting Mars exploration and need to be revised."

The Office of Planetary Protection is like an interplanetary Environmental Protection Agency, with a mission "to minimize the biological contamination that may result from exploring the solar system."

As far as Mars is concerned, say Fairén and Schulze-Makuch, such efforts are probably in vain, as "Earth life has most likely already been transferred to Mars." Meteorite impacts have had 3.8 billion years to spread Earth life forms to Mars, as could several spacecraft that visited the planet without undergoing sterilization procedures now in place.

If organisms transferred to Mars over the eons failed to survive, modern organisms would likely face the same fate. On the other hand, if they did survive, say Fairén and Schulze-Makuch, "it is too late to protect Mars from terrestrial life, and we can safely relax the planetary protection policies."

The researchers say spacecraft looking for life on Mars should still be cleaned to some extent to avoid confusing possible Martian organisms with organisms brought from Earth. But sterilization for other missions, like orbiters and geology-oriented explorers, could be scaled back. "As planetary exploration faces drastic budget cuts globally," they say, "it is critical to avoid unnecessary expenses and reroute the limited taxpayers' money to missions that can have the greatest impact on planetary exploration."

http://bit.ly/14zlpRa

Zoologger: Invasion of the sleepy raccoon dogs

Species: Nyctereutes procyonoides

Habitat: A native population in east Asia, including Japan, and an introduced population in Europe

11:46 27 June 2013 by Michael Marshall

Hurrying through a dangerous landscape, the moustachioed plumber comes across unexpected treasure: the furry skin of a raccoon dog, its innards nowhere to be seen. Hastily wrapping the skin around himself – because of course you would do that if you found an animal skin – he develops magical abilities. He can fly by wagging the tail, and transform into a statue at will.

Confused? Don't be. This happened to many thousands of people in the late 1980s, when they played Super Mario Bros. 3. In this game, Nintendo's heroic plumber occasionally acquired a "tanooki suit" that gave him exactly these magical abilities.

In real life, raccoon dogs do not fly or transform into statues. They are not related to raccoons, but they are related to dogs. In fact, they are among the most primitive canids still alive, and the only ones that hibernate. They are also spreading rapidly. Having spent the last ice age in South Korea, they have now made it as far as Scandinavia.

Tanuki trouble

In Japan, raccoon dogs are known as tanuki, and you often see statues of them outside restaurants – with very large testicles. They are native to the far east of Asia, particularly Korea and Japan. But between 1928 and 1957 the Soviet Union introduced them to countries near its western borders – mostly so they could be hunted for fur. Raccoon dogs are now established in eastern and central Europe. They are still spreading north and west, and have been spotted in France and Finland.

They have spread largely because they are adaptable; able to switch quickly to different diets and environments. In Europe, they climb trees to reach insects, whereas in Japan they often live off trash. Another factor in their favour is that young raccoon dogs can travel tens of kilometres to find a territory – although this does mean that youngsters are frequently killed on roads. Raccoon dogs are also excellent at coping with cold winters and food shortages, hence their spread into northern Europe. They can fast in the autumn, and even hibernate through the winter – often co-opting badger setts for the purpose.

On the move

Raccoon dogs were not always so cosmopolitan. Some 20,000 years ago, Earth was in the grip of the last ice age, and raccoon dogs were confined to a small area of east Asia. Mi-Sook Min of Seoul National University in

South Korea and colleagues have now examined raccoon dog genes to figure out how their populations have changed.
The team collected 147 raccoon dogs from Korea, Russia, China, Vietnam and Japan, and examined their DNA. The raccoon dogs divided neatly into two groups: one living in Japan, and one living on mainland Asia. That suggests the raccoon dogs survived the ice age by lurking on the Korean peninsula and in Japan. These two groups seem to have been isolated from one another.
The raccoon dog genomes also showed signs of a recent population expansion, suggesting their population had shrunk to a low level and then exploded. It seems that once the ice sheets began to retreat, the raccoon dogs thrived and spread throughout east Asia.
If we had left them to their own devices, they might only now be reaching central Asia. Instead, thanks to the former Soviet Union's predilection for their fur, they are all the way over in central Europe. And as the climate warms and the ice retreats, they're only going to spread further. It's a good thing they're so cute.
Journal reference: Journal of Zoology, DOI: 10.1111/jzo.12031

http://www.eurekalert.org/pub_releases/2013-06/uu-lsb062713.php

Link shown between Crohn's disease and virus

A new study reveals that all children with Crohn's disease that were examined had a commonly occurring virus – an enterovirus – in their intestines.

This link has previously not been shown for this chronic inflammatory intestinal disorder. The findings are being published today in the latest issue of the international journal Clinical and Translational Gastroenterology. These findings need to be confirmed in larger studies, but they are important, as this connection has never been pointed out before. This paves the way for a better understanding of what might be involved in causing the disease, says Alkwin Wanders, one of the scientists behind the study at Uppsala University and Uppsala University Hospital.
In Sweden several thousand adults live with Crohn's disease, and each year about 100 children and adolescents develop the disorder. The disease affects various parts of the gastrointestinal system and causes symptoms such as stomach aches, diarrhoea, and weight loss – in severe cases fistulas, or strictures in the intestines.
The cause of Crohn's disease is not known. Mutations in more than 140 genes have been shown to be associated with the disorder, but this genetic connection is not a sufficient explanation. Many of these genes play key roles in the immune defence, which has prompted theories that the disease might be caused by impaired immune defence against various microorganisms. In that case, the disease would be a consequence of interplay between heredity and environment.
Recent research has shown that some of the genes that are strongly linked to the disorder are important for the immune defence against a certain type of viruses that have their genetic material in the form of RNA, so-called RNA viruses. Using this as a point of departure, an interdisciplinary research team was established in Sweden to investigate what role this type of virus plays in the disease.
The research team includes the paediatrician Niklas Nyström, the pathologist Alkwin Wanders, virus researchers Gun Frisk and Oskar Skog, the molecular biologist Mats Nilsson, and the geneticist Ulf Gyllensten at Uppsala University and Uppsala University Hospital, along with cell biologists Jonas Fuxe and Tove Berg the paediatrician Yigael Finkel at Karolinska Institutet in Stockholm. This unique composition, with complementary clinical and scientific expertise, has been extremely fruitful for our studies, says Alkwin Wanders.
In the present study the researchers investigated whether the RNA virus were present in children with Crohn´s disease. They focused in particular on the prevalence of enteroviruses, a group of RNA viruses that are known to infect the intestinal mucous lining.
The results showed significant amounts of enteroviruses in the intestines of all of the children with Crohn´s disease, whereas the control group had no or only minimal amounts of enteroviruses in their intestines. Similar results were obtained using two different methods. Enteroviruses were found not only in intestinal mucous linings but also in so-called nerve cell ganglia in deeper segments of the intestinal wall. Receptors for a group of enteroviruses were also found in both the intestinal mucous linings and nerve cell ganglia, which may explain how the virus can make its way into the nerve system in the intestine.
Another interesting finding is that the enterovirus could be thought to be stored in nerve cells in the intestine and to spread to different parts of the intestine via nerve fibres. This would explain both the fact that the disease is periodic (comes and goes) and the fact that it often affects multiple segments of the intestines, says Alkwin Wanders.

The present study comprises nine children with advanced Crohn's disease and fifteen children with incipient Crohn's disease symptoms. The research now wants to go on to examine larger groups of patients and more control individuals. They also want to pursue experimental research to investigate the link further.
The study was funded by, among others, Uppsala County Council, the Swedish Society for Medical Research, Cancerfonden, Karolinska Institutet, and the Swedish Research Council.

http://www.eurekalert.org/pub_releases/2013-06/whoi-sdt062713.php

Scientists discover thriving colonies of microbes in ocean 'plastisphere'

Scientists have discovered a diverse multitude of microbes colonizing and thriving on flecks of plastic that have polluted the oceans—a vast new human-made flotilla of microbial communities that they have dubbed the "plastisphere."

In a study recently published online in Environmental Science & Technology, the scientists say the plastisphere represents a novel ecological habitat in the ocean and raises a host of questions: How will it change environmental conditions for marine microbes, favoring some that compete with others? How will it change the overall ocean ecosystem and affect larger organisms? How will it change where microbes, including pathogens, will be transported in the ocean?

The collaborative team of scientists—Erik Zettler from Sea Education Association (SEA), Tracy Mincer from Woods Hole Oceanographic Institution (WHOI), and Linda Amaral-Zettler from the Marine Biological Laboratory (MBL), all in Woods Hole, Mass.—analyzed marine plastic debris that was skimmed with fine-scale nets from the sea surface at several locations in the North Atlantic Ocean during SEA research cruises. Most were millimeter-sized fragments.

"We're not just interested in who's there. We're interested in their function, how they're functioning in this ecosystem, how they're altering this ecosystem, and what's the ultimate fate of these particles in the ocean," says Amaral-Zettler. "Are they sinking to the bottom of the ocean? Are they being ingested? If they're being ingested, what impact does that have?"

Using scanning electron microscopy and gene sequencing techniques, they found at least 1000 different types of bacterial cells on the plastic samples, including many individual species yet to be identified. They included plants, algae, and bacteria that manufacture their own food (autotrophs), animals and bacteria that feed on them (heterotrophs), predators that feed on these, and other organisms that establish synergistic relationships (symbionts). These complex communities exist on plastic bits hardly bigger than the head of a pin, and they have arisen with the explosion of plastics in the oceans in the last 60 years.

"The organisms inhabiting the plastisphere were different from those in surrounding seawater, indicating that plastic debris acts as artificial 'microbial reefs," says Mincer. "They supply a place that selects for and supports distinct microbes to settle and succeed." These communities are likely different from those that settle on naturally occurring floating material such as feathers, wood, and microalgae, because plastics offer different conditions, including the capacity to last much longer without degrading.

On the other hand, the scientists also found evidence that microbes may play a role in degrading plastics. They saw microscopic cracks and pits in the plastic surfaces that they suspect were made by microbes embedded in them, as well as microbes possibly capable of degrading hydrocarbons.

"When we first saw the 'pit formers' we were very excited, especially when they showed up on multiple pieces of plastic of different types of resins," said Zettler, who added that undergraduate students participating in SEA Semester cruises collected and processed the samples. "Now we have to figure out what they are by [genetically] sequencing them and hopefully getting them into culture so we can do experiments."

The plastic debris also represents a new mode of transportation, acting as rafts that can convey harmful microbes, including disease-causing pathogens and harmful algal species. One plastic sample they analyzed was dominated by members of the genus Vibrio, which includes bacteria that cause cholera and gastrointestinal maladies.

The project was funded by a National Science Foundation Collaborative grant, a NSF TUES grant, and a Woods Hole Center for Oceans and Human Health Pilot award.

http://www.eurekalert.org/pub_releases/2013-06/aaos-lba062613.php

Late bedtimes and less sleep may lead to weight gain in healthy adults

Chronic sleep restriction among adults with late bedtimes may be associated with weight gain due to the consumption of extra calories during late-night hours

DARIEN, IL – A new study suggests that healthy adults with late bedtimes and chronic sleep restriction may be more susceptible to weight gain due to the increased consumption of calories during late-night hours.

In the largest, most diverse healthy sample studied to date under controlled laboratory conditions, results show that sleep-restricted subjects who spent only four hours in bed from 4 a.m. to 8 a.m. for five consecutive nights

gained more weight than control subjects who were in bed for 10 hours each night from 10 p.m. to 8 a.m. The study found an overall increase in caloric intake during sleep restriction, which was due to an increase in the number of meals consumed during the late-night period of additional wakefulness. Furthermore, the proportion of calories consumed from fat was higher during late-night hours than at other times of day.

"Although previous epidemiological studies have suggested an association between short sleep duration and weight gain/obesity, we were surprised to observe significant weight gain during an in-laboratory study," said lead author Andrea Spaeth, a doctoral candidate in the psychology department at the University of Pennsylvania in Philadelphia, Pa.

The study, which appears in the July issue of the journal Sleep, was conducted in the Sleep and Chronobiology Laboratory at the Hospital of the University of Pennsylvania. The study group comprised 225 healthy, non-obese individuals, ranging in age from 22-50 years. Subjects were randomized to either the sleep restriction or control condition and spent up to 18 consecutive days in the laboratory.

Meals were served at scheduled times, and food was always available in the laboratory kitchen for participants who wanted to eat at other times of day. Subjects could move around but were not allowed to exercise. They were permitted to watch TV, read, play video games or perform other sedentary activities.

The study also found that during sleep restriction males gained more weight than females, and African Americans gained more weight than Caucasians.

"Among sleep-restricted subjects, there were also significant gender and race differences in weight gain," said Spaeth. "African Americans, who are at greater risk for obesity and more likely to be habitual short sleepers, may be more susceptible to weight gain in response to sleep restriction. Future studies should focus on identifying the behavioral and physiological mechanisms underlying this increased vulnerability."

The American Academy of Sleep Medicine reports that weight gain is a risk factor for obstructive sleep apnea (OSA), a common sleep illness that has a severe impact on health and quality of life. The risk of OSA increases as the degree of additional weight increases, with an extremely high prevalence of OSA in people with morbid obesity. Anyone who has experienced recent weight gain and has symptoms of OSA, such as loud and frequent snoring, should be evaluated by a board certified sleep medicine physician.

Last week the AASM issued a statement supporting the new policy of the American Medical Association (AMA) recognizing obesity as a disease requiring a range of medical interventions to advance treatment and prevention. In conjunction with obesity interventions, proper treatment of OSA can dramatically improve overall health and contribute to successful weight management.

To request a copy of the study, "Effects of experimental sleep restriction on weight gain, caloric intake, and meal timing in healthy adults," or to arrange an interview with an AASM spokesperson, please contact Communications Coordinator Lynn Celmer at 630-737-9700, ext. 9364, or lcelmer@aasmnet.org.

http://phys.org/news/2013-06-silver-colonization-bacteria-medical-devices.html

Can silver promote the colonization of bacteria on medical devices?

Recent study suggests that, in one material, increasing levels of silver may indirectly promote bacterial adhesion.

Biomaterials are increasingly being used to replace human organs and tissues. Since biomaterials are susceptible to microbial colonization, silver is often added to reduce the adhesion of bacteria to biomaterials and prevent infections. However, a recent study by researchers in Portugal suggests that – in one material – increasing levels of silver may indirectly promote bacterial adhesion.

Published in the journal Science and Technology of Advanced Materials, the study examined how surface properties affect the adhesion of Staphylococcus epidermidis bacteria to silver-titanium carbonitride (Ag-TiCN) coatings used for hip implant applications.

Normally found on human skin and mucous membranes, Staphyloccus epidermidis is one of the main pathogens associated with prosthetic device infections. A nanocomposite thin film, titanium carbonitride is non-toxic to human cells and features excellent wear resistance, high hardness and good corrosion resistance.

Previous studies have shown that the adhesion of bacteria to biomaterials can be affected by the surface properties of bacteria, the surface properties of the material, and environmental conditions. In this study, Isabel Carvalho and her colleagues found that as the silver content of Ag-TiCN films increased from 0 to 15 percent, the surface roughness of the films decreased from 39 nm to 7 nm, while the hydrophobicity of the surface increased.

In addition, the study found that surfaces that were less rough and more hydrophobic were associated with greater bacterial adhesion. This suggests that increasing levels of silver in Ag-TiCN thin films may promote bacterial adhesion via a hydrophobic effect.

More information: Carvalho, I. et al. Science and Technology of Advanced Materials, Vol. 14 (2013) p. 035009. DOI: 10.1088/1468-6996/14/3/035009

http://phys.org/news/2013-06-redefining-populations-survive.html

Redefining adaptation, the study of how populations grow and survive

How do organisms adapt over time? Do they evolve through a series of small beneficial steps as envisioned by Charles Darwin, or through a series of rare but large jumps? Or through a combination of both?

Phys.org - For example, "did a giraffe's neck get longer because there were thousands of mutations each resulting in a millimeter increase?" asks Christopher Marx, associate professor of organismic and evolutionary biology at Harvard University. "Or were there three or four changes over time that changed the size of the vertebrae dramatically?"

Marx's research focuses on adaptation, the process by which populations improve in their ability to grow and survive. "One of the major questions that we are trying to address is: What is the relative proportion of small beneficial mutations to big beneficial mutations?" he says. "And how does this outcome differ with the size of the population?"

Understanding how adaptation works in smaller populations is important because many scenarios—from new infections to cancer—involve small numbers of cells.

"Many current therapeutic approaches aim to reduce population sizes of pathogens in order to thwart their eventual success," Marx says. "This would work very well if these shrunken populations struggle to find beneficial mutations, but would be much less effective if big benefit mutations—to the pathogen or cancer—are actually fairly easy to achieve."

Until recently, many scientists held the classic Darwinian view that adaptation occurs gradually through a series of small changes, he says. Furthermore, they believed that it is extremely rare that a random mutation would actually benefit an organism in a given environment, he says.

"One consequence of the rarity of beneficial mutations would be that any improvement that arose would have a chance to take over before another beneficial mutation would arise, and would thus proceed unchallenged," Marx says. "This would lead to a series of rare, step-like jumps in performance. It would also mean that the mutations that won—rising to 100 percent of the population—would give a fairly clear picture of what is biologically possible for that organism."

In order to study adaptation, including how organisms can improve, Marx's laboratory grows hundreds of bacterial populations in the laboratory. Scientists can preserve live bacteria in an ultra-cold freezer, allowing them to revive and directly study their common ancestor, the one they used to initiate succeeding generations over time.

"Despite the diminutive physical size of these populations, each of which were grown in 1/50th of an ounce of liquid, the final population size could reach as high as 100 million cells," Marx says.

Recent work from a number of laboratories, including Marx's, has shown that beneficial mutations actually can occur much more readily than previously thought. "This changes adaptation dramatically because many innovations can arise at once and they cannot all win," he says.

He compares this competition between rival genetic innovations to what happens in a market economy when, for example, a new field opens and "many companies enter the race and, over time, the better ones beat out the weaker ones," he says.

"Because of the potential for having many new inventions present at once, the population size itself has a profound effect on adaptation," he adds. "The intuition has been that really amazing solutions to a problem are much less common than mediocre ones. Thus, the current theory is that small populations improve via little steps and big populations take big steps."

Marx is conducting his research under a National Science Foundation (NSF) Faculty Early Career Development (CAREER) award, which he received in 2009 as part of NSF's American Recovery and Reinvestment Act. The award supports junior faculty who exemplify the role of teacher-scholars through outstanding research, excellent education and the integration of education and research within the context of the mission of their organization. NSF is funding his work with $702,452 over five years.

The educational component of his grant includes a project-based lab course built around experimental evolution, and a website where scientists who work in microbial evolution can freely share educational materials.

Specifically, Marx has been studying Methylobacterium, a common microbe that lives on the surface of leaves and eats such things as methanol. "It's also the main cause of that pink scum in your shower," he says.

Based upon ongoing work evolving Methylobacterium in the laboratory, Marx and his graduate student, Nigel Delaney, have both confirmed and begun to question current beliefs.

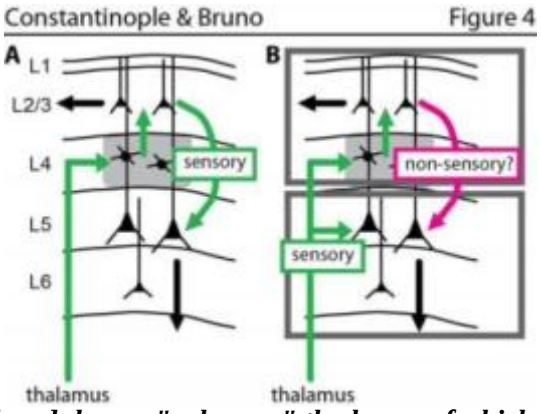
"If you change the population size, three things are supposed to happen," he says. "The first is that big populations should adapt faster than small ones, which turns out to be true. The second is that big populations should have more infighting than little populations, which is also true. The third is that big populations will move by big steps, and small populations will move by small steps."
Their work is ongoing; however, their current data suggest that the third point might not necessarily be true. "Our small and big populations both took big steps," he says. "Big mutations can happen easily. We've seen that in our bug, and it completely changes the picture."
The experiments conducted by Marx and others using populations of microbes in the laboratory that they can control allows them to learn about the range of adaptation possibilities in a way that is difficult when directly studying infectious diseases or cancer, where there will be confounding differences in environments, starting strains or host genetics, and medical treatments. "The recent use of sequencing to discover cancer variants within a polyp, for example, has re-discovered what researchers in the lab had already shown: many beneficial mutants tend to rise simultaneously, rather than sequentially," he says.
Marx's lab also has begun to examine the outcome of combining more than one beneficial mutation. "Do they stay equally valuable?" he says.
Last year, in a paper his team published in the journal Science, they reported on a general trend of diminishing returns. "It turns out that beneficial mutations become less valuable when combined with each other," he says. Similarly, a University of Houston group led by Marx's friend and colleague, Tim Cooper, an assistant professor of biology, found this identical trend in the evolution of Escherichia coli.
"We had given presentations right after each other at a conference the year before and were shocked by the similarity in our work," Marx says. "That the same trend emerged in two very different systems hinted that it might be a much more widespread finding. Indeed, later papers with viruses and yeast have seen the same."
Ultimately, Marx and Cooper decided to submit their papers at the same time, because "unlike the mutations we studied, we felt our work was more valuable when combined."

http://www.sciencedaily.com/releases/2013/06/130627141724.htm

Prevailing View of How the Brain Is Wired Overturned?

Studies topple convention, showing sensory information travels to two places at once: not only to the brain's mid-layer, but also directly to its deeper layers.

A series of studies conducted by Randy Bruno, PhD, and Christine Constantinople, PhD, of Columbia University's Department of Neuroscience, topples convention by showing that sensory information travels to two places at once: not only to the brain's mid-layer (where most axons lead), but also directly to its deeper layers. The study appears in the June 28, 2013, edition of the journal Science.
For decades, scientists have thought that sensory information is relayed from the skin, eyes, and ears to the thalamus and then processed in the six-layered cerebral cortex in serial fashion: first in the middle layer (layer 4), then in the upper layers (2 and 3), and finally in the deeper layers (5 and 6.) This model of signals moving through a layered "column" was largely based on anatomy, following the direction of axons -- the wires of the nervous system.
"Our findings challenge dogma," said Dr. Bruno, assistant professor of neuroscience and a faculty member at Columbia's new Mortimer B. Zuckerman Mind Brain Behavior Institute and the Kavli Institute for Brain Science. "They open up a different way of thinking about how the cerebral cortex does what it does, which includes not only processing sight, sound, and touch but higher functions such as speech, decision-making, and abstract thought."
The researchers used the well-understood sensory system of rat whiskers, which operate much like human fingers, providing tactile information about shape and texture. The system is ideal for studying the flow of sensory signals, said Dr. Bruno, because past research has mapped each whisker to a specific barrel-shaped cluster of neurons in the brain. "The wiring of these circuits is similar to those that process senses in other mammals, including humans," said Dr. Bruno.



(A) Since the 1950s, the cortex has been thought to be a collection of modules, or "columns," the layers of which sequentially process information before handing it off to another column. (B) This study shows that sensory signals are instead copied to two targets (L4 and L5B) and that the upper and lower halves of the cortex are independent. The "top brain" and "bottom brain," which contain different types of cells, are able to influence behavior via completely different neural pathways. **Christine Constantinople, PhD/Randy Bruno, PhD/Columbia University Medical Center**

The study relied on a sensitive technique that allows researchers to monitor how signals move across synapses from one neuron to the next in a live animal. Using a glass micropipette with a tip only 1 micron wide (one-thousandth of a millimeter) filled with fluid that conducts nerve signals, the researchers recorded nerve impulses resulting from whisker stimulation in 176 neurons in the cortex and 76 neurons in the thalamus. The recordings showed that signals are relayed from the thalamus to layers 4 and 5 at the same time. Although 80 percent of the thalamic axons went to layer 4, there was surprisingly robust signaling to the deeper layer.
To confirm that the deeper layer receives sensory information directly, the researchers used the local anesthetic lidocaine to block all signals from layer 4. Activity in the deeper layer remained unchanged.
"This was very surprising," said Dr. Constantinople, currently a postdoctoral researcher at Princeton University's Neuroscience Institute. "We expected activity in the lower layers to be turned off or very much diminished when we blocked layer 4. This raises a whole new set of questions about what the layers actually do."
The study suggests that upper and lower layers of the cerebral cortex form separate circuits and play separate roles in processing sensory information. Researchers think that the deeper layers are evolutionarily older -- they are found in reptiles, for example, while the upper and middle layers, appear in more evolved species and are thickest in humans.
One possibility, suggests Dr. Bruno, is that basic sensory processing is done in the lower layers: for example, visually tracking a tennis ball to coordinate the movement needed to make contact. Processing that involves integrating context or experience or that involves learning might be done in the upper layers. For example, watching where an opponent is hitting the ball and planning where to place the return shot.
"At this point, we still don't know what, behaviorally, the different layers do," said Dr. Bruno, whose lab is now focused on finding those answers.
Nobel-prize-winning neurobiologist Bert Sakmann, MD, PhD, of the Max Planck Institute in Germany, describes the study as "very convincing" and a game-changer. "For decades, the field has assumed, based largely on anatomy, that the work of the cortex begins in layer 4. Dr. Bruno has produced a technical masterpiece that firmly establishes two separate input streams to the cortex," said Dr. Sakmann. "The prevailing view that the cortex is a collection of monolithic columns, handing off information to progressively higher modules, is an idea that will have to go."
"Bruno's work goes a long way toward overturning the conventional wisdom and provides new insight into the functional segregation of sensory input to the mammalian cerebral cortex, the region of the brain that processes our thoughts, decisions, and actions," said Thomas Jessell, PhD, Claire Tow Professor of Motor Neuron Disorders in Neuroscience and a co-director of the Mortimer B. Zuckerman Mind Brain Behavior Institute and the Kavli Institute for Brain Science. "Developing a more refined understanding of cortical processing will take the combined efforts of anatomists, cell and molecular biologists, and animal behaviorists. The Zuckerman Institute, with its multidisciplinary faculty and broad mission, is ideally suited to building on Bruno's fascinating work."
Funding for the study was provided by the National Institute of Neurological Disorders and Stroke (Grant # NS069679), the Rita Allen Foundation, and the Klingenstein Fund.
C. M. Constantinople, R. M. Bruno. Deep Cortical Layers Are Activated Directly by Thalamus. Science, 2013; 340 (6140): 1591 DOI: 10.1126/science.1236425

http://www.sciencedaily.com/releases/2013/06/130627161434.htm

Early Brain Stimulation May Help Stroke Survivors Recover Language Function

Non-invasive brain stimulation may help stroke survivors recover speech and language function, according to new research in the American Heart Association journal Stroke.

Between 20 percent to 30 percent of stroke survivors have aphasia, a disorder that affects the ability to grasp language, read, write or speak. It's most often caused by strokes that occur in areas of the brain that control speech and language.
"For decades, skilled speech and language therapy has been the only therapeutic option for stroke survivors with aphasia," said Alexander Thiel, M.D., study lead author and associate professor of neurology and neurosurgery at McGill University in Montreal, Quebec, Canada. "We are entering exciting times where we might be able in the near future to combine speech and language therapy with non-invasive brain stimulation earlier in the recovery. This could result in earlier and more efficient aphasia recovery and also have an economic impact."
In the small study, researchers treated 24 stroke survivors with several types of aphasia at the rehabilitation hospital Rehanova and the Max-Planck-Institute for neurological research in Cologne, Germany. Thirteen received transcranial magnetic stimulation (TMS) and 11 got sham stimulation.

The TMS device is a handheld magnetic coil that delivers low intensity stimulation and elicits muscle contractions when applied over the motor cortex.
During sham stimulation the coil is placed over the top of the head in the midline where there is a large venous blood vessel and not a language-related brain region. The intensity for stimulation was lower intensity so that participants still had the same sensation on the skin but no effective electrical currents were induced in the brain tissue.
Patients received 20 minutes of TMS or sham stimulation followed by 45 minutes of speech and language therapy for 10 days. The TMS groups' improvements were on average three times greater than the non-TMS group, researchers said. They used German language aphasia tests, which are similar to those in the United States, to measure language performance of the patients. "TMS had the biggest impact on improvement in anomia, the inability to name objects, which is one of the most debilitating aphasia symptoms," Thiel said.
Researchers, in essence, shut down the working part of the brain so that the stroke-affected side could relearn language. "This is similar to physical rehabilitation where the unaffected limb is immobilized with a splint so that the patients must use the affected limb during the therapy session," Thiel said.
"We believe brain stimulation should be most effective early, within about five weeks after stroke, because genes controlling the recovery process are active during this time window," he said.
Thiel said the result of this study opens the door to larger, multi-center trials. The NORTHSTAR study has been funded by the Canadian Institutes of Health Research and will be launched at four Canadian sites and one German site later in 2013.
The Walter and Marga Boll and Wolf-Dieter-Heiss Foundations funded the current study.
Alexander Thiel, Alexander Hartmann, Ilona Rubi-Fessen, Carole Anglade, Lutz Kracht, Nora Weiduschat, Josef Kessler, Thomas Rommel, and Wolf-Dieter Heiss. Effects of Noninvasive Brain Stimulation on Language Networks and Recovery in Early Poststroke Aphasia. Stroke, June 27 2013 DOI: 10.1161/STROKEAHA.111.000574

http://www.sciencedaily.com/releases/2013/06/130627142410.htm

After Great Dane Success, Cancer Doc Eyes Brain Tumors

Two University of Colorado Cancer Center publications set stage for K9 cancer vaccine test with human glioblastoma.

Michael Graner, PhD, is a CU Cancer Center investigator and associate professor of neurosurgery at the CU School of Medicine. So when his 12-year-old Great Dane got sick, he knew what to do.
"We got Star from the Mid-Atlantic Great Dane Rescue," Graner says. "She got her name because she was always smiling, like a movie star waiting for photos. She'd already been to so many shelters, we didn't want to change her name again and so we kept it."
At 12, after many years with the Graners, Star had already reached about double the average lifespan for the breed. When she collapsed during a coughing fit, Graner discovered the cause: lung cancer, specifically advanced bronchoalveolar adenocarcinoma with metastasis to the lymph nodes. The prognosis was grim, with a median survival from diagnosis of only about 6-27 days. And Star was well past the age when she could've tolerated chemotherapy or radiation.
"With that diagnosis, chemotherapy has only a 10-15 percent response rate and she was old -- with her prognosis and the drug side effects let's just say chemotherapy wasn't viable. We didn't want to make her any sicker," Graner says.
So he turned to his specialty, immunotherapy. The idea is to circumvent the immune system's nasty habit of recognizing cancer as its own tissue instead of seeing it as an invading disease and attacking it. By using engineered vaccines to prime the immune system to recognize tumors, cancer immunologists are using the body's own defenses to clear itself of the disease. In this case, the treatment was fairly simple and carried almost no chance of side effects that could make Star any less comfortable: a 10-gram sample of her tumor was enriched into an injectable vaccine that contained a high concentration of heat shock proteins in "chaperone-rich cell lysate" (CRCL), which tell the immune system's T-cells what to attack.
"We expected to see solid metastases within days," said Graner. "But, you know, then the months started to go by. The important thing to us was her quality of life was really good. It was really simple and it certainly didn't hurt." You can read about the treatment and results in a paper in the International Journal of Hyperthermia, on which Graner collaborated with Laura Epple, DVM, now a PhD candidate in the Graner Lab.
Finally, at 44 weeks -- more than ten times the best they should have hoped for! -- Star showed aggressive progression of the disease. At nearly a year after the diagnosis of a disease that should have killed her within a month, Graner and his family made the difficult decision to euthanize Star.
"We still have a couple of her cell lines here in the lab," Graner says. "In that way, she's kind of immortal."

Another chance for Star's immortality comes from her potential for her experience to extend the lives of human brain cancer patients. See, Graner has continued his studies with the CRCL-rich vaccines of the type that led to Star's dramatic and prolonged improvement.
"It's one thing to treat mice in these fake systems and another to treat a naturally arising tumor that had a poor prognosis," Graner says. Along with Kevin Lellehei, chair of Neurosurgery at the University of Colorado School of Medicine, Graner recently submitted a proposal to the FDA to treat human glioblastoma with CRCL vaccine. "Star's success may make it much easier for the FDA to approve similar treatment with human glioblastoma," Graner says.
In Graner's proposed trial, human brain cancer patients would continue to receive the standard of care to treat the disease and would also intersperse treatment with the experimental vaccine, whose benefit he hopes to show, but which is also unlikely to cause additional harm.
He describes a similar protocol that failed to get approval from the European Medicines Agency.
"This isn't a brand new idea," Graner says. "But until now there had been some gaps in our understanding." One of these gaps was the fact that while previous researchers had hypothesized that tumor chaperone proteins carried the peptides that, when enriched and reinjected as a vaccine, could sensitize the immune system to tumor tissues, previous studies hadn't identified these peptides.
In another recent paper, also published in the International Journal of Hyperthermia, Graner describes what he calls, "taking these proteins and beating the peptides off them to see what they are." Sure enough, many of the peptides isolated from tumor samples were derived from proteins unique to cancer -- this means that a CRCL vaccine was likely to result in an immune response directed specifically at tumor tissue and not at surrounding, healthy tissues.
Graner writes that, "Parental proteins [that would be targets for the immune cells] are components of major signaling networks of vital importance for cancer cell survival, proliferation, and migration."
With the immune system sensitized, the unique genetic mutations that allow cancer cells to act cancerous would also mark them for destruction. With this research gap filled and with Star demonstrating the vaccine's effect, Graner is hopeful his proposed trial will make it to human patients soon.
"She was a real sweetie," Graner says of Star. "Hopefully her contribution to the world has just begun."
Laura M. Epple, Lynne T. Bemis, Ryan P. Cavanaugh, Anne Skope, Tehila Mayer-Sonnenfeld, Chad Frank, Christine S. Olver, Alex M. Lencioni, Nathaniel L. Dusto, Alona Tal, Michael Har-Noy, Kevin O. Lillehei, Emmanuel Katsanis, Michael W. Graner. Prolonged remission of advanced bronchoalveolar adenocarcinoma in a dog treated with autologous, tumour-derived chaperone-rich cell lysate (CRCL) vaccine. International Journal of Hyperthermia, 2013; : 1 DOI: 10.3109/02656736.2013.800997

http://bit.ly/19IFWWP

Woman's 'Foot Orgasm' Is First Known Case

A 55-year-old woman experienced unwanted orgasms that started in her foot.

Jun 28, 2013 11:55 AM ET // by Rachael Rettner, LiveScience

A 55-year-old woman in the Netherlands visited the doctor with an unusual complaint: She experienced unwanted orgasms that started in her foot, according to a new report of her case.
The orgasmic sensations — which occurred in her left foot — were sudden, not brought on by sexual desire or thoughts, and occurred about five to six times a day, the report said. The sensation traveled up her left leg to her vagina, and she said the experience felt exactly like an orgasm achieved during sex.
These orgasms were very embarrassing and worrying to the woman, said study author Dr. Marcel D. Waldinger, who treated the woman and is a neuropsychiatrist and professor in sexual psychopharmacology at Utrecht University in the Netherlands. "She felt terrible about it," Waldinger said.
Magnetic resonance images (MRI scans) of the woman's brain and her foot showed no abnormalities, although another test revealed some differences between the nerves of her left and right feet, Waldinger told LiveScience. Stimulating her left foot with an electric current induced a spontaneous orgasmin that foot, he said.
The woman was treated with an injection of anesthetic into one of her spinal nerves - the nerve that receives sensory information from the foot - and the orgasms stopped completely. The woman has not had any foot orgasms for eight months now, although she might need to return for another anesthetic injection if her symptoms return, Waldinger said.
The researchers believe the phenomenon was the result of a sort of mix-up in the brain.
About a year and half before the foot orgasms started, the woman spent three weeks in an intensive care unit - part of the time, in a coma - because of a sepsis infection. When she came out of the coma, she had tingling and burning sensations in her left foot, likely as a result of damage to tiny nerve fibers in the foot, Waldingersaid.

Interestingly, the nerve that registers sensory information from the foot enters the spinal cord at the same level as the nerve that registers sensory information from the vagina, Waldingersaid. Because of nerve damage in her foot, the woman's brain did not receive sensory information from her foot, but it did receive sensory information from the vagina.
After a year and a half, the nerve in the foot regenerated. When that happened, the researchers believe "the brain could not anymore differentiate between the foot and the vagina. So that it decided that every stimulus coming from the foot was actually coming from the vagina," Waldinger said. "And that means an orgasmic feeling," in the foot, he said. (See 7 Facts Women (And Men) Should Know About the Vagina).
The researchers called the woman's disorder "foot orgasm syndrome," and it is the only known case of its kind. (A foot orgasm has previously been reported in a man with a foot amputation).
Waldinger thinks there may be other people who have the condition, but are too embarrassed to talk about it. Waldinger wanted to publish the case report in part to reduce the stigma surrounding such conditions.
"It's not psychological," Waldinger said. "It's a neurological thing — we can explain it, we can treat it."
Waldinger is hoping to hear from more people who may have a similar condition, and has made a website for people to contact him. The study was published online June 19 in the Journal of Sexual Medicine.

http://www.bbc.co.uk/news/magazine-23051270

Taste and smell: What is it like to live without them?

Double Olympic gold medallist James Cracknell says he is unable to smell or taste very much due to a brain injury he suffered. What is life like without these senses?

By Denise Winterman BBC News Magazine

Duncan Boak lost his sense of smell in 2005 after a fall resulted in a serious brain injury. With smell said to be responsible for 80% of the flavours we taste, the impact of losing it has been huge.
"It's so hard to explain but losing your sense of smell leaves you feeling like a spectator in your own life, as if you're watching from behind a pane of glass," he says. "It makes you feel not fully immersed in the world around you and sucks away a lot of the colour of life. It's isolating and lonely."
Like Boak, double Olympic gold medallist James Cracknell suffered a serious brain injury. He was hit by a petrol tanker while riding a bike in the US in 2010. In an interview with the Radio Times this week he said he was now unable to smell or taste very much. Eating is just something he has to do to survive, like putting petrol in a car.
The loss of taste, known as ageusia, is rare and has much less of an impact on daily life, say experts. Most people who think they have lost their sense of taste have actually lost their sense of smell. It's known as anosmia and the physical and psychological impact can be devastating and far reaching.
"Studies have shown that people who lose their sense of smell end up more severely depressed and for longer periods of time than people who go blind," says Prof Barry C Smith, co-director and founder of the Centre for the Study of the Senses. "Smell is such an underrated sense. Losing it doesn't just take the enjoyment out of eating, no place or person smells familiar anymore. It is also closely linked to memory. Losing that emotional quality to your life is incredibly hard to deal with."
Sue Mounfield lost her sense of smell three years ago after having the flu. She says the smells she misses the most are not to do with food. "It's things like smelling my children, my home and my garden. When they're gone you realised just how comforting and precious these smells are. They make you feel settled and grounded. Without them I feel as if I'm looking in on my life but not fully taking part."
Losing your sense of smell also makes the world a much more dangerous place. Even in the womb smell and taste are "gatekeepers" for allowing things into our bodies and rejecting harmful toxins, says Smith.
It nearly had extremely serious consequences for Alan Curr, who lost his sense of smell after knocking himself out in a gym lesson when he was eight.
"When I was at university someone left the gas on by accident. I was home all day but never noticed. At about 3pm my flatmates returned and I was in a bit of a daze but had no idea why. They smelt gas as soon as they walked in the door."Boak says he only really started to understand why he was feeling depressed six years after his accident. He started to read about the sense of smell and had a "road to Damascus" realisation that it was the reason he was feeling such emotions. He has now set up the UK's first anosmia support group, Fifth Sense.
There are no official figures for how many people in the UK suffer from the loss of smell or taste, but estimates for the US and Europe put the number at 5% of the population.
Losing smell happens for several reasons. Some people are born without a sense of smell, it can be the result of a frontal head injury or something as mundane as an infection. Old age is also a factor, with smell and taste deteriorating rapidly after the age of 75.

Unexplained disturbances in smell and taste can indicate the onset of brain illnesses such as multiple sclerosis, Parkinson's and Alzheimer's, often years before other more recognisable symptoms emerge.
"An unexplained loss of smell or taste acts like a canary in cage, it is a warning that something is wrong," says Smith. "People need to get it checked out quickly but they don't."
Often the problem is dismissed as trivial by the medical profession, adds Smith. Sufferers agree they are regularly turned away doctors who dismiss the loss of smell as trivial and say there is no treatment.
"Because you're not in pain many doctors basically just tell you to live with it," says Mounfield.
Outside the medical profession people often find it amusing and something of an oddity.
The physical consequences can also be extreme. People often lose weight because they no longer get any pleasure from food. Boak says he has been contacted by people who have been hospitalised because they find eating so difficult.
Whether or not anosmia can be cured depends on the underlying cause. Smell can improve for some people but never return for others. It can come back but odours might have been re-coded by the brain so things don't taste the same. Chocolate can smell like beef.
But unlike sight and hearing, you can improve your smell by training it, say experts. Studies have also shown this applies to anosmia sufferers.
Research by Professor Thomas Hummel, who runs the Smell and Taste Clinic at the University of Dresden in Germany, found that smelling certain strong odours - including rose oil, lemon and cloves - repeatedly over a 12-week period resulted in some improvement in olfactory function.
But for Boak it is a case of working with what he has left. With his taste buds still working he can bring out things like the sweetness and saltiness of food. Textures have also become important.
"I can even detect the different texture of different types tomatoes," he says. "Not something I thought I would ever have mastered before losing my sense of smell."

http://nyti.ms/14Es78q

Breaking the Seal on Drug Research

More researchers are insisting on seeing all the data behind all clinical trials for drugs, not just the rosy reports that companies choose to release.

PETER DOSHI walked across the campus of Johns Hopkins University in a rumpled polo shirt and stonewashed jeans, a backpack slung over one shoulder. An unremarkable presence on a campus filled with backpack-toters, he is 32, and not sure where he'll be working come August, when his postdoctoral fellowship ends. And yet, even without a medical degree, he is one of the most influential voices in medical research today.
Dr. Doshi's renown comes not from solving the puzzles of cancer or discovering the next blockbuster drug, but from pushing the world's biggest pharmaceutical companies to open their records to outsiders in an effort to better understand the benefits and potential harms of the drugs that billions of people take every day. Together with a band of far-flung researchers and activists, he is trying to unearth data from clinical trials — complex studies that last for years and often involve thousands of patients across many countries — and make it public.
The current system, the activists say, is one in which the meager details of clinical trials published in medical journals, often by authors with financial ties to the companies whose drugs they are writing about, is insufficient to the point of being misleading.
There is an underdog feel to this fight, with postdocs and academics flinging stones at well-fortified corporations. But they are making headway. Last fall, after prodding by Dr. Doshi and others, the drug giant GlaxoSmithKline announced that it would share detailed data from all global clinical trials conducted since 2007, a pledge it later expanded to all products dating to 2000. Though that data has not yet been produced, it would amount to more than 1,000 clinical trials involving more than 90 drugs, a remarkable first for a major drug maker.
The European Medicines Agency, which oversees drug approvals for the European Union, is considering a policy to make trial data public whenever a drug is approved. And on June 17, the medical world saw how valuable such transparency could be, as outside researchers published a review of a spinal treatment from the device maker Medtronic. The review, which concluded that the treatment was no better than an older one, relied on detailed data the company provided to the researchers.
For years, researchers have talked about the problem of publication bias, or selectively publishing results of trials. Concern about such bias gathered force in the 1990s and early 2000s, when researchers documented how, time and again, positive results were published while negative ones were not. Taken together, studies have shown that results of only about half of clinical trials make their way into medical journals.

Problems with data about high-profile drugs have led to scandals over the past decade, like one involving contentions that the number of heart attacks was underreported in research about the painkiller Vioxx. Another involved accusations of misleading data about links between the antidepressant Paxil and the risk of suicide among teenagers.

To those who have followed this issue for years, the moves toward openness are unfolding with surprising speed.

"This problem has been very well documented for at least three decades now in medicine, with no substantive fix," said Dr. Ben Goldacre, a British author and an ally of Dr. Doshi. "Things have changed almost unimaginably fast over the past six months."

Much of that change is happening because of what Dr. Goldacre calls an "accident of history." In 2009, Dr. Doshi and his colleagues set out to answer a simple question about the anti-flu drug Tamiflu: Does it work? Resolving that question has been far harder than they ever envisioned, and, four years later, there is still no definitive answer. But the quest to determine Tamiflu's efficacy transformed Dr. Doshi and others into activists for transparency — and turned the tables on drug makers. Until recently, the idea that companies should routinely hand over detailed data about their clinical trials might have sounded far-fetched. Now, the onus is on the industry to explain why it shouldn't.

IN summer 2009, Dr. Doshi received a call from Dr. Tom Jefferson, a British epidemiologist based in Rome. That year, the swine flu pandemic was spreading worldwide, and Dr. Jefferson had been hired by the British and Australian governments to update an earlier review of Tamiflu, a drug produced by the Swiss company Roche, aimed at reducing the flu's severity and preventing more serious complications. He asked if Dr. Doshi wanted to help.

Determining Tamiflu's efficacy had significant economic as well as health consequences. Around the world, private companies and governments — including that of the United States — were stockpiling Tamiflu in case of influenza outbreaks, and their spending accounted for almost 60 percent of the drug's $3 billion in sales in 2009.

The review of Tamiflu was being conducted under the auspices of the Cochrane Collaboration, a well-regarded network of independent researchers, including Dr. Jefferson, who evaluate medical treatments' effectiveness by analyzing all available research.

At the time, Dr. Doshi knew little about clinical trials or even much about the drug industry. But he knew Dr. Jefferson. Dr. Doshi, after receiving undergraduate and master's degrees in anthropology and East Asian studies from Brown and Harvard, had shifted focus and was pursuing a doctorate at M.I.T., studying the intersection of medicine and politics. He met Dr. Jefferson, a prominent skeptic of the flu vaccine, after researching whether the Centers for Disease Control was exaggerating the deadliness of the disease.

"We were both lone wolves in the field of influenza," Dr. Doshi recalled.

Dr. Jefferson had conducted a Cochrane review of Tamiflu's effectiveness a few years earlier, concluding that the drug reduced the risk of complications from the flu. He assured Dr. Doshi and other researchers on his team that the update would be fairly simple.

But just as their work was getting under way, a simple comment arrived on the Cochrane Web site that changed the course of the research and would ultimately fuel a worldwide effort to force drug companies to be more transparent.

The author of that comment, Dr. Keiji Hayashi, had no connection to the Cochrane group; he was a pediatrician in Japan who had prescribed Tamiflu to children in his practice, but had come to question its efficacy. He was curious about one of the main studies on which Dr. Jefferson had relied in his previous analysis. Called the Kaiser study, it pooled the results of 10 clinical trials. But Dr. Hayashi noticed that the results of only two of those trials had been fully published in medical journals. Given that details of eight trials were unknown, how could the researchers be certain of their conclusion that Tamiflu reduced risk of complications from flu?

"We should appraise the eight trials rigidly," Dr. Hayashi wrote.

Reviews by the Cochrane group are known for being among the most thoroughly researched medical analyses available. But in trying to answer the pediatrician's question, Dr. Jefferson realized that there was a flaw: they relied too heavily on the assumption that the articles published in journals accurately represented the results of all clinical trials that had been conducted.

As he tried to track down the authors of the Kaiser study and the two published trials, Dr. Jefferson said he hit dead ends: One author said he had moved offices and no longer had the files; another said he had never seen the primary trial data, instead relying on a summary analysis provided by Roche. All the authors suggested that he contact the company.

"We took it on faith — on trust," Dr. Jefferson, 59, said recently in a phone interview. Dr. Hayashi's question had tested that faith. Dr. Jefferson began typing each new discovery in a private journal he called Hayashi's Problem, which, he said, "charted my transformation from Dr. Jekyll to Mr. Hyde."

Dr. Doshi said that medicine "relies on hierarchies of trust." He added: "A patient is not going to be in a position to review the entire evidence base themselves. But they trust that there is a watchdog out there."

As they dug into the Tamiflu research, Dr. Doshi said, he realized that such a watchdog didn't exist. Instead, he said, "we have partial watchdogs who see part of the full picture." It became his mission to see the full picture.

Having struck out with the authors of the disputed Kaiser paper and the two other published trials, Dr. Jefferson approached Roche itself, asking for the underlying data from the missing trials. But when he declined to sign a confidentiality agreement, Roche decided not to cooperate with the researchers.

Without more complete data about the clinical trials, the Cochrane group decided that it could not include the disputed study that summarized those results. In December 2009, the team reported that Tamiflu could not be shown to reduce complications like pneumonia or hospitalizations.

The British Medical Journal, which printed the team's conclusions, also published its own investigation, showing that Roche had hired ghost writers to author some of the articles involving Tamiflu, and that those writers had said they were under pressure to highlight positive messages about the drug. Roche responded that hiring such writers was common industry practice at the time of the articles, and it rejected the idea that they had been pressured to write positively about the drug.

The articles in the British journal created a sensation, and the Cochrane Collaboration's efforts became a cause célèbre. "Everyone knows about publication bias," said Dr. Steven Woloshin, a professor of medicine at the Dartmouth Institute for Health Policy and Clinical Practice and an advocate of more widespread sharing of clinical trial data. "But they just had so much energy and they brought so much attention to it."

The group's efforts seemed to make a difference: After the articles in the British journal, Roche turned over partial copies of study reports, amounting to a little more than 3,000 pages. Then, in 2011, the European Medicines Agency turned over more than 22,000 pages of documents for 19 trial reports to Dr. Jefferson and his team.

The door had been opened. As they read through the records, the researchers discovered the importance of documents called clinical study reports, which are thousands of pages long and contain details as varied as descriptions of trial protocol and design and the ingredients of the placebo pills.

"We used to know that there was a published paper and there were data behind it," said Dr. Fiona Godlee, the editor of the British Medical Journal. "But people haven't talked about these things, like clinical study reports, that are now being talked about a great deal." Last fall, the journal said it would publish the results of clinical trials only if drug companies and researchers agreed to provide data upon request.

In April, Roche said it would make available to the Cochrane researchers clinical study reports for all Roche-sponsored trials of Tamiflu. Dr. Jefferson, Dr. Doshi and their colleagues hope to complete another update to their review of the drug by year-end.

Some said it was a shame that it took this long for the company to relent. "All these years later, and we still don't know if Tamiflu is effective," said Dr. Harlan Krumholz, the Yale cardiologist who oversaw the review of Medtronic's bone treatment. "It's perplexing to have a billion-dollar drug, and you're still not willing to share everything you've got to know whether this thing is effective and safe."

THOUGH the Tamiflu question is not yet resolved, the Cochrane researchers have succeeded in a bigger way: by helping to change the conversation around companies' responsibility to reveal drug trial data.

Drug companies do not always credit the Cochrane Collaboration. In February, Roche followed Glaxo's lead and announced that it, too, would release detailed clinical data to outside researchers, upon request. But Daniel O'Day, chief operating officer of pharmaceuticals at Roche, denied that its pledge had been motivated by the Tamiflu experience. He said Roche has provided data to "thousands" of researchers.

Mr. O'Day said "there were probably errors on both sides" in how the Cochrane researchers and Roche communicated with each other, and said the relationship deteriorated after Dr. Jefferson refused to sign a confidentiality agreement. He said the company was trying to rebuild its relationship with the Cochrane researchers, but that it stood by the safety and efficacy of Tamiflu.

In 2010, Roche commissioned researchers at the Harvard School of Public Health to conduct a re-analysis of Tamiflu clinical data, which largely confirmed the positive conclusions of the Kaiser study.

Mr. O'Day asserted that the company's transparency pledge had arisen from "the call from society in general for greater transparency of the clinical trials that we have." But others say the Cochrane researchers are largely responsible for that call for transparency.

Andrew Witty, Glaxo's C.E.O., said in an interview that his promise to provide detailed clinical data had grown out of a companywide effort, initiated soon after he became chief in 2008, that would "really ensure that we were more in step with where I thought, frankly, society and the world was moving."
Glaxo, moreover, was in need of an image rehabilitation. Last year, it pleaded guilty to criminal charges and agreed to pay $3 billion in fines after the United States Justice Department accused the company, based in London, of failing to report safety data about its diabetes drug Avandia, and of publishing misleading information about Paxil, the antidepressant, in a medical journal. The settlement, which also included civil penalties over marketing of other drugs, was the largest ever involving a pharmaceutical company.
"We don't see any reason for this information to be held out of the public domain," Mr. Witty said, "provided that the people who are interrogating the information are legitimate researchers with a legitimate question to ask."
In a twist, Roche now finds itself on the same side as the Cochrane researchers — and against many in its own industry — in a debate over what kind of data the European Medicines Agency should be making public. On Monday, the agency released a draft policy, expected to take effect next year, in which it would release clinical trial data whenever it approved a new drug. While Roche and Glaxo have supported the policy, the Pharmaceutical Research and Manufacturers of America, a major industry group, and other drug companies have opposed it.
John J. Castellani, chief executive of PhRMA, said the industry had championed open-source efforts to develop better methods for testing cancer drugs, for example. But proposals like those from the Cochrane team and the European agency go too far, he said.
"If you dump onto the sidewalk all the data and you include commercially protected information," he said, "then you're essentially giving to competitors what we invested billions of dollars in."
Others warned that such a policy could discourage drug companies from investing in Europe. "If you, on the other hand, say, 'You guys are bad actors, we want to cut your prices, we want to take your confidential data and share it with any one of your competitors,' you don't get the same feeling of encouragement," Christopher A. Viehbacher, C.E.O. of the French pharmaceutical company Sanofi, told reporters in Brussels on Monday, according to Reuters.
Industry officials and regulators in the United States say the public already has access to vast amounts of information about clinical trials. The basic results of all clinical trials must now be registered in a federal clearinghouse, for example, and the Food and Drug Administration publishes staff reviews and other documents when it approves a new drug. The F.D.A. has said that it is monitoring the developments in Europe but that federal laws in the United States restrict what types of information can be released, particularly data that could reveal personal or commercially confidential information.
Cochrane group members point to the Medtronic study as an example of the value of a neutral perspective.
In 2011, Medtronic awarded a $2.5 million grant to Yale and asked it to oversee a detailed review of trial data for Infuse, a bioengineered material in spinal fusions to treat back pain. The company was facing claims that it had published misleading information about the treatment, and it turned over its data in an effort to address those criticisms. Two teams that examined the data came to similar conclusions: Infuse appeared to be no better than an older treatment, and may pose added risks.
EARLIER this month, Dr. Doshi opened what he hopes will be a new chapter in his quest for greater understanding of clinical trials. He and several other researchers published what amounted to an ultimatum to drug companies: publish your data, or we'll do it for you.
Under the plan, researchers would publish articles summarizing trial results in cases where the underlying data has already been released. In isolated cases, such information has been made public through litigation and Freedom of Information Act requests.
"It's really neat to see a larger opportunity for a larger impact," he said. "Tamiflu just happened to be the lever that opened that door."

http://www.eurekalert.org/pub_releases/2013-06/iop-cia062513.php

Cancer is a result of a default cellular 'safe mode,' physicist proposes

Physicist is trying to shed light on cancer with a theory that traces its origin to the dawn of multicellularity

With death rates from cancer have remained largely unchanged over the past 60 years, a physicist is trying to shed more light on the disease with a very different theory of its origin that traces cancer back to the dawn of multicellularity more than a billion years ago. In this month's special issue of Physics World devoted to the "physics of cancer", Paul Davies, principal investigator at Arizona State University's Center for Convergence of Physical Sciences and Cancer Biology, explains his radical new theory.

Davies was brought in to lead the centre in 2009 having almost no experience in cancer research whatsoever. With a background in theoretical physics and cosmology, he was employed to bring fresh, unbiased eyes to the underlying principles of the disease. He has since raised questions that are rarely asked by oncologists: thinking about why cancer exists at all and what place it holds in the grand story of life on Earth.

His new theory, drawn together with Charles Lineweaver of the Australian National University, suggests that cancer is a throwback to an ancient genetic "sub-routine" where the mechanisms that usually instruct cells when to multiply and die malfunctions, thus forcing the cells to revert back to a default option that was programmed into their ancestors long ago. "To use a computer analogy, cancer is like Windows defaulting to 'safe mode' after suffering an insult of some sort," Davies writes.

The result of this malfunction is the start of a cascade of events that we identify as cancer – a runaway proliferation of cells that form a tumour, which eventually becomes mobile itself, spreading to other parts of the body and invading and colonizing.

Orthodox explanations suppose that cancer results from an accumulation of random genetic mutations, with the cancer starting from scratch each time it manifests; however, Davies and Lineweaver believe it is caused by a set of genes that have been passed on from our very early ancestors and are "switched on" in the very early stages of an organism's life as cells differentiate into specialist forms.

The pair suggests that the genes that are involved in the early development of the embryo – and that are silenced, or switched off, thereafter – become inappropriately reactivated in the adult as a result of some sort of trigger or damage, such as chemicals, radiation or inflammation. "Very roughly, the earlier the embryonic stage, the more basic and ancient will be the genes guiding development, and the more carefully conserved and widely distributed they will be among species," Davies writes.

Several research teams around the world are currently providing experimental evidence that shows the similarities between the expression of genes in a tumour and an embryo, adding weight to Davies and Lineweaver's theory.

Davies makes it clear that radical new thinking is needed; however, just like ageing, he states that cancer cannot generally be cured but can be mitigated, which we can only do when we better understand the disease, and its place in the "great sweep of evolutionary history".

This month's special issue of Physics World can be downloaded free of charge from 1 July 2013 at http://www.physicsworld.com/cws/download/jul2013.

http://phys.org/news/2013-06-mega-quakes-volcanoes.html

Mega-quakes caused volcanoes to sink, research finds

Massive earthquakes can cause distant volcanoes to sink, according to research in Japan and Chile published on Sunday.

Massive earthquakes can cause distant volcanoes to sink, according to research in Japan and Chile published on Sunday. The magnitude 9.0 tsunami-generating quake that occurred off northeastern Japan in 2011 caused subsidence of up to 15 centimetres (9.3 inches) in a string of volcanoes on the island of Honshu as much as 200 kilometres (120 miles) from the epicentre, a Japanese study said.

And the 8.8-magnitude Maule quake in Chile in 2010 caused a similar degree of sinking in five volcanic regions located up to 220 km (130 miles) away, according to a US-led paper. It was not clear whether the phenomenon boosted eruption risk, the authors wrote.

Both the Japan and Chile quakes were of the subduction type, caused when one part of Earth's crust slides beneath another. If the movement is not smooth, tension can build up over decades or centuries before it is suddenly released, sometimes with catastrophic effect. In both cases, the sinking occurred in mountain ranges running horizontally to the quake.

The 2011 quake "caused east-west tension in eastern Japan," Youichiro Takada of the Disaster Prevention Research Institute at Kyoto University told AFP in an email. "Hot and soft rocks beneath the volcanoes, with magma at the centre, were horizontally stretched and vertically flattened. This deformation caused the volcanoes to subside."

The researchers for the Chilean volcanoes said subsidence occurred along a stretch spanning 400 km (250 miles). As in Japan, the ground deformation in Chile occurred in huge ellipse-shaped divots up to 15 km by 30 km (nine miles by 18 miles) in size, although the cause appears to be different. Pockets of hot hydrothermal fluids that underpinned the volcanic areas may have escaped through rock that had been stretched and made permeable by the quake.

Two earthquakes in the Chilean subduction zone in 1906 and 1960 were followed by eruptions in the Andean southern volcanic zone within a year of their occurrence. However, no big eruptions in this volcanic hotspot can

be associated with the 2010 temblor, says the study led by Matthew Pritchard of Cornell University in New York. Takada said the impact of the 2011 quake on volcano risk on Honshu was unclear.
"At this stage we do not know the relation between volcanic eruption and the subsidence we found. Further understanding of the magmatic movement would be necessary," he said.
The subsidence in Japan was spotted at the volcanoes Akitakoma, which last erupted in 1971; Kurikoma (1950); Zao (1940); Azuma (1977); and Nasu (1963).
The studies, published in the journal Nature Geoscience, used data from satellite radar which mapped terrain before and after the quakes.
More information: dx.doi.org/10.1038/ngeo1857 dx.doi.org/10.1038/ngeo1855 dx.doi.org/10.1038/ngeo1876 (News&Views)
http://www.eurekalert.org/pub_releases/2013-07/uosc-sms062513.php

Senior moment? Stereotypes about aging can hurt older adults' memory, but there's an easy fix

Scientists show that attributing every forgetful moment to getting older can actually worsen memory problems -- and reveal a surprising twist that can improve performance

Of the many negative stereotypes that exist about older adults, the most common is that they are forgetful, senile and prone to so-called "senior moments." In fact, while cognitive processes do decline with age, simply reminding older adults about ageist ideas actually exacerbates their memory problems, reveals important new research from the USC Davis School of Gerontology.
The study, forthcoming in the journal Psychological Science, is an extension of the idea of "stereotype threat" — that when people are confronted with negative stereotypes about a group with which they identify, they tend to self-handicap and underperform compared to their potential. In doing so, they inadvertantly confirm the negative stereotypes they were worried about in the first place.
The results highlight just how crucial it is for older adults, as well clinicians, to be aware of how ageist beliefs about older adults can affect older adults' real memory test performance.
"Older adults should be careful not to buy into negative stereotypes about aging — attributing every forgetful moment to getting older can actually worsen memory problems." said Sarah Barber, a postdoctoral researcher at the USC Davis School and lead author of the study.
However, there is a way to eliminate the problem, the study reveals: "No one had yet examined the intriuging possibility that the mechanisms of stereotype threat vary according to age," Barber said.
Barber and her co-author Mara Mather, professor of gerontology and psychology at USC, conducted two experiments in which adults from the ages of 59 to 79 completed a memory test. Some participants were first asked to read fake news articles about memory loss in older adults, and others did not. Notably, the researchers structured the test so that half of the participants earned a monetary reward for each word they remembered; the other half lost money for each word they forgot.
In past tests, 70 percent of older adults met diagnostic criteria for dementia when examined under stereotype threat, compared to approximately 14 percent when not assessed under threat.
But the latest research shows that stereotype threat can actually improve older adults' performance on memory tests, under certain conditions.
For participants who had something to gain, being confronted with age stereotypes meant poorer performance on memory tests. They scored about 20 percent worse than people who were not exposed to the stereotype.
But when the test was framed in terms of preventing losses due to forgetting, the results flipped: participants reminded of the stereotypes about aging and memory loss actually scored better than those who were under no stereotype threat.
"Stereotype threat is generally thought to be a bad thing, and it is well established that it can impair older adults' memory performance. However, our experiments demonstrate that stereotype threat can actually enhance older adults' memory if the task involves avoiding losses," Barber said.
Older adults, it seems, respond to stereotype threat by changing their motivational priorities and focusing more on avoiding mistakes. The study is part of a critical body of work on risk taking and decision making among older adults from the USC Davis School of Gerontology, named for AARP founder Leonard Davis and the leading research center in the world on aging and its biological, psychological, political and economic dimensions.
"Our experiments suggest an easy intervention to eliminate the negative effects of stereotype threat on older adults — clinicians should simply change the test instructions to emphasize the importance of not making mistakes," Barber said.
The research was funded by the National Institutes of Health (grant numbers T32-AG00037, R01-AG025340, R01-AG038043 and K02-AG032309).

http://www.bbc.co.uk/news/health-23072562

Medical students set bad example by doctors, says research

Under the watchful eye of Dr Matthias Schmidt, third-year medical students from Newcastle University are getting some hands-on experience, a vital part of their training.

By Dominic Hughes Health correspondent, BBC News

Sitting in his bed on the infectious diseases ward in the city's Royal Victoria Hospital, the patient, Sean, is recovering from a nasty bout of malaria. He is introduced to the group of students, who are using this opportunity to learn not just how to examine patients, but how to talk to them with compassion and respect.

These are skills, says Dr Schmidt, that are crucial for their development.

"Tomorrow's doctors want to be the doctors that are trained absolutely perfectly.

"And if I don't set a good example, if the medical school doesn't set a good example, then we won't be looked after well."

This kind of practical training is essential for medical students. But research from Cardiff and Dundee universities suggests that young medics often witness behaviour, or are asked to do things, that they just don't agree with. Surveys and interviews with hundreds of British medical students show that some senior doctors setting far from a good example.

Students say they have witnessed, or taken part in, breaches of patient safety and dignity - and commonly experience abuse from those who should be teaching them.

'You're so fat...'

Some of the testimonies gathered from medical students are jaw-dropping.

"A patient was told by the consultant... you shouldn't even be here. You're so fat I shouldn't even have considered you for surgery."

"The consultant said to me, 'You there - the decoration - why did you even come to med school? Do you have a brain in your pretty head?'"

"A fellow student performed an unconsented rectal examination on an anaesthetised patient."

Issues around consent are particularly troubling. I met one young medical student who didn't want to be identified because of the repercussions speaking out may have on his career.

He was asked to carry out an intimate examination of a 14-year-old boy who was under general anaesthetic - without the proper consent of the patient or his parents.

"The senior clinician supervising made it quite clear we had to get on and do this because it was part of our clinical training. "The difficulty is that without expressed consent or explicit consent it is very hard to justify your learning needs over-riding the dignity of a patient in that circumstance.

"It's also very hard after the event, or during, to actually report that to your seniors because it is seen as not demonstrating an appropriate level of deference to the clinician who was trying to help you advance your education."

Awkward

For the authors of the research, the big concern is that a failure to treat patients with compassion and dignity may be subtly influencing the future behaviour of today's medical students.

Dr Lynn Monrouxe of Cardiff University says these issues have a direct relationship to the sort of concerns raised by the Francis inquiry into poor care at Stafford Hospital.

"It's unnoticed patterns of behaviour that recur, again and again.

"And the students pick up these subtle patterns of behaviour and they come to learn this is how things are done around here, this is how work is done.

"The small subtle interactions, that happen day in, day out - not necessarily the big, shocking, news-grabbing headlines - it's the things that can't be counted that really count."

Newcastle University medical school is one of those that took part in the research.

The director of studies, Roger Barton, who oversees the training of medical students, says the school has looked again at its training.

But he argues some students may not be prepared for what they have to face.

"The Cardiff research actually uncovered some very interesting things, partly about almost the reluctance of medical students to get involved with intimate examinations because they almost felt it wasn't legitimate for them to do so.

"I think our perspective is, well, you might feel awkward but it is going to be something that is really necessary for you as a qualified practitioner, so we've got to go ahead and do it."

Tomorrow's doctors need to gain hands-on experience. Patients must be treated with dignity.

This research shows that striking that balance is not always easy.