http://www.eurekalert.org/pub_releases/2016-07/jhm-gem063016.php

Genetically engineered mice suggest new model for how Alzheimer's causes dementia

Experiments shed light on how 'plaques' and 'tangles' interact and take hold

Using a novel, newly developed mouse model that mimics the development of Alzheimer's disease in humans, Johns Hopkins researchers say they have been able to determine that a one-two punch of major biological "insults" must occur in the brain to cause the dementia that is the hallmark of the disease. A description of their experiments is published online in the journal Nature Communications.

For decades, Alzheimer's disease, the most common cause of dementia, has been known to be associated with the accumulation of so-called neurofibrillary tangles, consisting of abnormal clumps of a protein called tau inside brain nerve cells, and by neuritic plaques, or deposits of a protein called beta-amyloid outside these cells along with dying nerve cells, in brain tissue.

In Alzheimer's disease, tau bunches up inside the nerve cells and beta-amyloid clumps up outside these cells, mucking up the nerve cells controlling memory, notes Philip C. Wong, Ph.D., professor of pathology at the Johns Hopkins University School of Medicine.

What hasn't been clear is the relationship and timing between those two clumping processes, since one is inside cells and one is outside cells, says lead and corresponding study author Tong Li, Ph.D., an assistant professor of pathology at Johns Hopkins. Prior studies of early-onset Alzheimer's disease have suggested that the abnormal accumulation of beta-amyloid in the brain somehow triggers the aggregation of tau leading directly to dementia and brain cell degeneration. But the new research from Li, Wong and colleagues suggests that the accumulation of beta-amyloid in and of itself is insufficient to trigger the conversion of tau from a normal to abnormal state. Instead, their studies show, it may set off a chain of chemical signaling events that lead to the "conversion" of tau to a clumping state and subsequent development of symptoms.

"For the first time, we think we understand that the accumulation of amyloid plaque alone can damage the brain, but that's actually not sufficient to drive the loss of nerve cells or behavioral and cognitive changes," Wong says. "What appears to be needed is a second insult -- the conversion of tau -- as well."

In humans, the lag between development of the beta-amyloid plaques and the tau tangles inside brain nerve cells can be 10 to 15 years or more, Li says, but because the lifetime of a mouse is only two to three years, current animal models that successfully mimic the appearance of beta-amyloid plaques did not offer enough time to observe the changes in tau.

To address that problem, the Johns Hopkins researchers genetically engineered a mouse model that used a tau fragment to promote the clumping of normal tau protein. They then cross-bred these mice with mice engineered to accumulate beta-amyloid. The result was a mouse model that developed dementia in a manner more similar to what happens in humans, Li says.

The researchers found during brain dissections of the animals that the presence of beta-amyloid plaque alone was not sufficient to cause the biochemical conversion of tau, the repeat domain of tau -- the part of tau protein that is responsible for the conversion of normal tau to an abnormal state -- alone was insufficient for the conversion of tau, beta-amyloid plaques must be present in the brain for the conversion of tau and the tau fragments could "seed" the plaque-dependent pathological conversion of tau.

One implication of the new research, Wong says, is to possibly explain why some drugs designed to attack the disease after the conversion of tau haven't worked. "The timing may be off," he says. "If you were to intervene in the time period before the conversion of tau, you might have a good chance of ameliorating the deficits, brain cell loss and ensuing consequence of the disease."

The work also suggests that combination therapy designed to prevent both the beta-amyloid plaque formation as well as pathological conversion of tau may provide optimal benefit for Alzheimer's disease, the researchers say. Their mouse model could be used to test new therapies.

An estimated 5.4 million Americans are living with Alzheimer's disease, according to 2016 statistics from the Alzheimer's Association. There is no cure, but there are some medications that may help stabilize cognition for a limited time or help with related depression, anxiety or hallucinations.

Co-authors were Kerstin E. Braunstein, Juhong Zhang, Ashley Lau, Leslie Sibener and Christopher Deeble of Johns Hopkins.

The work was supported by the Ellison Medical Foundation, the Brain Science Institute at Johns Hopkins, the Johns Hopkins University Neuropathology Pelda Fund and the Johns Hopkins Alzheimer's Disease Research Center.

http://www.eurekalert.org/pub_releases/2016-07/miot-edp070116.php

Engineers design programmable RNA vaccines

Tests in mice show the vaccines work against Ebola, influenza, and a common parasite

CAMBRIDGE, MA -- MIT engineers have developed a new type of easily customizable vaccine that can be manufactured in one week, allowing it to be rapidly deployed in response to disease outbreaks. So far, they have designed vaccines against Ebola, H1N1 influenza, and Toxoplasma gondii (a relative of the parasite that causes malaria), which were 100 percent effective in tests in mice.

The vaccine consists of strands of genetic material known as messenger RNA, which can be designed to code for any viral, bacterial, or parasitic protein. These molecules are then packaged into a molecule that delivers the RNA into cells, where it is translated into proteins that provoke an immune response from the host.

In addition to targeting infectious diseases, the researchers are using this approach to create cancer vaccines that would teach the immune system to recognize and destroy tumors.

"This nanoformulation approach allows us to make vaccines against new diseases in only seven days, allowing the potential to deal with sudden outbreaks or make rapid modifications and improvements," says Daniel Anderson, an associate professor in MIT's Department of Chemical Engineering and a member of MIT's Koch Institute for Integrative Cancer Research and Institute for Medical Engineering and Science (IMES).

Anderson is the senior author of a paper describing the new vaccines in the Proceedings of the National Academy of Sciences the week of July 4, 2016. The project was led by Jasdave Chahal, a postdoc at MIT's Whitehead Institute for Biomedical Research, and Omar Khan, a postdoc at the Koch Institute; both are the first authors of the paper.

Customizable vaccines

Most traditional vaccines consist of an inactivated form of a virus or other pathogen. These vaccines usually take a long time to manufacture, and for some diseases they are too risky. Other vaccines consist of proteins normally produced by the microbe, but these don't always induce a strong immune response, requiring researchers to seek an adjuvant (a chemical that enhances the response).

RNA vaccines are appealing because they induce host cells to produce many copies of the proteins they encode, which provokes a stronger immune reaction than if the proteins were given on their own. The idea of using messenger RNA molecules as vaccines has been around for about 30 years, but one of the major obstacles has been finding a safe and effective way to deliver them.

Khan decided to package RNA vaccines into a nanoparticle made from a branched molecule known as a dendrimer. One key advantage of this material is that the researchers can give it a temporary positive charge, which allows it to form close associations with RNA, which is negatively charged. Khan can also control the size and pattern of the final structure. By inducing the dendrimer-RNA structure to fold over itself many times, Khan generated spherical vaccine particles with a diameter of about 150 nanometers. That makes them of similar size as many viruses, enabling the particles to enter cells by exploiting the same surface proteins that viruses use for this purpose.

By customizing the RNA sequences, the researchers can design vaccines that produce nearly any protein they want. The RNA molecules also include instructions for amplification of the RNA, so that the cell will produce even more of the protein.

The vaccine is designed to be delivered by intramuscular injection, making it easy to administer. Once the particles get into cells, the RNA is translated into proteins that are released and stimulate the immune system. Significantly, the vaccines were able to stimulate both arms of the immune system -- a T cell response and an antibody response.

In tests in mice, animals that received a single dose of one of the vaccines showed no symptoms following exposure to the real pathogen -- Ebola, H1N1 influenza, or Toxoplasma gondii. "No matter what antigen we picked, we were able to drive the full antibody and T cell responses," Khan says.

The researchers also believe that their vaccines would be safer than DNA vaccines, another alternative that scientists are pursuing, because unlike DNA, RNA cannot be integrated into the host genome and cause mutations.

"The option of rapidly creating a completely synthetic formulation that can be effective as a vaccine is an important addition to currently available vaccine strategies," says Hidde Ploegh, an MIT professor of biology, a member of the Whitehead Institute, and an author of the paper, who added that it will be important to assess safety and cost.

Rapid deployment

The ability to rapidly design and manufacture these vaccines could be especially beneficial for fighting influenza, because the most common flu vaccine manufacturing method, which requires the viruses to be grown inside chicken eggs, takes months. This means that when an unexpected flu strain appears, such as the 2009 pandemic-causing H1N1 virus, there is no way to rapidly produce a vaccine against it.

"Typically a vaccine becomes available long after the outbreak is over," Chahal says. "We think we can become interventional over the course of a real outbreak."

Khan and Chahal plan to start a company to license and commercialize the technology. In addition to the vaccines they have already designed, they hope to create vaccines for Zika virus and Lyme disease.

They are also working on cancer vaccines. At a recent "Mission: Possible" competition hosted by the Koch Institute, Khan and Chahal were part of a team that ended up withdrawing from the competition because an outside funder, the Advanced Medical Research Foundation, offered to support them.

For that project, the researchers designed vaccines that target genes that are normally turned on only during embryonic development. These genes, dormant in

adults, often become reactivated in a type of cancer known as non-small cell lung tumors.

"We are all excited about the potential of this new approach to provide a new way of vaccine delivery," says Robert Langer, the David H. Koch Institute Professor at MIT and an author of the paper.

Other authors of the paper include Whitehead Institute researchers Justine McPartlan, Lucas Tilley, Saima Sidik, and Sebastian Lourido; Koch Institute technical assistant Jonathan Tsosie; and U.S. Army Medical Research Institute of Infectious Diseases researchers Christopher Cooper and Sina Bavari.

The research was funded by the Department of Defense Office of Congressionally Directed Medical Research's Joint Warfighter Medical Research Program, MediVector Inc., the Ragon Institute of MGH, MIT, and Harvard, and the Defense Threat Reduction Agency/Joint Science and Technology Office program in vaccines and pre-treatments.

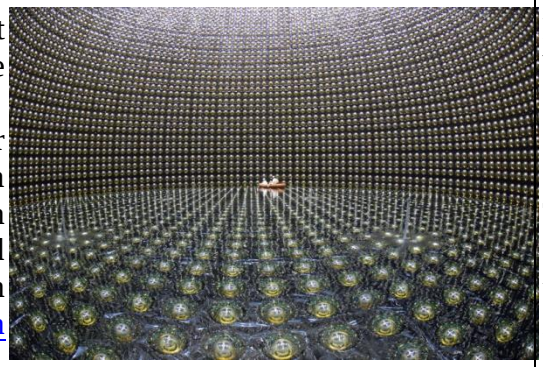
http://bit.ly/29tTnDd

Neutrinos hint at why antimatter didn't blow up the universe

Results from a pair of experiments designed to study the behaviour of neutrinos could mean we're starting to understand why

By Lisa Grossman

It could all have been so different. When matter first formed in the universe, our current theories suggest that it should have been accompanied by an equal amount of antimatter – a conclusion we know must be wrong, because we wouldn't be here if it were true. Now the latest results from a pair of experiments designed to study the behaviour of neutrinos – particles that barely interact with the rest of the universe – could mean we're starting to understand why.



Super-Kamiokande: a huge detector looking out for tiny particles **Kamioka Observatory/ICRR(Institute for Cosmic Ray Research)/The University of Tokyo**

Neutrinos and their antimatter counterparts, antineutrinos, each come in three types, or flavours: electron, muon and tau. Several experiments have found that neutrinos can spontaneously switch between these flavours, a phenomenon called oscillating.

The T2K experiment in Japan watches for these oscillations as neutrinos travel between the J-PARC accelerator in Tokai and the Super-Kamiokande neutrino detector in Kamioka, 295 kilometres away. It began operating in February 2010, but had to shut down for several years after Japan was rocked by a magnitude-9 earthquake in 2011.

Puff of radiation

In 2013, the team announced that 28 of the muon neutrinos that took off from J-PARC had become electron neutrinos by the time they reached Super-Kamiokande, the first true confirmation that the metamorphosis was happening.

They then ran the experiment with muon antineutrinos, to see if there was a difference between how the ordinary particles and their antimatter counterparts oscillate. An idea called charge-parity (CP) symmetry holds that these rates should be the same.

CP symmetry is the notion that physics would remain basically unchanged if you replaced all particles with their respective antiparticles. It appears to hold true for nearly all particle interactions, and implies that the universe should have produced the same amount of matter and antimatter in the big bang.

Matter and antimatter destroy one another, so if CP symmetry holds, both should have mostly vanished in a puff of radiation early on in the universe's history, well before matter was able to congeal into solid stuff. That's clearly not what happened, but we don't know why. Any deviation from CP symmetry we observe could help explain this discrepancy.

"We know in order to create more matter than antimatter in the universe, you need a process that violates CP symmetry," says Patricia Vahle, who works on NoVA, a similar experiment to T2K that sends neutrinos between Illinois and Minnesota. "So we're going out and looking for any process that can violate this CP symmetry."

Flavour changers

We already know of one: the interactions of different kinds of quarks, the constituents of protons and neutrons in atoms. But their difference is not great enough to explain why matter dominated so completely in the modern universe. Neutrino oscillations are another promising place to look for deviations.

This morning at the Neutrino conference in London, UK, we got our first signs of such deviations. Hirohisa Tanaka of the University of Toronto, Canada, reported the latest results from T2K. They have now seen 32 muon neutrinos morphing into the electron flavour, compared to just 4 muon antineutrinos becoming the anti-electron variety.

This is more matter and less antimatter than they expected to see, assuming CP symmetry holds. Although the number of detections in each experiment is small, the difference is enough to rule out CP symmetry holding at the 2 sigma level – in other words, there is only around a 5 per cent chance that T2K would see such differences if CP symmetry is preserved in this process.

Particle physicists normally wait until things reach the 3 sigma level before getting excited, and won't consider it a discovery until 5 sigma, so it's early days

for neutrinos breaking CP symmetry. But at the same conference, Vahle presented the latest results from NoVA that revealed the two experiments were in broad agreement about the possibility.

The extent of CP violation rests on a key parameter called delta-CP, which ranges from 0 to 2π. Both teams found that their results were best explained by setting the value equal to 1.5π. “Their data really does prefer the same value that T2K does,” says Asher Kaboth, who works on T2K. “All of the preferences for the delta-CP stuff are pointing in the same direction.”

NoVA plans to run its own antineutrino experiments next year, which will help firm up the results, and both teams are continuing to gather more data. It’s too soon to say definitively, but one of the mysteries of why we are here could be on the road to getting solved.

Additional reporting by Jacob Aron

http://www.bbc.com/news/health-36702215

Fungal infection 'threat' to human health

Fungal infections kill more people than malaria or breast cancer but are not considered a priority, say scientists.

By James Gallagher Health editor, BBC News website

Prof Neil Gow, from the University of Aberdeen, said more than one million people die from fungal infections around the world each year. Yet there are no vaccines and there is a "pressing need" for new treatments, he said. The warning comes as doctors in England say a new strain of fungi is causing outbreaks in hospitals. There are more than five million types of fungi, but only three major groups cause the majority of deaths in people:

Aspergillus - which affects the lungs

Cryptococcus - which mainly attacks the brain

Candida - which infects mucosal membranes including in the mouth and genitals

Prof Gow said: "Most people know about mild fungal infections, but nobody's ever died from athlete's foot. "However, a million people die a year from fungal infections and we need to understand these different types of infection and how to deal with them."

The infections are more deadly in people with weakened immune systems - such as patients with HIV - so the fungal problem is particularly acute in Africa.

"It's an underappreciated problem and it's a very serious challenge in the parts of the world least equipped to deal with it," Prof Gow added.

Patients having cancer therapy or who are taking immunosuppressant drugs after an organ transplant are also more susceptible to infection. Speaking to the BBC at the Royal Society's Summer Exhibition, he said: "Fungi are extremely tough and manipulate the immune system to prevent themselves being recognised, they are very slippery customers."

New fungus

Meanwhile, health officials have warned of a new strain of Candida auris which has caused an outbreak affecting 40 patients in one hospital in south-east England. The infection was first detected in 2009 in Japan, but has since been discovered across Asia and parts of south America.

Public Health England said "Candida auris appears to be unlike other pathogenic yeast species in its propensity for transmission between hospital patients" and warned it was resistant to the first choice anti-fungal drug.

Dr Berit Muller-Pebody, from Public Health England, said: "This species of Candida is emerging globally. "We are monitoring it, but as it's an emerging pathogen it is very difficult to talk about trends. "We needed to make the healthcare community aware of it as [doctors] now need to identify the species of Candida that require a more proactive approach."

http://www.eurekalert.org/pub_releases/2016-07/hu-npi070316.php

New prebiotic identified in fermented Japanese vegetable

Enzyme improves colon health in rats

An enzyme produced by fermenting a vegetable common in Japanese cuisine may be responsible for increasing the amount of at least one beneficial bacterium associated with healthy colons in a study using rats. The results of this prebiotic research study will be presented at the International Conference on Nutraceuticals and Nutrition Supplements in July 2016 by Norihisa Kato, Ph.D., and at the International Nutrition and Diagnostic Conference in October 2016 by doctoral student Yongshou Yang, both from Hiroshima University.

The vegetable, called burdock root in English and gobo in Japanese, has a minimal positive effect on colon health when eaten raw or cooked. Like many high-fiber foods, gobo must be eaten in unpalatable quantities to change the bacterial composition of the colon.

However, in a previous study, rats that ate gobo after it was fermented by the fungus Aspergillus showed improved colon health. Kato's research group has now further investigated the effect, and discovered that the fermentation process produces a protease preparation, a liquid full of different enzymes. These enzymes may be responsible for the boost in colon health.

"Rats that ate a diet supplemented with the protease preparation that was derived from gobo fermented by the fungus Aspergillus had amounts of the bacterium Bifidobacterium in their colons that were several hundred times higher than rats on a non-supplemented diet. In addition to the microflora improvements, we

observed a remarkable improvement of the overall luminal environment of their colons," said Kato.

An equivalent amount of the enzyme for an adult person to eat would be approximately 0.1 to 0.4 grams, or 0.04 to 0.16 teaspoons, per day. Comparatively, adults would need to consume about 20g, or about 5 teaspoons, per day of un-fermented gobo or other dietary fibers to experience a similar effect.

The research team's current, untested hypothesis is that, in the large intestine, the protease may break down undigested proteins into amino acids, the smaller building blocks of proteins. Greater availability of amino acids could contribute to improved nutrient utilization and therefore more favorable growth of beneficial bacteria.

The bacterium, Bifidobacterium, is a common member of a healthy intestine, but it becomes less numerous as people age. Other studies have correlated boosting Bifidobacterium numbers with better mental health, increased immune function, and lower rates of bowel diseases including colitis and colon cancer. However, the biological cause of these effects remains a mystery and researchers continue to search for practical methods to increase Bifidobacterium numbers in adult colons.

"Bifidobacterium is not normally included in probiotic foods like yogurt because it is so sensitive and not easy to keep alive or grow," said Kato.

Probiotic supplements containing beneficial bacteria add extra bacterial cells to the body. Prebiotic supplements, such as some dietary fibers and oligosaccharides, support the growth of beneficial bacteria that are already present in the intestine, avoiding the challenges of growing bacteria outside the body and adding it to food products. The protease preparation derived from Aspergillus may be a new prebiotic and it has a far stronger effect on Bifidobacterium in the colon than that of previous varieties of prebiotics, such as dietary fiber and oligosaccharides.

Japanese cuisine includes many foods fermented with Aspergillus, including the soybean paste miso, the rice wine sake, and many types of pickled vegetables eaten as a side-dish. However, the results from the Hiroshima University team indicate that regardless of the food, Aspergillus may be responsible for producing a variety of beneficial enzymes that the team is beginning to identify and study individually.

"We have completed three years of research on fermented gobo and we're beginning to understand what component of the fermented product has this beneficial impact on bacteria in the colon. We're excited to do more research to reveal how and why Aspergillus-fermented foods and enzymes, especially acid protease derived from Aspergillus, have positive health effects," said Kato.

Researchers are planning additional studies on the enzyme's long-term effects on the colon of rats and the enzyme's effects on the overall bacterial composition in the intestine of humans.

Professor Norihisa Kato will give a keynote seminar entitled "Aspergillus-derived protease as a novel bifidogenic factor" at the International Conference on Nutraceuticals and Nutrition Supplements. The second annual International Conference on Nutraceuticals and Nutrition Supplements will occur from 18 to 20 July 2016 in Bangkok, Thailand. Read more about the conference on their website: http://nutraceuticals.pharmaceuticalconferences.com/

This collaborative study is supported in part by the Amano Enzyme Co. Ltd., Nagoya, Japan.

http://www.medscape.com/viewarticle/865277

Do People Feel Pain While Sleepwalking?

This is the Medscape Neurology Minute. I'm Dr Alan Jacobs.

Alan R. Jacobs, MD

Researchers from the Department of Neurology at Gui de Chauliac Hospital in Montpellier, France, have published a study examining the impact and determinants of pain in sleepwalkers.

In their cross-sectional case-control study, compared with 100 controls, they assessed 100 patients with sleepwalking for disease characteristics, sleep disorders, pain conditions, mood disorders, and quality of life. Pain perception was retrospectively assessed during injurious parasomnia episodes. They found, after adjustments, that sleepwalking was associated with increased risk for headache and migraine only.

Interestingly, of 47 sleepwalkers with at least one previous violent parasomnia episode, 78.7% perceived no pain during the episode, allowing them to remain asleep despite injury.

For example, one patient sustained severe fractures after jumping out of a third-floor window while sleepwalking but didn't feel the pain until after waking up later in the night.

Another patient broke his leg during a sleepwalking episode in which he climbed onto the roof of his house and fell down, but he didn't wake up until morning.

The authors highlight the paradoxical increase in pain complaints during wakefulness and absence of pain experience during severe parasomnia episodes in these sleepwalking patients, suggesting a relationship between dissociated brain activity and nociceptive dysregulation.

This has been the Medscape Neurology Minute. I'm Dr Alan Jacobs.

Lopez R, Jaussent I, Dauvilliers Y. Pain in sleepwalking: a clinical enigma. Sleep. 2015;38:1693-1698.

http://www.eurekalert.org/pub_releases/2016-07/rb-fck070416.php

From climate killer to fuels and polymers

New catalyst converts carbon dioxide into ethylene

Researchers have discovered a catalyst that performs highly selective conversion of the greenhouse gas carbon dioxide into ethylene - an important source material for the chemical industry. In the journal "Nature Communications", a team headed by Prof Dr Beatriz Roldan Cuenya from Ruhr-Universität Bochum describes how plasma-treated copper can be used for this purpose.

Catalysts traditionally used for the electrochemical conversion of carbon dioxide into useful chemicals were not efficient enough. The reason: the materials do not have high selectivity; they produce a little ethylene and too many unwanted side products. This has now been changed.

More selectivity through plasma treatment

PhD student Hemma Mistry from the Institute for Experimental Physics IV in Bochum used copper films treated with oxygen or hydrogen plasmas as catalysts. Through these plasma treatments, she altered the properties of the copper surface, rendering it rougher or less rough, for example, and oxidizing the material. The researcher varied the plasma parameters systematically until she hit on the optimal surface properties.

Her best catalyst boasts a higher ethylene production rate than traditional copper catalysts. At the same time, it acts in a highly selective manner, which means that the amount of unwanted side products is considerable reduced. "It's a new record for this material," concludes Beatriz Roldan Cuenya.

Mechanism decoded

The researchers also identified the reason why this form of plasma treatment has been successful. Using synchrotron radiation, they analysed the copper film's chemical state during the catalysis of the reaction. Through these measurements, they detected the cause of the higher ethylene selectivity. The key component was positively charged copper ions at the catalyst surface.

It had been assumed that copper can only exist in its metallic form under reaction conditions. The researchers' discovery has now disproved this assumption, and their findings were confirmed by additional microscopic analysis. "The results open up new possibilities for designing catalysts on the nanoscale with specific activity and selectivity," says Beatriz Roldan Cuenya.

Cooperation partners

For the purpose of the study, the group led by Prof Dr Beatriz Roldan Cuenya from Bochum collaborated with the group headed by Prof Dr Peter Strasser from Technische Universität Berlin, the group headed by Prof Dr Judith C. Yang from University of Pittsburgh, and the group headed by Dr Eric A. Stach from Brookhaven National Laboratory. The team also utilized the facilities at Stanford Synchrotron Radiation Lightsource.

Financial backing for the study was provided by the Federal Ministry of Education and Research (#03SF0523, CO2EKAT), the German Research Foundation under the umbrella of the Cluster of Excellence RESOLV (EXC 1069), as well as the US National Science Foundation (NSF-Chemistry 1213182 and NSF-DMR 1207065) and the Office for Basic Energy Sciences at the US Department of Energy (DE-FG02-08ER15995).

Original publication

Hemma Mistry et al.: Highly selective plasma-activated copper catalysts for carbon dioxide reduction to ethylene, in: Nature Communications, 2016, DOI: 10.1038/ncomms12123
http://www.nature.com/ncomms/2016/160630/ncomms12123/full/ncomms12123.html

http://www.eurekalert.org/pub_releases/2016-07/qmuo-cgb070416.php

Could goats become man's best friend?

Goats have the capacity to communicate with people like other domesticated animals, such as dogs and horses, according to scientists from Queen Mary University of London (QMUL).

In a new paper in the journal Biology Letters, researchers from QMUL's School of Biological and Chemical Sciences found that goats respond to people by gazing at them when facing a problem they cannot solve alone, and their responses change depending on the person's behaviour.

To investigate, the team trained goats to remove a lid from a box to receive a reward. In the final test, they made the reward inaccessible and recorded their reaction towards the experimenters, who were either facing the goats or had their backs to them.

Goats redirected their gaze frequently between the inaccessible reward and human experimenters. They also gazed towards a forward facing person earlier, more often and for longer compared to when the person was facing away.

First author Dr Christian Nawroth, said: "Goats gaze at humans in the same way as dogs do when asking for a treat that is out of reach, for example. Our results provide strong evidence for complex communication directed at humans in a species that was domesticated primarily for agricultural production, and show similarities with animals bred to become pets or working animals, such as dogs and horses."

The research indicates that the domestication of animals has a much broader impact on human-animal communication than previously believed. For example, it's thought that the capacity of dogs to perceive information from humans is the result of changes to the brain from becoming a companion animal through domestication.

"Goats were the first livestock species to be domesticated, about 10,000 years ago," said lead author Dr Alan McElligott from the School's Department of Biological and Experimental Psychology.

"From our earlier research, we already know that goats are smarter than their reputation suggests, but these results show how they can communicate and interact with their human handlers even though they were not domesticated as pets or working animals."

The researchers hope the study will lead to a better understanding of how skilled livestock are in their aptitude to solve problems and interact with humans based on their cognitive abilities - and to an improvement in animal welfare in general.

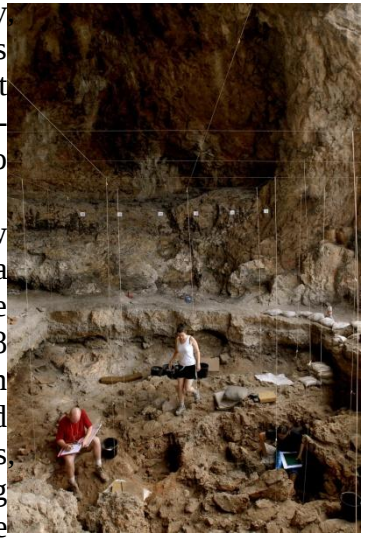
The research was funded by the Deutsche Forschungsgemeinschaft and Farm Sanctuary 'The Someone Project' and was carried out at Buttercups Sanctuary for Goats in Kent UK.

http://www.eurekalert.org/pub_releases/2016-07/uoaa-pdb070516.php

Reconstruction of 12,000 year old funeral feast brings ancient burial rituals to life

One of the earliest funeral banquets ever to be discovered reveals a preplanned, carefully constructed event that reflects social changes at the beginning of the transition to agriculture in the Natufian period

The woman was laid on a bed of specially selected materials, including gazelle horn cores, fragments of chalk, fresh clay, limestone blocks and sediment. Tortoise shells were placed under and around her body 86 in total. Sea shells, an eagle's wing, a leopard's pelvis, a forearm of a wild boar and even a human foot were placed on the body of the mysterious 1.5 meter-tall woman. Atop her body, a large stone was laid to seal the burial space.



Hebrew University archaeologists uncover 12,000 year old grave inside a cave in northern Israel. **Naftali Hilger**

It was not an ordinary funeral, said the Hebrew University archeologist who discovered the grave in a cave site on the bank of the Hilazon river in the western Galilee region of northern Israel back in 2008 (LINK to PNAS). Three other grave pits have been found at the site of Hilazon Tachtit since 1995, and most contained bones of several humans. Nevertheless the unusual objects found inside the grave, measuring approximately 0.70 m x 1.00 m x 0.45 m, point to the uniqueness of the event and the woman at its center.

Eight years after the discovery, Prof. Leore Grosman from the Institute of Archeology at the Hebrew University of Jerusalem and Prof. Natalie Munro from the University of Connecticut, have identified the sequence of events of the mysterious funeral ritual that took place 12,000 years ago.

"We've assigned the event to stages based on field notes, digitized maps, stones, architecture and artifact frequency distributions and concentrations," said Prof. Grosman, adding that, "The high quality of preservation and recovery of a well-preserved grave of an unusual woman, probably a shaman, enabled the identification of six stages of a funerary ritual."

The research, published in the journal Current Anthropology (LINK), details the order of the six-step sequence and its ritual and ideological importance for the people who enacted it.

It began with the excavation of an oval grave pit in the cave floor. Next, a layer of objects was cached between large stones, including seashells, a broken basalt palette, red ochre, chalk, and several complete tortoise shells. These were covered by a layer of sediment containing ashes, and garbage composed of flint and animal bones. About halfway through the ritual, the woman was laid inside the pit in a child-bearing position, and special items including many more tortoise shells were placed on top of and around her. This was followed by another layer of filling and limestones of various sizes that were placed directly on the body. The ritual concluded with the sealing of the grave with a large, heavy stone.

A wide range of activities took place in preparation for the funerary event. This included the collection of materials required for grave construction, and the capture and preparation of animals for the feast, particularly the 86 tortoises, which must have been time-consuming.

"The significant pre-planning implies that there was a defined 'to do' list, and a working plan of ritual actions and their order," said Prof. Grosman.

The study of funerary ritual in the archaeological record becomes possible only after humans began to routinely bury their dead in archaeologically visible locations. The Natufian period (15,000-11,500 years ago) in the southern Levant marks an increase in the frequency and concentration of human burials.

"The remnants of a ritual event at this site provide a rare opportunity to reconstruct the dynamics of ritual performance at a time when funerary ritual was becoming an increasingly important social mediator at a crucial juncture deep in human history," the researchers said.

This unusual Late Natufian funerary event in Hilazon Tachtit Cave in northern Israel provides strong evidence for community engagement in ritual practice, and its analysis contributes to the growing picture of social complexity in the Natufian

period as a predecessor for increasingly public ritual and social transformations in the early Neolithic period that follows.

The unprecedented scale and extent of social change in the Natufian, especially in terms of ritual activities, make this period central to current debates regarding the origin and significance of social and ritual processes in the agricultural transition.

http://www.eurekalert.org/pub_releases/2016-07/uoaa-pdb070516.php

Parkinson's disease biomarker found in patient urine samples

The biomarker, the protein kinase LRRK2, is a promising candidate for future exploration

BIRMINGHAM, Ala. - For more than five years, urine and cerebral-spinal fluid samples from patients with Parkinson's disease have been locked in freezers in the NINDS National Repository, stored with the expectation they might someday help unravel the still-hidden course of this slow-acting neurodegenerative disease.

Now, research by Andrew West, Ph.D., and colleagues at the University of Alabama at Birmingham has revealed that the tubes hold a brand-new type of biomarker -- a phosphorylated protein that correlates with the presence and severity of Parkinson's disease. West and colleagues, with support from the National Institutes of Health, the Michael J. Fox Foundation for Parkinson's Disease Research and the Parkinson's Disease Foundation, are digging deeper into these biobanked samples, to validate the biomarker as a possible guide for future clinical treatments and a monitor of the efficacy of potential new Parkinson's drugs in real time during treatment.

"Nobody thought we'd be able to measure the activity of this huge protein called LRRK2 (pronounced lark two) in biofluids since it is usually found inside neurons in the brain," said West, co-director of the Center for Neurodegeneration and Experimental Therapeutics, and the John A. and Ruth R. Jurenko Professor of Neurology at UAB. "New biochemical markers like the one we've discovered together with new neuroimaging approaches are going to be the key to successfully stopping Parkinson's disease in its tracks. I think the days of blindly testing new therapies for complex diseases like Parkinson's without having active feedback both for 'on-target' drug effects and for effectiveness in patients are thankfully coming to an end."

A biomarker helps physicians predict, diagnose or monitor disease, because the biomarker corresponds to the presence or risk of disease, and its levels may change as the disease progresses. Validated biomarkers can aid both preclinical trial work in the laboratory and future clinical trials of drugs to treat Parkinson's. West and others are paving the way for an inhibitor drug that prevented neuroinflammation and neurodegeneration in an animal model of the disease, as reported last year by West and colleagues.

The new biomarker findings were published in Neurology in March and Movement Disorders in June. The biomarker, LRRK2, has been shown to play a role in hereditary Parkinson's, and the most common of these mutations -- called G2019S -- causes the LRRK2 kinase to add too many phosphates to itself and other proteins. Why this leads to Parkinson's disease is not yet clear.

The key to West's biomarker approach was the recognition that LRRK2 can be purified from a new type of vesicle called exosomes found in all human biofluids, like urine and saliva. Cells in the body continually release exosomes that contain a mixture of proteins, RNA and DNA derived from different kinds of cells. West and colleagues were able to purify exosomes from 3- or 4-ounce urine samples donated by patients, and then measure phosphorylated LRRK2 in those exosomes.

The findings

In the Neurology study, they found that elevated phosphorylated LRRK2 predicted the risk for onset of Parkinson's disease for people carrying a mutation in LRRK2, which is about 2-3 percent of all Parkinson's disease patients. These findings were first tested with a preliminary, 14-person cohort of urine samples from the Columbia University Movement Disorders Center. That was followed by a larger replication study of 72 biobanked urine samples from the Michael J. Fox Foundation LRRK2 Cohort Consortium. All samples were provided to UAB in a blinded fashion to ensure the approach was rigorous.

The follow-up Movement Disorders paper -- the first study of its type -- expanded the scope to people without LRRK2 mutations, which is most Parkinson's disease patients. Using 158 urine samples from Parkinson's disease patients and healthy controls enrolled in the UAB Movement Disorder Clinic as part of the NIH Parkinson's Disease Biomarker Program, West and colleagues found that approximately 20 percent of people without LRRK2 mutations but with Parkinson's disease also showed highly elevated phosphorylated LRRK2 similar to people with LRRK2 mutations, and this was not present in healthy controls. The study speculates that people with elevated phosphorylated LRRK2 may be particularly good candidates for future drugs that reduce phosphorylated LRRK2.

Next steps

Questions remain for this evidence of biochemical changes in LRRK2 in idiopathic Parkinson's disease. One is finding out where the urinary exosomes come from. Given a suspected role for inflammation in Parkinson's disease, it is interesting that LRRK2 is highly expressed in cells of the innate immune system. A possible explanation for the phosphorylated LRRK2 in patients with more severe disease may be an increased inflammation in those patients who have aggressive progression of disease.

In May, West was awarded a new U01 collaborative grant from the National Institute of Neurological Disorders and Stroke to further explore urinary exosomes and extend the observations to cerebral-spinal fluid as a marker for disease prediction and prognosis.

Besides West, authors of the Neurology paper, "Urinary LRRK2 phosphorylation predicts parkinsonian phenotypes in G2019S LRRK2 carriers," are Kyle B. Fraser and Mark S. Moehle, of the Center for Neurodegeneration and Experimental Therapeutics and Department of Neurology, UAB School of Medicine; and Roy N. Alcalay, M.D., Columbia University Department of Neurology.

Besides West, authors of the Movement Disorders paper, "Ser(P)-1292 LRRK2 in urinary exosomes is elevated in idiopathic Parkinson's disease," are Fraser, Ashlee B. Rawlins, Rachel G. Clark and David G. Standaert, M.D., Ph.D., of the UAB Center for Neurodegeneration and Experimental Therapeutics and Department of Neurology; Alcalay; and Nianjun Liu, Ph.D., Department of Biostatistics, UAB School of Public Health.

Standaert is the John N. Whitaker Professor and chair of the Department of Neurology at UAB.

The MJFF LRRK2 Cohort Consortium provided samples and is coordinated and funded in part by the Michael J. Fox Foundation for Parkinson's Disease Research. The Parkinson's Disease Foundation supported the collection of samples from Columbia University.

http://www.bbc.com/news/health-36717828

Viral hepatitis 'kills as many as Aids or TB'

Viral hepatitis is one of the leading killers across the globe, with a death toll that matches Aids or tuberculosis, research in the Lancet suggests.

By Smitha Mundasad Health reporter

The report estimates that hepatitis infections and their complications led to 1.45m deaths in 2013 - despite the existence of vaccines and treatments. World Health Organization data shows there were 1.2m Aids-related deaths in 2014, while TB led to 1.5m deaths. The WHO has put forward a global strategy to tackle hepatitis.

'Startling findings'

Researchers say these plans must be put into action urgently to tackle the crisis.

Viral hepatitis refers to five different forms of virus (known as A, B, C, D, E) - some can be spread through contact with infected bodily fluids and others (A and E) through contaminated food or water. Most deaths worldwide are due to B and C, which can cause serious liver damage and predispose people to liver cancer. But because people don't always feel the symptoms of the initial infection, they can be unaware of the long-term damage until it is too late.

Scientists from Imperial College London and the University of Washington examined data from 183 countries, collected between 1990 and 2013. They found the number of deaths linked to viral hepatitis rose by more than 60% over two decades - partly due to a growing population. Deaths from diseases such as TB and malaria have dropped.

Dr Graham Cooke of Imperial College London described the findings as startling. He said: "Although there are effective treatments and vaccines for viral hepatitis, there is very little money invested in getting these to patients - especially compared to malaria, HIV/AIDS and TB. "We have tools at our disposal to treat this disease - we have vaccines to treat hepatitis A and B and we have new treatments for C. "However the price of new medicines is beyond the reach of any country - rich or poor."

The study suggests the problem is biggest in East Asia. But unlike many other diseases, deaths from viral hepatitis were higher in high and middle income countries than in lower income nations.

The WHO hepatitis strategy, which was put forward in May 2016, includes targets to reduce new cases of hepatitis B and C by 30% by 2020, alongside a 10% reduction in mortality. The WHO says countries and organisations will need to expand vaccination programmes, focus on preventing mother-to-child transmission of hepatitis B and increase access to treatment for hepatitis B and C, to help ensure these targets are met.

http://bit.ly/29ERHEW

Making the Case That Animals Are Impressively Smart

The world is brimming with brainy beings

By Steve Mirsky on July 1, 2016

Twenty years ago I wrote a profile of primatologist and author Frans de Waal for another magazine. As a placeholder for the title until we could think of a better one, I came up with “The Writing on de Waal.” I'm both delighted and appalled to say that either by an act of editorial commission or by one of omission, the piece was published with that title. Now I have the chance to write on de Waal again, in the context of the arrival of his latest book, Are We Smart Enough to Know How Smart Animals Are? The answer: sometimes, with great effort.

Imagine judging Michael Jordan's basketball skills by watching him hit .202 when he played Minor League Baseball. Gauging an animal's brightness poses similar issues: “We need to familiarize ourselves with all facets of the animal and its natural history before trying to figure out its mental level,” de Waal writes. “And instead of testing animals on abilities that we are particularly good at … why not test them on their specialized skills?” De Waal thus prefers the term “evolutionary cognition” to “animal intelligence” for this field of study. “It seems highly unfair to ask if a squirrel can count to ten,” de Waal writes, “if counting is not really what a squirrel's life is about.” You could even say it's nuts.

Consider the story in the book about a test administered to gibbons, pretty good apes. (Not great apes. They're technically lesser or smaller apes.) The tree dwellers were asked to reach out with a thin stick to move a banana close enough

to their enclosure to pick it up. Chimpanzees and some monkeys could get their bananas lickety-split. But gibbons flopped and were thus considered intellectually backward.

Until a researcher named Benjamin Beck realized that their hooklike hands, excellent for traveling among the tree limbs, were miserable at the kind of manipulations the task required. When Beck redesigned the experiment so that the provided tools were in the subjects' anatomical wheelhouse, well, blue ribbons for the gibbons.

De Waal reviews numerous studies involving crows, dolphins, whales, bats, sheep and other fauna showing off their brainpower. But as a longtime chimp researcher—he is director of the Living Links Center at Emory University's Yerkes National Primate Research Center—he devotes the lion's share of his time to our close cousins.

One anecdote involves a colony of 25 chimps at Burgers' Zoo in Arnhem, Netherlands, which de Waal studied for six years, starting in 1975. The chimps spent nights inside but were let out onto an adjoining island all day. One morning he and some colleagues carried a crate overflowing with grapefruits past the watchful chimps and out to the island—the first time either group of primates had ever engaged in this behavior. “We thought we would get a reaction from them, but they sort of ignored the grapefruits,” de Waal told me when he visited New York City in April.

The researchers then hid the grapefruits on the island to study how the chimps would search for them later. “And then we came back with an empty crate,” he said. “And that's when they reacted. They saw an empty crate, and they started jumping around and hollering and slapping one another on the back. And I've never seen animals so excited for no fruit.... They must have deduced that we cannot go out with a crate of grapefruits and come back with it empty without these things staying” on the island, where they would soon be able to party hearty on the citrus snacks.

But there's more. When the troop got to the island, some went right past the site of a few grapefruits buried not quite completely in the sand. The human observers assumed all the chimps had overlooked the cache. But later, when his Pan pals were taking a siesta, a low-ranking male nonchalantly returned to the buried fruit. “He knew exactly where they were,” de Waal said to me, “but he had decided not to react at the moment that he saw them.” Presumably because if he had, higher-ranking individuals would have pilfered his produce. That's some quick, strategic thinking that shows off impressive evolutionary cognition.

So when somebody says they don't believe that humans evolved from ape ancestors, I tell myself I'm better off talking to de Waal.

http://www.eurekalert.org/pub_releases/2016-07/su-wor070716.php

Weathering of rocks by mosses may explain climate effects during the Late Ordovician

It has been hard to explain how the Ordovician climate cooled enough for glaciation to occur

During the Ordovician period, the concentration of CO2 in the earth's atmosphere was about eight times higher than today. It has been hard to explain why the climate cooled and why the Ordovician glaciations took place.

A new study, published in Nature Communications, shows that the weathering of rock caused by early non-vascular plants had the potential to cause such a global cooling effect. "When we can better understand the carbon cycle in the past, we can better predict what happens with the climate in the future," says Philipp Porada of Stockholm University, one of the authors of the study.

Non-vascular plants, such as mosses, hornworts and liverworts, probably evolved during the Ordovician period, around 450 million years ago. They are older than vascular plants, such as trees and grasses, and together with lichens, which are a symbiosis of fungi and algae, they formed the earliest terrestrial vegetation. Today's successors of these organisms are distributed worldwide and are characterised by their ability to survive in environments in which the supply of both water and nutrients is scarce. They are found in both cold and warm desert regions and are able to grow on rock surfaces and the bark of trees. Although they do not have real roots, they affect the surfaces on which they grow: the release of various organic acids dissolves underlying rock minerals.

This process of dissolution and chemical transformation of rock minerals is called chemical weathering. Non-vascular plants and lichens may considerably increase weathering rates of the rock surfaces on which they grow.

This has important implications for the climate system, since chemical weathering of silicate rocks such as granite results in a drawdown of atmospheric CO2 and may therefore lead to global cooling. During the weathering process CO2 dissolves in water as acid, and is then transported to the ocean where the carbon is buried as carbonate rock. Consequently, it has been hypothesised that early non-vascular vegetation caused an interval of glaciations at the end of the Ordovician period, when they became globally abundant.

Without the drawdown of atmospheric CO2 caused by the enhancement of weathering rates, the Ordovician glaciations are hard to explain, since they started under conditions of eight times higher atmospheric CO2 than today. "I believe that the most interesting thing about the study is that tiny plants such as mosses and lichens can influence global climate in the long run," says Philipp Porada.

"However, it is difficult to extrapolate today's weathering rates by non-vascular plants and lichens measured in the field to a global effect on chemical weathering in the Ordovician. In our study we therefore use a process-based numerical model of non-vascular vegetation to simulate weathering by these organisms in the Late Ordovician. We find a high potential for weathering, which means that the emergence of early non-vascular plants and lichens indeed may have been the reason for the Late Ordovician glaciations."

http://www.eurekalert.org/pub_releases/2016-07/uotb-tfe070716.php

The first evidence of Neanderthal cannibalism in northern Europe is discovered

99 skeletal remains belonging to at least 5 individuals have been retrieved from a site in Goyet (Belgium)

The Neanderthals displayed great variability in their behaviour and one of the aspects in which this becomes clear is their relationship with the dead. There is evidence on different sites (e.g. Chapelle-aux-Saints in France, and Sima de las Palomas on the Iberian Peninsula) that the Neanderthals buried the dead. Yet other sites show that the Neanderthals ate the meat and broke the bones of their fellow Neanderthals for food. Evidence of this cannibal behaviour has been discovered at various sites in France (e.g., Moula-Guercy, Les Pradelles) and on the Iberian Peninsula (Zafarraya, El Sidrón).

***The highly fragmented Neanderthal collection of the third cave at Goyet represents at least five individuals. Dating indicates that the ones marked with an asterisk go back to between 40,500 and 45,500 years ago. Scale=3cm Asier* Gómez-Olivencia et al.**

However, there are very few sites with Neanderthal remains north of latitude 50º, as only two of these sites have provided information on possible funerary treatment. Partial skeletons have been found in Feldhofer (Germany) and in Spy (Belgium), and the study of them as well as that of their context allows one to deduce that they were interred. In fact, the excavation notes on the Spy II individual indicate that it was a complete skeleton found in a contracted position.

A new study, led by Dr Hélène Rougier, and which the Ikerbasque researcher at the UPV/EHU Asier Gómez-Olivencia has participated in, has discovered the largest number of Neanderthal human remains in northern Europe, not only in terms of the number of remains but also in terms of the number of individuals represented, a total of five: 4 adolescents or adults and one child. The site is the "Troisième caverne" in Goyet (Belgium).

A third of the Neanderthal remains on this site display cut marks, and many remains bear percussion marks caused when the bones were crushed to extract the marrow. The comparison of the Neanderthal remains with other remains of fauna recovered on the site (horses and reindeer) suggests that the three species were consumed in a similar way. This discovery enables the range of known Neanderthal behaviour in northern Europe with respect to the dead to the expanded.

What is more, five human Neanderthal remains display signs of having been used as soft percussors to shape stone. The Neanderthals used boulders to shape stone tools and also used bone in some cases to sharpen the cutting edges (one example closer to home can be found in the bone retouchers, mainly belonging to deer, recovered on the Azlor site in Dima, Bizkaia). So far, there have been three sites in which the Neanderthals are known to have used the bones of a fellow Neanderthal to shape stone tools: a femur fragment in the case of Krapina in Croatia and Les Pradelles, and a skull fragment at La Quina in France. Goyet has provided 5 sets of human remains used as retouchers, which almost doubles the record known so far on a single site.

It has also been possible to date this collection of Neanderthal remains. It has been revealed that these Neanderthals lived between 40,500 and 45,500 years ago. The exceptional preservation of the collection has also enabled the mitochondrial DNA of these remains to be recovered, which when compared with that of other Neanderthals, reveals that genetically the Neanderthals at Goyet resembled those of Feldhofer (Germany), Vindija (Croatia) and El Sidrón (Asturias, Spain). This great genetic uniformity, notwithstanding the geographical distances, indicates that the Neanderthal population that inhabited Europe was small.

Rougier, H., Crevecoeur, I., Beauval, C., Posth, C., Flas, D., Wissing, C., Furtwängler, A., Germonpré, M., Gómez-Olivencia, A., Semal, P., van der Plicht, J., Bocherens, H., Krause, J. Neanderthal cannibalism and Neanderthal bones used as tools in Northern Europe. Scientific Reports. DOI: 10.1038/srep29005

http://www.eurekalert.org/pub_releases/2016-07/miot-nct070516.php

New clue to how lithium works in the brain

Biologists find a possible explanation for why the drug helps bipolar patients

CAMBRIDGE, MA -- Since the 1970s, U.S. doctors have prescribed lithium to treat patients with bipolar disorder. While the drug has a good success rate, scientists are still unsure exactly how it achieves its beneficial effects.

MIT biologists have now discovered a possible explanation for how lithium works. In a study of worms, the researchers identified a key protein that is inhibited by lithium, making the worms less active.

While these behavioral effects in worms can't be translated directly to humans, the results suggest a possible mechanism for lithium's effects on the brain, which the researchers believe is worth exploring further. "How lithium acts on the brain has been this great mystery of psychopharmacology," says Joshua Meisel, an MIT postdoc and lead author of the study. "There are hypotheses, but nothing's been proven."

Dennis Kim, an associate professor of biology, is the senior author of the paper, which appears in the July 7 issue of Current Biology.

Mysterious effects

Lithium's ability to act as a tranquilizer for people suffering from mania and bipolar disorder was discovered in 1949 by the Australian psychiatrist John Cade, but the drug was not approved by the U.S. Food and Drug Administration until 1970.

Lithium interacts with many proteins and other molecules in the brain, so it has been difficult for scientists to determine which of these interactions produce mood stabilization. Some of the hypothesized targets are an enzyme that produces inositol, a simple sugar involved in cell signaling, and an enzyme called GSK3, which inactivates other proteins. However, no studies have conclusively linked these targets to lithium's effects on bipolar patients.

The MIT team did not set out to study lithium but fell upon it while exploring interactions between Caenorhabditis elegans and its microbial environment. This worm has a simple nervous system consisting of 302 neurons, most of which occur in pairs.

In a paper published in 2014, Meisel and Kim discovered that a pair of neurons known as ASJ neurons are necessary for the worm's avoidance of harmful bacteria. Previous studies from other labs had shown that the ASJ neurons are also required for reawakening from a starvation-induced hibernation state. This reactivation, known as the dauer exit, occurs when food becomes more plentiful.

As a follow-up to that study, the researchers performed a genetic screen in which they looked for mutated genes that disrupt ASJ neurons. To their surprise, one of the genes implicated by this screen was one that codes for a protein called BPNT1, which was already known to be inhibited by lithium.

BPNT1 is a protein that removes phosphate groups from a compound known as PAP, a process that is critical to maintaining normal cell function.

When the researchers knocked out the gene for BPNT1, they found that the ASJ neurons entered a dormant state and the worms could no longer execute either avoidance behavior or the dauer exit. They also found the same behavioral effects in worms treated with lithium.

New hypothesis

The findings suggest that lithium treatment silences activity in neurons that rely on BPNT1, which Meisel and Kim found intriguing because many human brain cells also depend on this protein. In humans, PAP, which BPNT1 degrades, is usually found in neurons that secrete dopamine, epinephrine, or norepinephrine, which are all neurotransmitters that stimulate brain activity.

"We think that it's perfectly reasonable to add BPNT1 onto the list of hypotheses for how lithium is affecting the brain," Meisel says. "Silencing dopaminergic neurons I would think would make you less manic because of how dopamine affects the brain."

While Kim's lab focuses on worms, the researchers hope that other labs will test the new hypothesis in other animals.

"Establishing that this happens in C. elegans, by no means does it prove how lithium works in humans, but it provides a very solid experimental foundation for exploring a hypothesis that lithium might have therapeutic effects in specific neurons through inhibition of BPNT1," Kim says. "We hope that other groups that work on mammalian systems may be interested to explore this question further."

The research was funded by the National Institutes of Health.

http://www.eurekalert.org/pub_releases/2016-07/aaft-eot070516.php

Evolution of the tail: From water to land

As early vertebrates emerged from the water, their tails may have played a crucial role in helping them move across land, a new study reports.

The results, based on animal and robot models, as well as mathematical analysis, may shed light on the origins of terrestrial life on Earth.

Life first dwelled in the watery depths of the oceans - until roughly 385 to 360 million years ago when early tetrapods made a move to land. These animals, which were adapted for water, would have had to find unique ways to move their bodies across land - and the nature of shorelines, with granular surfaces and sloping banks, only added to the challenge.

To gain more insights into the early locomotion required for this transition, Benjamin McInroe and colleagues studied the movement of the modern

mudskipper, a fish that sometimes enjoys a "stroll" on land using its fins, and occasionally jumps using its tail.

The researchers found that on flat land, using its tail only provides minimal benefit for lateral movement. Yet, as the slope of a surface increased - as one might see along a riverbank - the tail became significantly more important in helping the mudskipper propel itself forward. For example, at slopes of 10° the tail was used in roughly one third of all "steps," and at slopes of 20° it was used during more than half of all steps. On flat ground, the tail was rarely used.

The team created a robot that mimics various movements of the mudskipper and early tetrapods, manipulating its limbs to better understand how the fins and tails move in concert to propel a fish forward on land. On flat land, the angle at which the robot could move its "fins" towards its body was key; at higher slopes, similar to the mudskipper, the tail became a dominant factor for lateral movement, the authors show. The tail was also useful for anchorage, so that the robot didn't slide backwards down the slope.

A Perspective by John Nyakatura discusses the study in more detail.

http://bit.ly/29FeWic

Former Japanese Airline Pilot Fulfills Dream to Fly in Space

Astronaut Takuya Onishi scores a first.

By Tony Reichhardt

For all the regional pilots out there hauling passengers on short routes, day after day, night after night, for low pay and little glory—this one's for you. Takuya Onishi may not be the first airline pilot to entertain the Walter Mittyish dream of becoming an astronaut, but last night (early Thursday morning in Kazakhstan) the dream turned real when he blasted off on a Soyuz rocket bound for the space station, where he'll live and work for four months as a member of the six-person crew.

Many astronauts have backgrounds as military pilots, and a few, like veteran space shuttle commander Hoot Gibson, go on to fly commercial airliners after leaving NASA. But Onishi, at the age of 40, may be the first to go straight from civilian airline pilot to astronaut. He began his career at All Nippon Airlines (ANA) in 1998, working behind the check-in counter at Tokyo's Haneda airport, where he also helped disabled passengers in boarding. After flight training in the United States and Japan, he became a pilot for ANA, eventually flying Boeing 767s on both domestic and international routes. He was selected as a Japanese Space Agency (JAXA) astronaut in 2009, from a pool of nearly 1,000 applicants.

In an interview with Yomiuri Shimbun, Onishi said he was inspired to become an astronaut after watching Apollo 13 when he was an aeronautics and astronautics major at the University of Tokyo. Onishi has been asked many times about the differences between airline pilots and astronauts; he generally stresses the similarities, including the need for teamwork and attention to detail.

His former airline is clearly proud of its pilot-turned-astronaut, releasing photos of Onishi in his ANA uniform, as well as organizing public viewings of yesterday's Soyuz liftoff.

Along with Soyuz MS-01 crewmates Anatoly Ivanishin and Kate Rubins of NASA, Onishi is scheduled to dock at the station just after midnight (12:12 a.m., U.S. Eastern time) on Friday night/Saturday morning. Normally their trip from the launch pad to the station would take only six hours, but this is the first flight for the new MS-01 variant of the Soyuz, and program managers wanted additional time to check out the vehicle's new computers and other upgrades before docking.

If Onishi is the first former airline pilot to reach space, he won't be the last. French astronaut Thomas Pesquet, who's scheduled to ride a Soyuz to the station in November, used to fly Airbus A320's for Air France, although he had a background in space engineering before getting his commercial pilot's license.

http://www.eurekalert.org/pub_releases/2016-07/qu-dbs070716.php

Deadly bug strikes in a day

New pathway discovered for bacteria

A deadly bacteria that can be picked up by a simple sniff can travel to the brain and spinal cord in just 24 hours, a new Griffith University and Bond University study has found.

The pathogenic bacteria Burkholderia pseudomallei, which causes the potentially fatal disease melioidosis, kills 89,000 people around the world each year and is prevalent in northern Australia and southeast Asia. Previously, researchers did not understand how the bacteria travelled to the brain and spinal cord, or just how quickly.

The findings, published in Immunity and Infection this week, could mean further discoveries in how the common staphylococcus and acne bacterium also end up in the spinal cord, as well as how chlamydia travels to the brain in Alzheimer's patients.

It could also provide answers for common back problems where bacteria have infected the bone, causing pain that could be simply treated with antibiotics.

In Australia a person with melioidosis has a 20-50 per cent chance of dying once it infects the brain. The bacterium is found in soil in populated areas such as Darwin. Dr James St John, Head of Griffith's Clem Jones Centre for Neurobiology and Stem Cell Research, said the scary bacteria could slip into your system without you even knowing it.

"Imagine walking around and you sniff it up from the soil and the next day you've got this bacteria in your brain and damaging the spinal cord," he said.

"It can be at a very low level, the body doesn't even know it's there. You could have it and don't know it, that's scary. "It could just be sitting there waiting for an opportune moment, or it could just be doing small incremental damage over a lifetime. You could lose the function in your brain incrementally."

Together with Associate Professor Jenny Ekberg from Bond University and Professor Ifor Beacham from the Institute for Glycomics, the team studied mice to find that the bacteria travels from the nerves in the nasal cavity before moving to the brain stem and then into the spinal cord.

In Southeast Asia 50 per cent of the population may be positive for melioidosis and in places like Cambodia the mortality rate is as high as 50 per cent.

Associate Professor Ekberg, from Bond's Faculty of Health Sciences and Medicine, said it was frightening how easily and quickly the bacteria could get into the brain. "But what are the long term consequences? Do the bacteria hide away until sometime later and do little bits of incremental damage, or do they immediately cause full blown infection? We are now working on these questions."

Dr St John said this could be a pathway for many other common bacteria. "What excites me most is the idea that other bacteria could also use this route," he said.

"Bacteria have been implicated as a major causative agent of some types of back pain. We now need to work out whether the bacteria that cause back pain also can enter the brainstem and spinal cord via the trigeminal nerve".

By discovering the pathway, researchers will now work on ways to stimulate supporting cells that could remove the bacteria.

Dr St John said the work was important as the bacteria had the potential to be used as a bioweapon and knowing how to combat it was extremely important.

Professor Beacham said the olfactory mucosa, located in the nose, is very close to the brain and it had long been known that viruses could reach the brain from the olfactory mucosa.

"Our latest results represent the first direct demonstration of transit of a bacterium from the olfactory mucosa to the central nervous system (CNS) via the trigeminal nerve; bacteria were found a considerable distance from the olfactory mucosa, in the brain stem, and even more remarkably in the spinal cord," he said.

"These results add considerably to our understanding of this particular disease. It seems likely, however, that other bacteria may also transit from nose to CNS, although this has yet to be determined.".

The Clem Jones Centre for Neurobiology and Stem Cell Research is located in the Eskitis Institute for Drug Discovery, a centre focused on developing new therapies for infectious disease, cancer and neurological diseases.

The full paper can be found here http://iai.asm.org/content/early/2016/06/28/IAI.00361-16.full.pdf+html

http://nyti.ms/29sdGwh

Juno Halts Cancer Trial Using Gene-Altered Cells After 3 Deaths

Three patients in a study testing the use of genetically engineered cells as a treatment for cancer have died from swelling in the brain, dealing a setback to one of the most exciting pursuits in oncology.

By ANDREW POLLACK JULY 7, 2016

Juno Therapeutics, the company conducting the clinical trial, said on Thursday that the Food and Drug Administration had temporarily halted the study.

The deaths were “difficult and humbling for everyone involved,” Hans Bishop, the company’s chief executive, said in a conference call with securities analysts.

Shares of Juno stock plunged 27 percent in after-hours trading.

Mr. Bishop and other Juno executives said they believed that the problems resulted from a combination of the particular cells being used and a chemotherapy drug. The company proposed to the F.D.A. that the trial continue without the drug.

It is not clear whether the agency will agree, or when it will make a decision, though Juno executives said it could be within 30 days.

Juno is working on what is known as CAR-T therapy. This involves taking blood from a patient to extract immune cells, genetically engineering them to make them kill cancer cells, and then putting them back into the bloodstream to go to work.

Early studies have shown some striking results in treating certain types of leukemia and lymphoma, generating excitement among oncologists, patients and investors.

But the therapy can provoke severe side effects, particularly immune system overreactions and neurological toxicity, including swelling in the brain, known as cerebral edema. There have been several deaths from these side effects.

Juno, which is based in Seattle, is in a three-way race to bring the first of these treatments to market, competing against Kite Pharma and Novartis. Juno executives said the setback would probably mean that its initial treatment would not get to market by the end of 2017, as it had hoped.

That could clear the way for Kite to be the first, but the company’s shares fell about 10 percent after-hours Thursday. Investors were apparently concerned that Juno’s problems could portend more regulatory scrutiny or other difficulties for the entire field.

Chemotherapy is used as part of the treatment to kill some of the patient’s immune system, making room for the genetically engineered cells that are put back into the body.

Juno initially used only one chemotherapy drug for this, cyclophosphamide. But it more recently added a second drug, fludarabine, saying the dual chemotherapy could make the treatment more effective.

All three of the deaths, two of them occurring last week, were among the six or seven patients so far who had received both chemotherapy drugs. There have been no such deaths among the 13 or 14 patients in the study who received cyclophosphamide alone, the company said.

Juno executives said they had proposed to the F.D.A. that the trial, which was treating adults with acute lymphoblastic leukemia, continue using only cyclophosphamide. In an earlier study, about 80 percent of adults with that cancer had at least temporary complete remissions using cyclophosphamide alone. That would still represent a big advance for those patients, they said.

Executives said Juno would continue to use fludarabine in other trials that have different genetically engineered cells.

http://www.eurekalert.org/pub_releases/2016-07/sri-sfs070816.php

Scripps Florida scientists link bipolar disorder to unexpected brain region

While bipolar disorder is one of the most-studied neurological disorders--the Greeks noticed symptoms of the disease as early as the first century--it's possible that scientists have overlooked an important part of the brain for its source.

JUPITER, FL - Scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown for the first time that ensembles of genes within the striatum--a part of the brain that coordinates many primary aspects of our behavior, such as motor and action planning, motivation and reward perception--could be deeply involved in the disorder. Most modern studies of bipolar disorder have concentrated on the brain's cortex, the largest part of the brain in humans, associated with higher-level thought and action.

"This is the first real study of gene expression in the striatum for bipolar disorder," said Ron Davis, chair of the Department of Neuroscience at TSRI, who directed the study. "We now have a snapshot of the genes and proteins expressed in that region."

The study, published recently online ahead of print in the journal Molecular Psychiatry, also points to several pathways as potential targets for treatment.

Bipolar disorder is a mental illness that affects about 2.6 percent of the U.S. adult population--some 5.7 million Americans--with a sizable majority of these cases classified as severe. The disease runs in families, and more than two-thirds of people with bipolar disorder have at least one close relative with the illness or with unipolar major depression, according to the National Institute of Mental Health.

In the new research, tissue samples from 35 bipolar and non-bipolar control subjects were analyzed. The number of genes differentially expressed in tissue samples from the two groups turned out to be surprisingly small--just 14 in all. However, co-expression network analysis also revealed two modules of interconnected genes that were particularly rich in genetic variations associated with bipolar disorder, suggestive of a causal role in the disorder. One of these two modules was particularly striking, as it seemed to be highly specific to the striatum.

"Our finding of a link between bipolar disorder and the striatum at the molecular level complements studies that implicate the same brain region in bipolar disorder at the anatomical level, including functional imaging studies that show altered activity in the striatum of bipolar subjects during tasks that involve balancing reward and risk," said TRSI Research Associate Rodrigo Pacifico, who was first author of the new study. Analyzing reactions to risk was important because bipolar patients may act impulsively and engage in high-risk activities during periods of mania.

Pathway analysis also found changes in genes linked to the immune system, the body's inflammatory response, and cells' energy metabolism. Davis noted, "We don't know if these changes are a cause of the disease or the result of it. But they provide additional gene markers in bipolar disorder that could potentially lead to the future development of diagnostics or treatments."

The study, "Transcriptome Sequencing Implicates Dorsal Striatum-Specific Gene Network, Immune Response and Energy Metabolism Pathways in Bipolar Disorder," http://www.nature.com/mp/journal/vaop/ncurrent/full/mp201694a.html was supported by funding from the State of Florida.

http://www.eurekalert.org/pub_releases/2016-07/tl-tls070716.php

The Lancet: Study maps transmission of MERS virus in South Korean hospital from one 'super-spreader' patient

Overcrowded emergency room was high risk location of infection

Super-spreader patient linked to 82 of the 186 MERS cases seen in the 2015 South Korean outbreak

Tracing the movements of patients at a South Korean hospital has helped identify how Middle East Respiratory Syndrome (MERS) virus was transmitted from a single super-spreader patient in an overcrowded emergency room to a total of 82 individuals over three days including patients, visitors and health-care workers. The study, published today in The Lancet, maps the transmission of South Korea's first outbreak of MERS virus and the case of highest transmission of MERS virus from a single patient outside the Middle East.

The study demonstrates the potential for outbreaks of MERS Coronavirus (MERS-CoV - the virus behind MERS) from a single spreader, as has been previously documented for SARS (Severe Acute Respiratory Syndrome). The authors say that as long as the MERS transmission in the Middle East continues, governments and health-care providers should be prepared for emerging infections.

Since it was first identified in 2012, MERS-CoV has spread to 27 countries. Patients develop severe acute respiratory illness with symptoms of fever, cough and shortness of breath. Approximately 3-4 out of every 10 patients reported with MERS-CoV have died, most of whom had an underlying medical condition [1].

Previous studies have suggested that the potential for MERS-CoV to spread to large numbers of people was low. However, an outbreak in Saudi Arabia in 2013 saw one patient transmit the virus to seven others, raising concerns about so-called super-spreaders - patients who infect disproportionally more secondary contacts than others also infected with the same disease.

In between May and July 2015, there was a MERS-CoV outbreak in South Korea, where 186 cases were confirmed within 2 months. The 'index patient' (where the outbreak originated) was a man aged 68, otherwise known as Patient 1, who had travelled to Bahrain, the United Arab Emirates, Saudi Arabia and Qatar between 18 April and 3 May 2015 before returning to South Korea. He first visited the Samsung Medical Center in Seoul on 17 May, and was isolated on 18 May under the suspicion of MERS and finally diagnosed with MERS on 20 May. However, before arriving at Samsung Medical Centre, Patient 1 had already transmitted the virus to several individuals in other hospitals, including another man (Patient 14), aged 35 with whom he shared a ward. Patient 14 was admitted to Samsung Medical Center with no information on possible exposure to MERS-CoV on 27 May - and it was this patient who led to the hospital outbreak at Samsung.

Samsung Medical Center is a large 1982-bed hospital with an emergency room that sees more than 200 patients a day. The research team did a retrospective investigation of the outbreak at the hospital, including a review of closed-circuit security video footage and electronic medical records.

A total of 1576 people were estimated to have been exposed to Patient 14 in the emergency room and a total of 82 people - 33 patients, 8 health-care workers, and 41 visitors - were infected between 27-29 May (table 1). Exposed people were classified into different groups depending on their proximity to Patient 14 (table 1, figure 4). Patients staying in the same zone of the emergency room as Patient 14 had the highest risk of infection (20% [23/117 patients]), compared with 5% (3/58) in those with brief exposure to Patient 14 at the registration area or the radiology suite of the emergency room, and 1% (4/500) in other patients who stayed in different zones. The risk of infection was 2% (5/218) in health-care workers, and 6% (38/683) in visitors. Nine cases were not included in the analysis due to a lack of reliable data.

On average, the incubation period was 7 days but there was wide variation depending on the proximity to Patient 14 - 5 days for patients in the closest proximity to Patient 14 (group A) to 11 days for patients further away (group C). There were no confirmed cases of patients or visitors who visited the emergency room on 29 May, after Patient 14 had been isolated, and who were exposed only to potentially contaminated environment.

In contrast, Patient 1 was in contact with 285 other patients and 193 health-care workers but no further transmissions occurred at the hospital between presenting to the emergency room on 17 May and being isolated on 18 May. However, Patient 1 had previously infected 28 other patients in another hospital. The authors say that the difference in transmissibility between Patient 1 and Patient 14 could be caused by a number of factors such as time from onset of disease, symptoms, duration of contact, pattern of movement and the spread of the virus itself.

Study authors Professor Doo Ryeon Chung and Yae-Jean Kim, Division of Infectious Diseases at the Samsung Medical Center, Seoul, South Korea, warn that the results of this study need to be interpreted with caution due to the retrospective nature of the analysis but say: "This study is the first to document the spread of MERS-CoV virus through a hospital by providing specific infection risk depending on the proximity of patients to the infected patient. Our results show the increased potential of MERS virus infection from a single patient in an overcrowded emergency room. Overcrowding is an important issue for this outbreak but also a common feature of modern medicine which should be of concern to governments and health-care providers in the context of future possible outbreaks. Emergency preparedness and vigilance in hospitals, laboratories, and government agencies are crucial to the prevention of further large outbreaks not only of MERS-CoV infections, but also other emerging infectious diseases." [2]

Writing in a linked Comment, Professor David S Hui from the Department of Medicine & Therapeutics and Stanley Ho Center for Emerging Infectious Diseases, The Chinese University of Hong Kong, China, says: "The data suggest that the location (and hence the timing) of exposure to Patient 14 was an important factor in determining the attack rate and incubation period. Several other predisposing factors to this superspreading event included failure to implement strict isolation of patients and quarantine of contacts at the first outbreak hospital (Pyeongtaek St Mary's Hospital), poor communication and knowledge of patient movement between hospitals, overcrowding in the emergency room, inadequate ventilation with only three air changes per h, and

limited availability of isolation rooms in the emergency room... Failure in infection control and prevention in health-care facilities has resulted in large numbers of secondary cases of MERS-CoV infection involving health-care workers, existing patients, and visitors in Saudi Arabia and several other countries in the past few years. Common risk factors include exposure to contaminated and overcrowded health-care facilities, poor compliance with appropriate personal protection equipment when assessing patients with febrile respiratory illness, application of potential aerosol generating procedures (eg, resuscitation, continuous positive airway pressure, nebulised drugs), and lack of proper isolation room facilities."

The study received no funding.

[1] https://www.cdc.gov/coronavirus/mers/downloads/factsheet-mers_en.pdf

[2] *Quote direct from authors and cannot be found in text of Article.*

http://www.eurekalert.org/pub_releases/2016-07/esoc-smb070516.php

Statins may be associated with reduced mortality in 4 common cancers

High cholesterol diagnosis associated with lower risk of death in lung, breast, prostate and bowel cancers

Florence, Italy - A diagnosis of high cholesterol is associated with reduced mortality and improved survival in the four most common cancers, according to research presented today at Frontiers in CardioVascular Biology (FCVB) 2016.1 The 14 year study from nearly one million patients found that a high cholesterol diagnosis was associated with lower risk of death in lung, breast, prostate and bowel cancers.

"The discovery of a link between obesity and high cholesterol as risk factors for cancer has been exciting for researchers and the public," said lead author Dr Paul Carter from the ACALM Study Unit at Aston Medical School, Aston University in Birmingham, UK. "Even trendier is the idea that if high cholesterol can cause cancer, then cholesterol lowering interventions such as statins could reduce this risk."

He continued: "We previously found an association between having high cholesterol and developing breast cancer.2 Animal studies show that giving statins for high cholesterol can reduce the risk of breast cancer. We wanted to see if there was any effect of high cholesterol on mortality amongst cancer patients."

The current study investigated the association between high cholesterol and mortality in patients with lung, breast, prostate and bowel cancer, the four most common cancers in the UK. Patients admitted to UK hospitals with these cancers between 1 January 2000 and 31 March 2013 were recruited from the Algorithm for Comorbidities, Associations, Length of stay and Mortality (ACALM) clinical database, which also had information on co-existing conditions such as high cholesterol. Mortality data was obtained from the Office for National Statistics.

Out of a total of 929 552 patients in the ACALM study, 7997 had lung cancer, 5481 had breast cancer, 4629 had prostate cancer, and 4570 had bowel cancer.

After adjusting for factors which might influence mortality, including age, gender, ethnicity, and the ten most common causes of death in the UK, the researchers found that patients with cancer were less likely to die if they had a diagnosis of high cholesterol than if they did not. Having a diagnosis of high cholesterol was associated with a 22% lower risk of death in patients with lung cancer, 43% lower risk of death in breast cancer, 47% lower risk of death in prostate cancer, and 30% lower risk of death in bowel cancer.

Dr Carter said: "Our research suggests that there's something about having a high cholesterol diagnosis that improves survival and the extent to which it did that was quite striking in the four cancers studied. Based on previous research we think there's a very strong possibility that statins are producing this effect."

He continued: "Because we saw the association amongst all four cancers we studied, we think this effect is caused by medications used for high cholesterol such as statins. These findings are likely to be seen in other cancers as well but this is only speculation and would need to be confirmed by studies in different types of cancer."

Dr Rahul Potluri, senior author and founder of the ACALM Study Unit, said: "Statins have some of the best mortality evidence amongst all cardiovascular medications and statin use in patients with a diagnosis of high cholesterol is possibly the main reason that this diagnosis appears to be protective against death in patients with lung, breast, prostate and bowel cancer. Other cardiovascular medications may also be protective and explain the varying levels of risk reduction in the four cancer types. For example, prostate cancer is associated with heart disease and these patients tend to take ACE inhibitors and beta-blockers."

He added: "The results of this study strengthen the argument for a clinical trial evaluating the possible protective effect of statins and other routinely used cardiovascular medications such as aspirin, blood pressure medications, beta-blockers and ACE inhibitors in patients with cancer. Whether it is statins and/or other cardiovascular drugs in combination that have an effect on mortality remains to be seen."

Dr Potluri concluded: "Patients with cancer who are at high risk or have established cardiovascular disease should be given statins as per current guidelines. I don't think at the moment we can give statins for cancer per se. But this could change if there was a positive result in the clinical trial."

http://bit.ly/29weFis

Antibiotic resistance discovered in the guts of ancient mummies

Incan mummies on display

By Andy Coghlan

The gut bacteria inside 1000-year-old mummies from the Inca Empire are resistant to most of today's antibiotics, even though we only discovered these drugs within the last 100 years.

"At first we were very surprised," Tasha Santiago-Rodriguez of California Polytechnic State University in San Louis Opisbo, told the Annual Meeting of the American Society for Microbiology last month.

Her team studied the DNA within the guts of three Incan mummies dating back to between the 10th and 14th centuries and six mummified people from Italy, from between the 15th and 18th centuries. They found an array of genes that have the potential to resist almost all modern antibiotics, including penicillin, vancomycin and tetracycline.

These ancient genes were largely in microbes whose resistance is problematic today, including Enteroccocus bacteria that can infect wounds and cause urinary tract infections. But they found that many other species, including some harmless ones, carried some of these resistant genes too.

Enterococcus enigma

"When you think about it, almost all these antibiotics are naturally produced, so it makes sense to find antibiotic genes as well," says Santiago-Rodriguez.

Their finding shows that genes that can confer resistance to antibiotics were relatively widespread hundreds of years before Alexander Fleming discovered penicillin in 1928. "It's ridiculous to think evolution of antibiotic resistance began when penicillin was discovered," said team-member Raul Cano, also at California Polytechnic State University, at the meeting while discussing the findings. "It's been going on for 2 billion years."

These genes existed long before antibiotics became common, but it is our overuse of these drugs in both people and livestock that caused the superbug resistance to explode worldwide, said Cano.

"This is exciting data," says Adam Roberts, who studies antibiotic resistance genes at University College London. While it is already well known that antibiotic resistance occurred naturally before people started using antibiotics, this study shows that resistance genes were already within the human gut long before we started using these drugs, he says.

"It begs the question of what was selecting for these genes at this time? Was it the natural production of antibiotics by other bacteria, or were there other, as yet unknown forces at play?" asks Roberts.

http://nyti.ms/29yo62a

Was Mary Todd Lincoln Driven 'Mad' by a Vitamin Deficiency?

Could pernicious anemia, a disease caused by a vitamin B12 deficiency, have explained the many strange behaviors of Mary Todd Lincoln?

By DENISE GRADY JULY 8, 2016

She was not exactly a model first lady. Historians have had a field day describing her violent temper, wild shopping sprees (she owned 300 pairs of kid gloves), depressed moods and all-consuming fears of burglars, storms and poverty. Late in life, at her son's urging, she was committed to a mental hospital for several months.

Plenty of theories, none proven, have been floated. She was bipolar. She had syphilis or that well known cause of feminine madness, menstrual trouble. She was spoiled and narcissistic. She never recovered from a road accident in which her head hit a rock. She lost her mind grieving the deaths of three of her four sons and her husband's assassination.

The latest addition to the list of possible diagnoses comes from Dr. John G. Sotos, a cardiologist, technology executive at Intel and one of the medical consultants who helped dream up the mystery diseases that afflicted patients on the television show "House."

Dr. Sotos has long been interested in difficult diagnoses, and has written a self-published book suggesting that Abraham Lincoln had a genetic syndrome that caused cancers of the thyroid and adrenal glands.

In an interview, Dr. Sotos said that while he was studying President Lincoln, he came across something that intrigued him about Mrs. Lincoln: an 1852 letter mentioning that she had a sore mouth. He knew that vitamin B deficiencies could cause a sore tongue, and he began looking into her health.

Pernicious anemia could explain many of her problems, both mental and physical, he reported in an article published this week in Perspectives in Biology and Medicine.

The disease develops gradually in people who cannot absorb enough vitamin B12, which the body needs to make DNA. Deficiencies impair the ability to make red blood cells and can affect every organ, including the brain and nervous system.

Severe cases are not often seen now because blood tests can diagnose the disease early and doctors can treat it. But that was not so in Mrs. Lincoln's day.

"With any complex disease that affects so many organs, you get a long list of symptoms," Dr. Sotos said. "Mary had just about all of them."

Among her symptoms: pallor, weakness, fatigue, fevers, headaches, rapid heartbeat, swelling and puffiness in her hands and face, periods of unexplained

weight loss and eye trouble. Her mental symptoms also fit the bill — irritability, delusions and hallucinations, but with a clear mind much of the time.

Photographs of Mrs. Lincoln are portraits of the disease, Dr. Sotos said. He writes, "she was stocky, with a wide face, wide jaw, and widely separated blue eyes," adding that those characteristics are common in people with the disease, though no one knows why. In addition, he said, her parents were cousins, with ancestors from a part of Scotland where pernicious anemia was found in the 1960s to be unusually common.

Dr. Sotos said he hoped the diagnosis would lead historians to look more kindly on Mrs. Lincoln as "simply a woman with a biochemically injured mind."

He said his findings had changed his own attitude. At first, when he read accounts of her hitting her husband and insulting him in front of guests, Dr. Sotos said, "I really didn't like her very much. I feel bad about that now."

Dr. Christopher Crenner, a physician and medical historian, called Dr. Sotos' work "ingenious, meticulously researched and argued," and said the diagnosis was medically plausible.

But he went on to say in an email, "it still amounts to little more than a parlor game for smart physicians. Diagnosing famous figures from the past is entertaining, but it rarely adds much to understanding history."

Dr. Crenner, who is chairman of the department of history and philosophy of medicine at the University of Kansas Medical Center, and president of the American Society for the History of Medicine, said it was already widely recognized that Mrs. Lincoln was mentally ill, though the exact nature of her illness was not known.

History should regard her with sympathy regardless of the cause, he said. A physical illness that can affect the mind - like B12 deficiency - is no more deserving of compassion than one that is strictly mental. "Perhaps we might better engage in fighting the stigmas of mental illness directly," Dr. Crenner said, "regardless of whether it might have been confused with what we now call pernicious anemia."

http://nyti.ms/29wfDLE

A Medical Mystery of the Best Kind: Major Diseases Are in Decline

Something strange is going on in medicine. Major diseases, like colon cancer, dementia and heart disease, are waning in wealthy countries, and improved diagnosis and treatment cannot fully explain it.

Gina Kolata @ginakolata JULY 8, 2016

Scientists marvel at this good news, a medical mystery of the best sort and one that is often overlooked as advocacy groups emphasize the toll of diseases and the need for more funds. Still, many are puzzled. "It is really easy to come up with interesting, compelling explanations," said Dr. David S. Jones, a Harvard historian of medicine. "The challenge is to figure out which of those interesting and compelling hypotheses might be correct."

Of course, these diseases are far from gone. They still cause enormous suffering and kill millions each year.

But it looks as if people in the United States and some other wealthy countries are, unexpectedly, starting to beat back the diseases of aging. The leading killers are still the leading killers — cancer, heart disease, stroke — but they are occurring later in life, and people in general are living longer in good health.

Colon cancer is the latest conundrum. While the overall cancer death rate has been declining since the early 1990s, the plunge in colon cancer deaths is especially perplexing: The rate has fallen by nearly 50 percent since its peak in the 1980s, noted Dr. H. Gilbert Welch and Dr. Douglas J. Robertson of the Geisel School of Medicine at Dartmouth and the Veterans Affairs Medical Center in White River Junction, Vt., in a recent paper.

Screening, they say, is only part of the story. "The magnitude of the changes alone suggests that other factors must be involved," they wrote. None of the studies showing the effect of increased screening for colon cancer have indicated a 50 percent reduction in mortality, they wrote, "nor have trials for screening for any type of cancer."

Then there are hip fractures, whose rates have been dropping by 15 to 20 percent a decade over the past 30 years. Although the change occurred when there were drugs to slow bone loss in people with osteoporosis, too few patients took them to account for the effect — for instance, fewer than 10 percent of women over 65 take the drugs.

Perhaps it is because people have gotten fatter? Heavier people have stronger bones.

Heavier bodies, though, can account for at most half of the effect, said Dr. Steven R. Cummings of the California Pacific Medical Center Research Institute and the University of California at San Francisco. When asked what else was at play, he laughed and said, "I don't know."

Dementia rates, too, have been plunging. It took a few reports and more than a decade before many people believed it, but data from the United States and Europe are becoming hard to wave off. The latest report finds a 20 percent decline in dementia incidence per decade, starting in 1977.

A recent American study, for example, reports that the incidence among people over age 60 was 3.6 per 100 in the years 1986-1991, but in the years 2004-2008 it had fallen to 2.0 per 100 over age 60. With more older people in the population

every year, there may be more cases in total, but an individual's chance of getting dementia has gotten lower and lower.

There are reasons that make sense. Ministrokes result from vascular disease and can cause dementia, and cardiovascular risk factors are also risk factors for Alzheimer's disease. So the improved control of blood pressure and cholesterol levels should have an effect. Better education has also been linked to a lower risk of Alzheimer's disease, although it is not known why. But the full explanation for the declining rates is anyone's guess. And the future of this trend remains a contested unknown.

The exemplar for declining rates is heart disease. Its death rate has been falling for so long — more than half a century — that it's no longer news. The news now is that the rate of decline seems to have slowed recently, although it is still falling. While heart disease is still the leading cause of death in the United States, killing more than 300,000 people a year, deaths have fallen 60 percent from their peak. The usual suspects: Better treatment, better prevention with drugs like statins and drugs for blood pressure, and less smoking, are, of course, helping drive the trend. But they are not enough, heart researchers say, to account fully for the decades-long decline.

The heart disease effect has been examined by scientist after scientist. Was it a result of better prevention, treatment, lifestyle changes?

All three played a role, researchers said.

Dr. Jones said the current explanation reminds him of the Caucus-race in "Alice's Adventures in Wonderland," in which the Dodo, officiating, declared that "EVERYBODY has won, and all must have prizes."

It's not as if the waxing and waning of diseases has never happened before. And all too often these medical mysteries remain mysteries.

Until the late 1930s, stomach cancer was the No. 1 cause of cancer deaths in the United States. Now just 1.8 percent of American cancer deaths are the result of it. No one really knows why the disease has faded — perhaps it is because people stopped eating so much food that was preserved by smoking or salting. Or maybe it was because so many people took antibiotics that H. pylori, the bacteria that can cause stomach cancer, have been squelched.

In the 19th century, experts tried to explain why tuberculosis was a leading killer. That's what happens when people live in cities, doctors said, and there is little to be done. By the start of the 20th century, one out of every 170 Americans lived in a tuberculosis sanitarium.

Then, even before the eventual development of drugs effective against it, TB started to go away in the United States and Western Europe. But experts disagree about why. Some say it was improvements in public health and sanitation. Others say it was changes in medical care. Others split the difference and say it was both.

The tuberculosis surprise was eclipsed in the 1930s as heart disease became ascendant. It would kill us all, the experts said.

And sure enough, by 1960, a third of all American deaths were from heart disease. Now, cardiologists are predicting it will soon fall from its perch as the No. 1 killer of Americans, replaced by cancer, which itself has a falling death rate.

Predicting future trends, Dr. Jones notes, "is often a suspect science in which slight changes in assumptions lead to substantial differences in projected futures."

But Dr. Cummings, intrigued by the waning of disease, has a provocative idea for further investigation. He starts with two observations: Rates of disease after disease are dropping. Even the rate of "all-cause mortality," which lumps together chronic diseases, is falling. And every one of those diseases at issue is linked to aging.

Perhaps, he said, all these degenerative diseases share something in common, something inside aging cells themselves. The cellular process of aging may be changing, in humans' favor. For too long, he said, researchers have looked under the lamppost at things they can measure.

"I want to look inside cells," Dr. Cummings said. Inside, there could be more clues to this happy mystery.

http://bit.ly/29Em1kM

Joint Cartilage Does not Renew, According to Radiocarbon Dating

Using radiocarbon dating as a forensic tool, researchers have found that human cartilage rarely renews in adulthood.

Jean Mendoza

The study, published in the 6 July issue of Science Translational Medicine, suggests that joint diseases may be harder to treat than previously thought.

The dating technique reveals that cartilage is an essentially permanent tissue in healthy and osteoarthritic adults alike. The findings present new challenges for treating osteoarthritis and other joint diseases, and may redirect efforts to preventing injury and protecting joints from further damage.

"The fact that you don't have renewal explains why it's so difficult to heal cartilage or to make it good again," said Michael Kjaer from the University of Copenhagen, Denmark, co-author of the study. "Once you have a damaged cartilage, one should not have too much hope of getting a renewal of it."

Researchers have debated whether cartilage, the tissue lining the surface of joints, regenerates or remains "fixed" throughout life, and little is known about the effects of joint diseases on cartilage turnover.

In the United States, more than 700,000 knee replacement surgeries are performed annually, according to the Centers for Disease Control and Prevention. The average cost for a total knee replacement procedure is about $30,000, according to a study by The Blue Cross Blue Shield Association.

"The special thing about the cartilage is that once you get an injury, there doesn't seem to be a good potential for regeneration. The question now is what is happening? Is there a very, very slow turnover of the tissue that can't be influenced?" said Kjaer.

To answer this question, Kjaer and colleagues turned to the bomb pulse method, which exploits the fact that all living things through their diet incorporate carbon-14 from the atmosphere. Atmospheric levels of this carbon isotope spiked due to the testing of nuclear bombs during the Cold War, leaving a detectable imprint in all organisms living at the time.

The technique has been used to estimate the age of the heart, fat, muscle, and other tissues. Kjaer and his colleagues applied it to cartilage in knee joints from eight healthy and 15 osteoarthritic individuals born between 1935 and 1997.

Across all individuals, the researchers detected virtually no formation of new collagen in cartilage, even in diseased knees, suggesting that the tissue is an essentially permanent structure.

Cartilage renews through adolescence, said Kjaer, but "you're left with what you have after you're 16 [years old]."

Previous studies have suggested that injury may spur cartilage to self-repair. "That speculation can now be totally abolished by this data. They show that the tissue turnover is not larger in people with osteoarthritis," said Kjaer.

The findings help explain the limited success of cartilage transplant and stem cell therapy for osteoarthritis.

"For many years, people have tried to do transplantation of cartilage and it's been very, very difficult," said Kjaer. "The fact the tissue is not very good at renewing is a challenge for transplantation therapy. And if you imagine now that you will give substances to make cartilage grow, drugs to stimulate cells to grow new cartilage, it will not do so."

"So we're basically back to prevention," said Kjaer, who noted that developing strategies for predicting patients' risk of developing a joint injury should be a priority. "If we could measure and detect the quality of the cartilage, maybe we can come in at an early stage" to prevent injury in the first place, he said.

http://bit.ly/29FpQot

Killer fungus destroys Zika mosquitoes from the inside

Fungus develops into blastospores and kill mosquitoes swiftly

Zoë Schlanger

As Zika fears mount and the Aedes aegypti mosquitoes that carry it proliferate this summer, so will applications of chemical pesticides—chemicals that may come with their own health and environmental dangers. What if there were a better way? According to a study published in the journal PLOS Pathogens this week, that way may lie in Metarhizium brunneum, a type of fungus that develops quite literally a killer structure when it is suspended in water. The fungus develops into blastospores—which attach themselves onto baby mosquitoes, called larvae, and kill the insects relatively swiftly.

Larvae are surrounded by a protective cuticle, but the fungi blastospores produce “copious” amounts of a thick mucus to attach themselves to the cuticle. Then, the researchers write, the blastospores penetrate the cuticle “using a combination of enzymes and mechanical force.”

The water-borne blastospores were also able to kill the larvae a second way, quite literally from the inside out: The researchers watched while the larvae “readily ingested” the fungus, and when it would arrive in the larvae’s gut it would “penetrate the gut wall,” killing the larvae. “Multiple entry points and gross damage to the cuticle and gut results in rapid larval death,” the researchers write, killing the larvae in water within 12 to 24 hours.

Tariq Butt, an author on the study and a biosciences professor at Swansea University in the U.K., and his colleagues conducted the same analysis using the same fungi species spread on land, and found that because they do not form a blastosphere structure outside of water, the fungi are less effective at killing mosquito larvae.

The researchers conclude that using any type of fungi known to kill insects would be much more effective if done in the watery environments where the Aedes aegypti breeds. These blastospores may prove an efficient way of eradicating the mosquitos, which carry yellow fever, dengue, and Chikungunya in addition to Zika.

http://www.bbc.com/news/world-asia-36735687

Are we too scared of radiation?

It's more than five years since the earthquake and tsunami off the coast of Japan caused a huge leak of radioactive material into the world's oceans.

By Helen Briggs Environment Correspondent

Workers battled to prevent the Fukushima nuclear plant going into complete meltdown and radiation levels rose by a factor of tens of millions.

However, a new report by Australian scientists has revealed that radiation in the Pacific Ocean is rapidly returning to normal and should be at its previous level by 2020. So what does this say about radiation and us?

Time has stood still around the Fukushima nuclear plant, with homes and possessions abandoned - perhaps forever. Efforts to curb further leaks of radioactive water are ongoing: an underground frozen wall of soil is being constructed to try to minimise the amount of radioactive material that seeps out into the sea.

Huge challenges remain in the future as decontamination efforts continue and it's going to take several decades before the plant is fully decommissioned.

The seafloor and harbour near Fukushima are still highly contaminated, meaning monitoring of radioactivity levels and sea life in that area must continue for years to come. But some sort of normal is returning to the wider ocean.

Nuclear energy is an emotive issue - besides the political, environmental and economic arguments, some believe radioactivity has a psychological dimension that prods at our inner fears.

In terms of human evolution, it's not that long ago since we were hunter gatherers facing dangers all around us - from poisonous plants to predators.

Because we're hardwired to react to the dangers we can see, smell or taste, radioactivity - which is an invisible threat - perhaps has a particular resonance.

Human beings are particularly useless about being able to assess risk but surprisingly, there is a bunch of academics who study this stuff.

Measuring up

•A becquerel (Bq), named after French physicist Henri Becquerel, is a measure of radioactivity

•A quantity of radioactive material has an activity of 1Bq if one nucleus decays per second - and 1kBq if 1,000 nuclei decay per second

•A sievert (Sv) is a measure of radiation absorbed by a person, named after Swedish medical physicist Rolf Sievert

And it seems our perceptions of risk from radiation are somewhat fickle.

Since Fukushima, polling internationally has shown large declines in support for nuclear power in countries including Germany, France and Japan. Indeed, the German government decided to close down its nuclear plants, as a result of Fukushima. But in the UK and US, there remain as many people in favour as are opposed to nuclear power in such polls.

Of course, for those who experienced Fukushima first hand it's a different story.

Many died as a result of the earthquake and tsunami, but, according to the World Nuclear Association, nobody died or suffered radiation sickness from the radiation itself.

There were acts of altruism - a group of retired engineers and other pensioners volunteered to go into the plant, arguing they should be facing the dangers of radiation, not the young.

Hundreds of thousands of children from Fukushima are being monitored for cancer, but experts believe there will be few extra cases because of the radioactivity released. However, government figures suggest more than a thousand evacuees have died from causes "related to the disaster".

A UN report in 2014 said the most important health effect was on mental and social well-being, from the enormous impact of the accident and the fear and stigma related to radiation and uncertainty about ever going home.

As one professor put it: "Nobody has died from the radiation, but it may actually have killed their souls."

http://www.eurekalert.org/pub_releases/2016-07/ehs-dra070716.php

Diabetes reversal after bypass surgery linked to changes in gut microorganisms

Duodenum-jejunum gastric bypass surgery in diabetic mice results in changes in gut microbiota, improved metabolism, and diabetes remission, according to a new report in The American Journal of Pathology

Philadelphia, PA - Studies have shown that bariatric surgery can lead to remission of type 2 diabetes mellitus (T2DM) in rodents and humans, but this beneficial effect cannot be explained solely by weight loss. In a new study published in The American Journal of Pathology, researchers investigating gastric bypass in a mouse model of T2DM confirmed that bypass surgery improves glucose tolerance and insulin sensitivity. Interestingly, the improved metabolism occurred in conjunction with changes in gut microorganisms, suggesting a potential role for gut microbiota in diabetes remission.

"Our research showed that duodenum-jejunum gastric bypass (DJB) surgery may be applied to cure diabetes of both genetic (mutation) and environmental (diet-induced) origin," explained lead investigator Xiang Gao, PhD, of State Key Laboratory of Pharmaceutical Biotechnology and MOE Key Laboratory of Model Animal for Disease Study, Model Animal Research Center, Nanjing Biomedical Research Institute and the Collaborative Innovation Center of Genetics and Development, Nanjing University. "We found that DJB surgery induced gut microbiota alterations, which may be the key reason for diabetes remission after bariatric surgery. Our data indicate that suppressed inflammation is the result, not the cause, of diabetes reversal in these genetically modified mice."

The research was performed in the T2DM mouse model that mimics key symptoms including insulin resistance, high blood levels of lipids, metabolic

inflammation, and obesity. These mice harbor genetic mutation in brain-derived neurotrophic factor (Bdnf) leading to Bdnf deficiency. Bdnf is a member of the neurotrophic family of growth factors and is a key regulator of both brain function and metabolic balance.

"Our findings suggest that Bdnf deficiency-induced diabetes can be reversed by DJB surgery in mice, which has potential for the treatment of diabetes in humans," stated Dr. Gao. He and his team found that bypass surgery reversed the metabolic abnormalities indicative of diabetes without changing Bdnf expression directly. Glucose tolerance and insulin sensitivity were greatly improved and there was less fat accumulation in liver and white adipose tissue. Insulin sensitivity reached normal levels within two weeks following surgery and lasted for at least eight weeks. Six weeks after bypass surgery, oral glucose tolerance in the treated mice was significantly lower than in the diabetic mice that had undergone a sham operation and was similar to levels observed in untreated controls.

Examination of the composition of bacteria and other microorganisms in the gut of mutated mice before and after bypass surgery and in the control group, showed a decrease in pathogenic bacteria and an increase in beneficial microflora that coincided with the onset of better glycemic control. "More mechanistic studies of gut microbiota alterations after bypass surgery are needed to explain how different families of microbiota may regulate nutrient metabolism in the host," noted Dr. Gao.

Inflammation, especially in white fat tissue and liver, is thought to play an important role in obesity and T2DM. Eight weeks after bypass surgery, significant reductions in inflammatory indicators occurred in the liver and fat tissue, although the post-surgical anti-inflammatory effects occurred after insulin sensitivity improved. "These results indicate that the alleviation of inflammation was not the direct cause of the improvement in insulin sensitivity that resulted from bypass surgery," commented Dr. Gao.

http://bit.ly/29GsPys

Thumb-Sucking, Nail Biting Kids May Have Lower Allergy Risk

Young children who suck their thumbs or bite their nails may be less likely to develop allergies later in childhood, according to a new study that spanned three decades.

By Agata Blaszczak-Boxe, Contributing Writer | July 11, 2016 01:56am ET

Although the results do not suggest that kids should take up these habits, the findings do suggest the habits help protect against allergies that persists into adulthood, the researchers said.

"Many parents discourage these habits, and we do not have enough evidence to [advise they] change this," said Dr. Robert Hancox, an associate professor of respiratory epidemiology at the University of Otago in New Zealand. "We certainly don't recommend encouraging nail-biting or thumb-sucking, but perhaps if a child has one of these habits and [it] is difficult [for them] to stop, there is some consolation in the knowledge that it might reduce their risk of allergies."

In the study, the researchers pulled data from an ongoing study of more than 1,000 children born in New Zealand in 1972 or 1973. The children's parents were asked about their kids' thumb-sucking and nail-biting habits four times: when the kids were 5, 7, 9 and 11 years old. Researchers also tested the children for allergies using a skin-prick test when they were 13, and then followed up with the kids again when they were 32.

It turned out that 38 percent of the children who had sucked their thumbs or bit their nails had at least one allergy, whereas among kids who did not have these habits, 49 percent had at least one allergy.

Moreover, the link between these childhood habits and a lower risk of allergies was still present among the study participants when they were 32 years old. The link persisted even when the researchers took into account potentially confounding factors that may also affect a person's risk of allergies, such as whether their parents had allergies, whether they owned pets, whether they were breast-fed as infants and whether their parents smoked.

In addition, the researchers found that the kids who both sucked their thumbs and bit their nails at a young age were even less likely to have allergies at age 13, compared with kids who had just one of the two habits. However, this association was no longer found when the participants were 32 years old, according to the findings, published today (July 11) in the journal Pediatrics.

The new results are in line with the findings of another study, published in 2013 in the same journal, which found that children whose mothers sucked the kids' pacifiers clean had a lower risk of developing allergies. "Although the mechanism and age of exposure [to pathogens] are different, both studies suggest that the immune response and risk of allergies may be influenced by exposure to oral bacteria or other microbes," the researchers wrote in the new study.

The new findings also lend support the so-called hygiene hypothesis, which holds that environments that have too little dirt and germs may make children more susceptible to certain conditions, including allergies. It seems that "exposure to microbial organisms influences our immune system and makes us less likely to develop allergies," Hancox told Live Science.