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Another Look: Linking Hygiene, Asthma, and Allergies

Nicholas Gross, MD, PhD

Is Too Clean a Real Thing?

Asthma and the Hygiene Hypothesis: Does Cleanliness Matter?

Weber J, Illi S, Nowak D, et al

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The frequency of asthma appears to have increased over the past few decades. There may also have been an increase in allergic disorders too. Why?

That the increase in these disorders seems to have occurred in more affluent countries has led to the suggestion that greater hygiene has been responsible.

The theory is that exposure to extraneous agents and microorganisms in early life somehow primes the immune system to tolerate such agents.

Conversely, the absence of such exposures in early life may result in the expression of undesirable responses such as allergies and asthma.[1]

The theory has never been convincingly supported. In this prospective study, a comprehensive questionnaire was given to households with children.

Markers of exposure such as serum endotoxin were also obtained. Children in 553 families were included and follow-ups were continued until the children reached 11 years of age.

The findings showed that cleanliness was inversely related to markers of infection, as one would expect. However, the authors found no relationship between aspects of hygiene and asthma, atopy, allergies, or hay fever.

Viewpoint

These findings appear to discount the "hygiene hypothesis." Despite the absence of a relationship between hygiene and asthma or allergies, some uncertainties remain.

As the authors acknowledge, follow-up was incomplete in that all data were obtained in only 72% of children. Also, all the children were from urban/suburban neighborhoods of Munich, Germany.

Customs and habits in that relatively small and uniform environment may well not bear much relationship to children in entirely different circumstances.

As others have stated, the attack rate in children for viruses like respiratory syncytial virus is 100%, yet only a limited number of children develop allergic features.[2]

The question demands more consideration. Perhaps a more informative trial would be to compare populations between typical Western societies, where hygiene tends to be high, with populations on less well-developed continents.

Abstract

Is Too Clean a Real Thing?Asthma and the Hygiene Hypothesis: Does Cleanliness Matter?

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Weber J ; Illi S ; Nowak D ; Schierl R ; Holst O ; von Mutius E ; Ege MJ

RATIONALE: The early hygiene hypothesis explained the development of allergies by a lack of infections; nowadays, the aspect of excessive cleanliness in affluent populations seems to have replaced this concept.

Yet, no investigation has shown that home or personal cleanliness relate to allergic diseases.

OBJECTIVES: To relate personal and home cleanliness to risk of asthma and allergies.

METHODS: Comprehensive questionnaire information on home or personal cleanliness and allergic health conditions at school age was collected in 399 participants of the urban Perinatale Asthma Umwelt Langzeit Allergie Studie (PAULA) birth cohort. Bacterial markers were assessed in floor and mattress dust and were related to cleanliness and allergic diseases.

MEASUREMENTS AND MAIN RESULTS: Personal cleanliness was inversely related to bacterial compounds on floors and mattresses, whereas home cleanliness effectively reduced dust amount but not microbial markers.

Exposure to muramic acid related to a lower prevalence of school-age asthma (adjusted odds ratio, 0.59 [95% confidence interval, 0.39; 0.90]). Mattress endotoxin in the first year of life was inversely associated with atopic sensitization (0.73 [0.56-0.96]) and asthma at school age (0.72 [0.55-0.95]). Despite the associations of dust parameters both with cleanliness and allergic health conditions, the development of allergies was not related to home and personal cleanliness.

CONCLUSIONS: Bacterial exposure in house dust determined childhood asthma and allergies. Personal cleanliness, such as washing hands, and home cleanliness were objectively reflected by dust parameters in homes. However, neither personal nor home cleanliness was associated with a risk for asthma and allergies. Other microbial components in house dust not affected by personal hygiene are likely to play a role.

- ***PreMedline Identifier:25584716***

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http://www.eurekalert.org/pub_releases/2015-06/sri-ssa060815.php

Scientists show antitumor agent can be activated by natural response to cell stress

Findings point to new therapy against prostate and other cancers

JUPITER, FL - Scientists from the Florida campus of The Scripps Research Institute (TSRI) have found that a drug candidate with anticancer potential can be activated by one of the body's natural responses to cellular stress. Once activated, the agent can kill prostate cancer cells.

"There is no proven drug right now with these activities," said Ben Shen, vice chair of TSRI's Department of Chemistry and senior author of the new study, "so this points the way toward a new therapeutic opportunity."

The study, published this week by the journal Proceedings of the National Academy of Sciences, highlights the potential of the natural compound called leinamycin (LNM) E1 for development as a "prodrug," a medication converted through a metabolic process in the body to become an active therapy.

Shen's research has focused on developing natural products into potential therapies. As part of this effort, he heads the Natural Products Initiative at TSRI, a library available for screening with 500 pure natural products, 2,000 fractions, and 7,500 crude extracts, prepared from 4,000 Actinomycetals.

Among these are "antitumor antibiotics" like LNM, which are produced by species of the soil dwelling bacterium Streptomyces and are known to impede cancer cell growth and multiplication. Some antitumor antibiotics are already in use as chemotherapy agents.

In the new study, the Scripps Florida team collaborated with scientists at the University of Wisconsin, Madison to examine whether LNM E1 can be activated by reactive oxygen species, which are naturally occurring molecules containing oxygen that play essential roles in cell signaling. During times of stress, levels of reactive oxygen species can rise significantly and may trigger apoptosis or programmed cell death. It is now widely accepted that many cancer cells are, by their very nature, under high oxidative stress.

The results were promising. "Our study shows unambiguously that when LNM E1 is activated by cellular reactive oxygen species, it causes DNA damage and cell death in cancer cells," said Ming Ma, co-first author of the study with Sheng-Xiong Huang.

The team further demonstrated the therapeutic potential of LNM E1 by showing it to be effective against two prostate cancer cell lines, which are known to exist under high oxidative stress and with increased levels of reactive oxygen species.

The study also reveals critical new insights into LNM biosynthesis, setting the stage to tailor intermediate steps in the creation of new LNM analogues.

In addition to Shen, Ma and Huang, other authors of the study, "Leinamycin E1 Acting as an Anticancer Prodrug Activated by Reactive Oxygen Species," include Dong Yang and Jeremy R. Lohman of TSRI; Bong-Sik Yun, Gudrun Ingenhorst, Yong Huang, Hirak S. Basu, Dawn R. Church, Gong-Li Tang, Jianhua Ju and George Wilding of the University of Wisconsin-Madison.

The work was supported in part by the National Institutes of Health (grant CA106150).

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Martian glass -- window into possible past life

Glasses may provide a delicate window into the possibility of past life on Mars

PROVIDENCE, R.I. - Researchers from Brown University have used satellite data to detect deposits of glass within impact craters on Mars. Though formed in the searing heat of a violent impact, the glasses just might provide a delicate window into the possibility of past life on the Red Planet.

Over the last few years, several research groups have shown that, here on Earth, ancient biosignatures can be preserved in impact glass. One of those studies, led by Brown geologist Peter Schultz and published last year, found organic molecules and even plant matter entombed in glass formed by an impact that occurred millions of years ago in Argentina. Schultz suggested that similar processes might preserve signs of life on Mars, if indeed they were present at the time of an impact.

'The work done by Pete and others showed us that glasses are potentially important for preserving biosignatures. Knowing that, we wanted to go look for them on Mars and that's what we did here,' said Kevin Cannon, a Ph.D. student at Brown and the lead author of the new research. 'Before this paper no one had been able to definitively detect them on the surface.'

Cannon and co-author Jack Mustard, professor of Earth, environmental and planetary sciences at Brown, showed that large glass deposits are present in several ancient yet well-preserved craters scattered across the Martian surface. The study suggests that glass deposits are relatively common impact features on Mars and could be targets for future exploration.

The research is published online in the journal Geology.

Picking out the glassy deposits was no easy task. To identify minerals and rock types remotely, scientists measure the spectra of light reflected off the planet's surface. But impact glass doesn't have a particularly strong spectral signal.

'Glasses tend to be spectrally bland or weakly expressive, so signatures from the glass tend to be overwhelmed by the chunks of rock mixed in with it,' Mustard said. 'But Kevin found a way to tease that signal out.'

In the lab, Cannon mixed together powders with a similar composition of Martian rocks and fired them in an oven to form glass. He then measured the spectral signal from that glass. Once he had the signal from the lab glass, he used an algorithm designed to pick out similar signals in data from the Compact Reconnaissance Imaging Spectrometer for Mars (CRISM), which flies aboard NASA's Mars Reconnaissance Orbiter. Mustard is the deputy principal investigator for the instrument.

The technique was able to pinpoint deposits around several crater central peaks, the craggy mounds that often form in the center of a crater during a large impact. The fact that the deposits were found on central peaks is a good indicator that they have an impact origin.

Knowing that impact glass can preserve ancient signs of life -- and now knowing that such deposits exist on the Martian surface today -- opens a potential new strategy in the search for ancient Martian life, the researchers say.

'We think these could be interesting targets for future exploration,' Mustard said. In fact, Mustard and Cannon have a particular spot in mind.

One of the craters found to contain glass is called Hargraves, and it's located near the Nili Fossae trough, a 400-mile-long depression that stretches across the Martian surface. The region is one of the leading landing site contenders for the Mars 2020 rover, a mission that aims to cache soil and rock samples for possible future return to Earth.

Nili Fossae trough is already of scientific interest because the crust in the region is thought to date from when Mars was a much wetter place. The region is also rife with what appear to be ancient hydrothermal fractures, warm vents that could have provided energy for life to thrive just beneath the surface.

'If you had an impact that dug in and sampled that subsurface environment, it's possible that some of it might be preserved in a glassy component,' Mustard said. 'That makes this a pretty compelling place to go look around, and possibly return a sample.'

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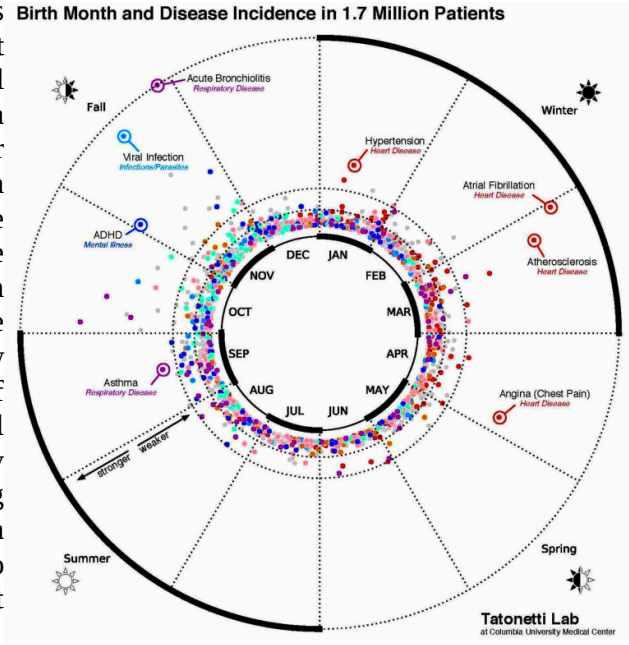
Data scientists find connections between birth month and health

Columbia University scientists have developed a computational method to investigate the relationship between birth month and disease risk.

VIDEO: Dr. Tatonetti explains his study.

NEW YORK, NY - The researchers used this algorithm to examine New York City medical databases and found 55 diseases that correlated with the season of birth. Overall, the study indicated people born in May had the lowest disease risk, and those born in October the highest. The study was published in the Journal of American Medical Informatics Association.

"This data could help scientists uncover new disease risk factors," said study senior author Nicholas Tatonetti, PhD, an assistant professor of biomedical informatics at Columbia University Medical Center (CUMC) and Columbia's Data Science Institute. The researchers plan to replicate their study with data from several other locations in the U.S. and abroad to see how results vary with the change of seasons and environmental factors in those places. By identifying what's causing disease disparities by birth month, the researchers hope to figure out how they might close the gap.



This data visualization maps the statistical relationship between birth month and disease incidence in the electronic records of 1.7 million New York City patients. **Dr. Nick Tatonetti**

Earlier research on individual diseases such as ADHD and asthma suggested a connection between birth season and incidence, but no large-scale studies had been undertaken. This motivated Columbia's scientists to compare 1,688 diseases against the birth dates and medical histories of 1.7 million patients treated at NewYork-Presbyterian Hospital/CUMC between 1985 and 2013.

The study ruled out more than 1,600 associations and confirmed 39 links previously reported in the medical literature. The researchers also uncovered 16 new associations, including nine types of heart disease, the leading cause of death in the United States. The researchers performed statistical tests to check that the 55 diseases for which they found associations did not arise by chance.

"It's important not to get overly nervous about these results because even though we found significant associations the overall disease risk is not that great," notes Dr. Tatonetti. "The risk related to birth month is relatively minor when compared to more influential variables like diet and exercise."

The new data are consistent with previous research on individual diseases. For example, the study authors found that asthma risk is greatest for July and October

babies. An earlier Danish study on the disease found that the peak risk was in the months (May and August) when Denmark's sunlight levels are similar to New York's in the July and October period.

For ADHD, the Columbia data suggest that around one in 675 occurrences could relate to being born in New York in November. This result matches a Swedish study showing peak rates of ADHD in November babies.

The researchers also found a relationship between birth month and nine types of heart disease, with people born in March facing the highest risk for atrial fibrillation, congestive heart failure, and mitral valve disorder. One in 40 atrial fibrillation cases may relate to seasonal effects for a March birth. A previous study using Austrian and Danish patient records found that those born in months with higher heart disease rates--March through June--had shorter life spans.

"Faster computers and electronic health records are accelerating the pace of discovery," said the study's lead author, Mary Regina Boland, a graduate student at Columbia. "We are working to help doctors solve important clinical problems using this new wealth of data."

The paper is titled, "Birth Month Affects Lifetime Disease Risk: A Phenome-Wide Method." The contributors are: Mary Regina Boland, Zachary Shahn, David Madigan, George Hripcsak, Nicholas P. Tatonetti (CUMC).

Study link: http://jamia.oxfordjournals.org/content/early/2015/06/01/jamia.ocv046

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Hybrid scanner combines five molecular imaging technologies

Preclinical imaging system will be used to pioneer new drugs and imaging research

Baltimore, Md. -- Scientists are taking medical imaging research and drug discovery to a new level by developing a molecular imaging system that combines several advanced technologies for all-in-one imaging of both tissue models and live subjects, say presenters at the 2015 annual meeting of the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

The preclinical and intra-vital molecular imaging system houses a window for tissue observation in addition to a larger imaging chamber. Together they are being used to peer into the microenvironment of tumors and other tissues while learning about the co-registration of multiple lines of imaging data.

'This technology allows us to obtain in-depth knowledge of molecular imaging techniques, how to optimize them, and how to leverage data with statistical analysis while advancing new radiotracers and contrast agents for the imaging and treatment of a range of diseases,' said Zhen Liu, Ph.D. candidate and lead author of the study from the department of nuclear medicine at Technical University Munich, in Munich, Germany.

Each technology has its own strengths. Direct positron imaging is a nuclear medicine technique that allows researchers to gain physiological information from radiolabeled imaging agents that bind to targets in the body, which are then imaged with a specialized detector. The hybrid system applies both conventional and hyperpolarized MRI. The former is ideal for soft-tissue contrast, and the latter has extremely fine imaging resolution due to a revolution in the technology called dynamic nuclear spin polarization, which is used to track minute biochemistry in the body -- such as the transition of the naturally occurring chemical pyruvate to lactate. This exchange, which takes place throughout the body, has been found to be an excellent biomarker for disease. Finally, luminescence, fluorescence and optical imaging are all state-of-the-art imaging techniques that can be used to paint targets as small as a strand of DNA with glowing substances to make them stand out when scanned or observed under a very powerful microscope.

'Understanding the physiology behind multimodal imaging is very challenging due to discrepancies between macroscopic and microscopic images and between images of extracted or transplanted tissues versus images of a live subject,' said Liu. 'This establishment of high-resolution multimodal intra-vital imaging can bridge these discrepancies and offer a tool for the long-term observation of underlying physiology.'

For this study, a tumor cell line was transplanted into a rat and imaged with each of the following: conventional MRI, the radiotracer carbon-13 (C-13) pyruvate and hyperpolarized MRI at a resolution of 2.5 mm, Medipix positron detector, luminescence sensor and a fluorescence microscope.

Results of the study showed that increased lactate production was found by hyperpolarized MRI in areas of hypoxia, or low-oxygenation, and higher levels of FDG binding represented areas of hypermetabolic activity surrounding the hypoxic areas. These are indications that areas of diseased tissue could be dying, while other parts of a tumor could be rapidly growing or becoming more aggressive. These details tell researchers about the heterogeneity of tumors, which is essential for developing appropriate research and drug protocols that can navigate all the inherent complexity of not just the anatomy and physiology being imaged but also how imaging technologies intersect to capture as much information as possible.

Scientific Paper 59: 'A multimodal intravital molecular imaging system based on dorsal skin window chamber tumor model,' Z. Liu, B. Feuerecker, S. Düwel, G. Topping, M. Schwaiger, S.I. Ziegler, K. Shi, Nuclear Medicine, Technical University Munich, Munich, Germany; T.

Cheng, K. Steiger, Surgery Department, Technical University Munich, Munich, Germany; R. Braren, Radiology Department, Technical University Munich, Munich, Germany, SNMMI's 62nd annual meeting, June 6-10, 2015 in Baltimore, Md.

http://www.eurekalert.org/pub_releases/2015-06/su-sed060815.php

Stanford engineers develop state-by-state plan to convert US to 100 percent renewable energy

One potential way to combat ongoing climate change, eliminate air pollution mortality, create jobs and stabilize energy prices involves converting the world's entire energy infrastructure to run on clean, renewable energy.

This is a daunting challenge. But now, in a new study, Mark Z. Jacobson, a professor of civil and environmental engineering at Stanford, and colleagues, including U.C. Berkeley researcher Mark Delucchi, are the first to outline how each of the 50 states can achieve such a transition by 2050. The 50 individual state plans call for aggressive changes to both infrastructure and the ways we currently consume energy, but indicate that the conversion is technically and economically possible through the wide-scale implementation of existing technologies.

"The main barriers are social, political and getting industries to change. One way to overcome the barriers is to inform people about what is possible," said Jacobson, who is also a senior fellow at the Stanford Woods Institute for the Environment and at the Precourt Institute for Energy. "By showing that it's technologically and economically possible, this study could reduce the barriers to a large scale transformation."

The study is published in the online edition of Energy and Environmental Sciences. An interactive map summarizing the plans for each state is available at http://www.thesolutionsproject.org. Jacobson and his colleagues started by taking a close look at the current energy demands of each state, and how those demands would change under business-as-usual conditions by the year 2050. To create a full picture of energy use in each state, they examined energy usage in four sectors: residential, commercial, industrial and transportation.

For each sector, they then analyzed the current amount and source of the fuel consumed - coal, oil, gas, nuclear, renewables - and calculated the fuel demands if all fuel usage were replaced with electricity. This is a significantly challenging step - it assumes that all the cars on the road become electric, and that homes and industry convert to fully electrified heating and cooling systems. But Jacobson said that their calculations were based on integrating existing technology, and the energy savings would be significant.

"When we did this across all 50 states, we saw a 39 percent reduction in total end-use power demand by the year 2050," Jacobson said. "About 6 percentage points of that is gained through efficiency improvements to infrastructure, but the bulk is the result of replacing current sources and uses of combustion energy with electricity." The next step involved figuring out how to power the new electric grid. The researchers focused on meeting each state's new power demands using only the renewable energies - wind, solar, geothermal, hydroelectric, and tiny amounts of tidal and wave - available to each state.

They analyzed each state's sun exposure, and how many south-facing, non-shaded rooftops could accommodate solar panels. They developed and consulted wind maps and determined whether local offshore wind turbines were an option. Geothermal energy was available at a reasonable cost for only 13 states. The plan calls for virtually no new hydroelectric dams, but does account for energy gains from improving the efficiency of existing dams.

The report lays out individual roadmaps for each state to achieve an 80 percent transition by 2030, and a full conversion by 2050. Jacobson said that several states are already on their way. Washington state, for instance, could make the switch to full renewables relatively quickly, thanks to the fact that more than 70 percent of its current electricity comes from existing hydroelectric sources. That translates to about 35 percent of the state's all-purpose power if Washington were 100-percent electrified; wind and solar could fill most of the remainder.

Iowa and South Dakota are also well-positioned, as they already generate nearly 30 percent of their electricity from wind power. California, which was the focus of Jacobson's second single-state roadmap to renewables after New York, has already adopted some of his group's suggestions and has a plan to be 60 percent electrified by renewables by 2030.

The plan calls for no more than 0.5 percent of any state's land to be covered in solar panels or wind turbines. The upfront cost of the changes would be significant, but wind and sunlight are free. So the overall cost spread over time would be roughly equal to the price of the fossil fuel infrastructure, maintenance and production.

"When you account for the health and climate costs - as well as the rising price of fossil fuels - wind, water and solar are half the cost of conventional systems," Jacobson said. "A conversion of this scale would also create jobs, stabilize fuel prices, reduce pollution-related health problems and eliminate emissions from the United States. There is very little downside to a conversion, at least based on this science."

Jacobson said that if the conversion is followed exactly as his plan outlines, the reduction of air pollution in the U.S. could prevent the deaths of approximately 63,000 Americans who die from air pollution-related causes each year. It would also eliminate U.S. emissions of greenhouse gases produced from fossil fuel, which would otherwise cost the world $3.3 trillion a year by 2050.

http://www.medscape.com/viewarticle/845716

Could It Be... E?

The Evolution of Hepatitis E

David A. Johnson, MD

The Evolution of Hepatitis E

Hello. I am Dr David Johnson, professor of medicine and chief of gastroenterology at Eastern Virginia Medical School in Norfolk, Virginia.

There has been a lot in the literature about another type of hepatitis—hepatitis E. We have hepatitis A, B, C, and D, and now E has been getting more attention. I thought this was a good opportunity to talk about hepatitis E. What is it? What role does it play in your practice?

Risk Factors and Epidemiologic Trends

Several years ago, it was believed that hepatitis E was endemic only in areas outside of the United States. We recognized epidemiologic trends in the subcontinent of Africa, the Middle East, Asia, and South America. Hepatitis E was very widely distributed. It was probably the most common cause of hepatitis worldwide, with significant associated morbidity and mortality, with approximately 100,000 annual deaths attributed to hepatitis E. For some reason, pregnant women seem to have a very high mortality rate from hepatitis E infection.[1] Nonetheless, it is a very prevalent disease with high mortality and worldwide implications.

Hepatitis E virus has four separate genotypes. Genotypes 1 and 2 are seen in China and the Far East, and only in humans. Genotypes 3 and 4 are endemic in both humans and animals. These genotypes are increasingly found in industrialized countries, including the United States. Genotypes 3 and 4 seem to be prevalent in certain animals (swine) and in those who have direct contact with swine or who ingest meat from these animals, such as solid organs (liver) or sausage.

Transmission of Hepatitis E

The transmission of hepatitis E is by the fecal-oral route, analogous to that of hepatitis A.

The typical incubation period for acute hepatitis E infection is 2-5 weeks. Patients present with elevated liver enzymes and the same prodrome that is typical of hepatitis A. The infection typically resolves on its own, and most people don't know what caused their illness.

Blood donor studies in the United States and health surveys that included antibody status show that the prevalence ranges from 4% to 20%.[2] Some areas of the Midwest have the highest prevalence, possibly because of higher ingestion of contaminated meat products.

Hepatitis E also is associated with exposure to game (wild boar and deer) and undercooked meat. Hepatitis E is found in 10%-11% of swine liver or sausage sold in grocery stores.[3] If these foods are cooked for 1 hour at 140º F, 1% of the virus will continue to live. Killing the virus completely requires cooking at 160 degrees for 20 minutes.[4] Those who consume deer sausage should be counseled on cooking the meat adequately.

The Drug-Induced Liver Injury Network has looked at the serologic prevalence of hepatitis E in patients with drug-induced liver disease and no attributable cause for liver disease other than drug exposure. They found that 1 in 6 patients has hepatitis E antibody, and their liver disease may actually be related to hepatitis E rather than drug exposure.[5]

The Role of Immunosuppression

Another significant risk factor is solid organ transplantation, especially the liver, pancreas, and kidney, because the seroprevalence in these patients may be in excess of 5%-6%, leading to chronic liver disease.

Hepatitis E infection in immunocompromised patients does not seem to lead to chronic liver disease. In these patients, the infection can lead to a more fulminant form of liver disease, although that is very rare in the general population.

In the transplant population, however, it may be somewhat of a concern. Typically, hepatitis E resolves spontaneously, but transplant patients can develop chronic hepatitis E infection. Reducing the level of immunosuppression can lead to spontaneous clearance in approximately two thirds of these patients.[6] Some patients have required treatment with ribavirin for 6-12 weeks or longer if there is no clearance or clearance is delayed. Interferon monotherapy has been used in this population as well.

The patients in whom you should think about hepatitis E are those with chronic liver disease or acute worsening of chronic liver disease; those who have had solid organ transplants (particularly liver, kidney, and pancreas); and immunocompromised patients. A couple of cases have been described in the non-transplant setting; one was a patient with non-Hodgkin lymphoma who was on rituximab, and a few others were patients with HIV. Immunosuppression should prompt consideration of hepatitis E.

Testing for Hepatitis E

Testing for hepatitis E is not widely available.

You should check with your local laboratories, but there is variability in the IgM and the IgG antibody sensitivities for detection. The gold standard is an RNA polymerase chain reaction (PCR) test, and you may have to request that the lab interact with the Centers for Disease Control and Prevention to facilitate this testing.

Think about hepatitis E in those patients with possible drug-induced liver disease; in those aged 60 years and older (especially men); and in those with a history of exposure to deer, venison, undercooked pork, or contact with swine. Question patients about their ingestion of sausage and organ meats, which raises the risk for hepatitis E.

Hopefully this steers you in the right direction during your next opportunity to evaluate a patient with elevated liver enzymes.

I am Dr David Johnson. See you next time for another *GI Common Concerns—Computer Consult*. Thanks again for listening.

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The Lancet Oncology: 2 large trials provide further evidence that 1 dose of HPV vaccine could prevent the majority of cervical cancers

Single dose of the bivalent human papillomavirus vaccine may offer a similar level of protection against HPV-16/18 infections

A single dose of the bivalent human papillomavirus (HPV) vaccine (Cervarix®, GlaxoSmithKline group of companies) may offer a similar level of protection against HPV-16/18 infections, which cause about 70% of cervical cancers, as the current two- and three-dose schedules, according to new research combining data from two large phase 3 trials published in The Lancet Oncology.

"Our findings question the number of HPV vaccine doses truly needed to protect the majority of women against cervical cancer, and suggest that a one-dose schedule should be further evaluated. If one dose is sufficient, it could reduce vaccination and administration costs as well as improve uptake. This is especially important in less developed regions of the world where more than 80% of cervical cancer cases occur," says co-lead author Dr Aimée Kreimer from the National Cancer Institute (NCI), National Institutes of Health, USA. [1]

Worldwide, cervical cancer is the fourth most common cancer in women. The bivalent vaccine targets HPV types 16 and 18 that are responsible for about 70% of cervical cancers. The HPV-16/18 vaccine was initially approved to be given in three doses over 6 months, but many countries are moving to a two-dose schedule in adolescents.

This new combined analysis of two independent trials strengthens previous findings from the NCI Costa Rica HPV Vaccine Trial (CVT) which reported that young women who received three, two, or one dose of the bivalent vaccine were equally protected against infection with HPV-16/18 for at least 4 years after vaccination.

Due to the lack of efficacy data on fewer than three doses, the researchers conducted a post-hoc analysis combining data from the CVT that included 7466 healthy women aged 18-25 years old and the Papilloma Trial against Cancer in Young Adults (PATRICIA) trial in 18644 healthy women aged 15-25 years from Asia-Pacific, Europe, Latin America, and North America. Women in both trials were randomly assigned to receive the HPV-16/18 vaccine or a control (hepatitis A) vaccine, given in three doses: at enrolment, 1 month, and 6 months. However, some of the women received fewer than three doses, mainly because their vaccination was discontinued due to pregnancy.

After excluding women with no follow up or who had cervical HPV infection at enrolment, the investigators calculated vaccine efficacy against HPV infection after three doses (22327 women), two doses (1185), and one dose (543). Women were followed on average for 4 years.

High vaccine efficacy was seen against incident HPV-16/18 infections regardless of the number of doses received. This result was also observed in a subgroup of women with no sign of HPV infection either before or at the time of first vaccination, suggesting that these results are relevant to sexually-naïve girls in the recommended age range for HPV vaccination (ie, 11-12 years).

In further analyses, partial protection against other HPV types not included in the vaccine formulation was seen among women who received two doses 6 months apart, similar to that reported for three doses.

The authors caution that more data are needed before policy guidelines can be changed. Dr Cosette Wheeler, co-lead author from the University of New Mexico Health Sciences Center, Albuquerque, USA, explains, "Using existing data, we

showed that a single dose of the bivalent HPV vaccine may be sufficient to substantially reduce cervical cancer incidence. Yet, a new randomised study will be needed to confirm these findings and move the field forward.

Additionally, duration of protection from a single dose must be demonstrated beyond 4 years."[1]

Dr Julia Brotherton from the Victorian Cytology Service Registries, Melbourne, Australia said of the findings, "If HPV vaccines could be delivered as one dose, while retaining their efficacy against the most oncogenic HPV types 16 and 18, the global burden of cervical cancer would substantially decrease. Data from studies have shown how effective one-vaccine dose campaigns can be in even the most resource-poor settings (eg, meningitis A vaccines in sub-Saharan Africa). We can imagine that such campaigns could happen every 5-10 years with the aim of vaccination of, for example, all 9-14 year old girls with one dose of the HPV vaccine. This campaign would not need ongoing resources to sustain annual vaccination programmes against HPV in settings with many pressing health priorities and small numbers of health-care workers."[1]

CVT was funded by the US National Cancer Institute intramural research program, National Institutes of Health Office of Research on Women's Health, and Ministry of Health of Costa Rica; GlaxoSmithKline Biologicals SA funded the PATRICIA trial.

http://bit.ly/1IBORuM

Overworking Your Brain Can Spark Ideas

Mental exhaustion can unleash creativity, research shows

By Madhuvanthi Kannan | June 9, 2015

If you walk down to the office gallery at Pearlfisher Inc., a design agency based in London, you are bound to hear the unmistakable cluck of plastic balls colliding. At first, you might dismiss it as the sound of employees chilling out on a ping pong game. But if you walk further, following signs for "*Jump In!*," the sound will turn into a rattle like that of maracas. What you see next might take your breath away – a huge ball pit filled with 81,000 white plastic balls. But frolicking in the pit are not preschoolers or kindergartners. They are in fact corporate managers and associates, dressed in business suits, in an afternoon brainstorming session.

Companies relying on innovation go to astonishing lengths to imbue creativity in their staff. *Jump In!*, the wacky brainchild of Pearlfisher's creative strategist, is for instance, built on the premise that interleaving work and play can spark creativity in grown-ups, just like it did back in school days. Many companies including Google, Skype and Facebook similarly emphasize the power of play, while others, such as the news website The Huffington Post, insist on peace and quiet during the break hours. Their offices instead sport nap nooks, where employees can grab some z's and feel refreshed before returning to write. In theory, both strategies can inspire creativity – one perhaps better than the other depending on whether, for instance, you design products or pen stories for a living. They essentially have the same effect on us: they help us relax and unwind, restoring some of our dulled senses.

But it turns out that mental exhaustion from overwork can itself unleash creativity. When we are tired, our mind can be too weary to control our thoughts, and eccentric ideas that might normally be filtered out as non-relevant can bubble up, suggests a recent study by Rémi Radel at the University of Nice Sophia-Antipolis, France. This means that perhaps creative ideas can be hatched at the workplace, right when we feel drained from a mental overload.

In their study, Radel and colleagues overtaxed the minds of a group of undergrads by having them perform a computerized task that demanded attention: finding the direction of a center arrow by ignoring the directions of surrounding arrows. The task was iterated across 2000 trials. In conflict trials, the center and surrounding arrows pointed in opposite directions whereas in non-conflict trials, all arrows pointed in the same direction. The controls and test subjects faced conflict in 10% and 50% of the trials, respectively. After the students finished the attention task, the scientists measured their creativity in verbal tests. First, they asked the students to enlist multiple, innovative uses for common objects, such as *paperclip*, *newspaper*, *shoe*. Next, they tested the students' ability to connect unrelated words. They presented the students with a "priming word" followed by "target word" – for example, they flashed the word *tiger* followed by the word *loni*, jumbled from *lion* – and asked the students to vote whether the target word was a real or a non-existent word.

Radel found that students who took the rigorous attention task turned out to be more creative than others who had taken milder versions of the task. They came up with more numerous and quirkier ideas than the latter – one student, for instance, proposed to use a *paperclip* as a plectrum for guitar, and another saw its use as a compass when inserted into a piece of cork. These students were also more likely to connect unrelated words in the word association test. They identified more non-existent words as real words especially when the prime-target pairs were seemingly related, such as *tiger* and *loni*. They perceived *loni* as *lion* when it appeared after *tiger* and hence, called it a real word. Their ability to associate unrelated words, Radel suggests, came from a reduced filtering of irrelevant information – here, for instance, the priming word *tiger* – from the mind. Radel's attention task induced creativity in the students by exhausting their inhibition, which is the brain's ability to sift out unwanted information from the conscious mind. Although inhibition is essential for day-to-day activities such as

problem-solving and focusing on tasks, it stifles creative thinking by gating out eccentric thoughts and ideas. Uninhibited minds, on the other hand, can unleash our creative genius.

Low inhibition is in fact the basis of the paradoxical creativity seen in psychosis and the reason behind enviable accounts of sudden artistic output. For example, in a certain type of psychiatric disorder called fronto-temporal dementia, patients acquire artistic skills anew as their disease progresses. Bruce Miller, a neurologist at the University of California, San Francisco, is an expert in the field. He proposes that in these patients, the damage to parts of the prefrontal cortex – the brain's seat of execution, in the area of the forehead – particularly in the analytical left hemisphere, releases the inhibition on the right side. As a result, their right prefrontal cortex – the region that fosters visual expression and metaphorical thinking – is liberated from control, and allows a flowering of creativity. The patients develop a sudden compulsive interest in painting. Of course, the sustained loss of inhibition has devastating problems on behavior including changes in social conduct and poor impulse control.

Creative, healthy minds on the other hand can control their inhibition more effectively. In an elegant experiment, back in 2008, neuroscientist Charles Limb at Johns Hopkins University captured brain activity in jazz pianists as they played a specially designed keyboard inside a functional MRI scanner. He saw that the pianists switched to an uninhibited state when they spontaneously improvised a musical piece but not when they played the C-major scale from memory. In the former case, which requires more creativity, Limb could observe a waning of activity in regions of the prefrontal cortex associated with planning, execution and self-assessment, unveiling newer activity in areas for self-expression and individuality. Of course, the inhibition was intact when the pianists played a learned order of notes from memory, a task requiring greater attention.

Being creative is not just about achieving a state of low inhibition, which is probably what we get from alcohol or drugs, but about tweaking inhibition for brief stints without losing control. Harvard psychologist Shelly Carson, author of *Your Creative Brain*, calls this process "flexing the brain." She says that creative people can turn down the volume of inhibition to let novel ideas inspire them, and then, turn the volume back up to put their ideas to meaningful use.

Any strategy aimed at upping our creativity should do exactly this – help "manipulate" our inhibition. For beginners, Radel's technique of overtaxing the brain, to find a sweet window for a creative spell, may be a good place to start. As we go through our day, juggling multiple tasks and deadlines, our mind works hard to stay focused on a single task. There is the added pressure to keep distractions at bay – meetings, e-mails, news updates, and so on. At the end of it all, we are left feeling exhausted. At such times, instead of shutting down and relaxing, we should perhaps learn to capitalize on the mental fatigue and try to kindle our creative genius.

http://www.eurekalert.org/pub_releases/2015-06/wsu-wsr060815.php

WSU Spokane researchers isolate smallest unit of sleep to date

Scientists control sleep in a petri dish

SPOKANE, Wash. - Washington State University Spokane scientists have grown a tiny group of brain cells that can be induced to fall asleep, wake up and even show rebound sleep after "staying up late."

The study - the first to document that sleep originates in small neural networks - opens the door to deeper understanding of the genetic, molecular and electrical aspects underlying sleep disorders.

WSU Regents professor James Krueger and doctoral student Kathryn Jewett cultured neurons and glial cells that matured over two weeks into active neural networks exhibiting some of the same EEG sleep patterns seen in the brains of animals. The networks are the simplest unit of sleep identified to date.

Krueger predicted 20 years ago that sleep originates in small networks of neurons and glia. He said this study supports the hypothesis and will allow sleep to be independently isolated for research without the intrusion of physiological factors like changing body temperature.

The findings were recently published in the European Journal of Neuroscience. The work was funded by the National Institutes of Health/National Institute of Neurological Disease and Stroke and the National Science Foundation.

Sleep in a dish

Sleep clinics typically use EEG (electroencephalogram) measurements such as slow wave voltage (SW) and synchronization (SYN) to determine if a patient has fallen asleep.

For the study, Krueger and Jewett used a number of readings including SW and SYN to determine sleep states of the mature cell cultures.

Krueger said the normal state of cultured neurons is sleep-like. To drive them into deeper sleep, the researchers added tumor necrosis factor (TNF) to the petri dish, which also contained an array of EEG electrodes. TNF is an immune protein that helps regulate sleep and is found in all animals from fruit flies to humans.

"TNF is also known to stabilize synapses - the junction between two neurons - so you don't lose old memories and can simultaneously retain new memories," he said.

Krueger and Jewett reversed the effects of TNF and awakened the neurons by applying mild electrical stimulation. During this period, the cells displayed EEG signs equivalent to wakeful activity.

When the researchers prolonged electrical stimulation, the cells responded with a miniature version of sleep homeostasis seen in animals; that is, after their extra activity, the nerve cells "slept in" the next day.

"Everyone has experienced this type of homeostasis," said Krueger. "If you stay up late one night, you sleep more the next night to catch up."

The researchers said the pathway for this sleep-wake cycle is consistent with the way sleep occurs in life. When the neuron cultures are activated they signal that activity by releasing ATP, which in turn releases TNF and another immune hormone called interleukin-1. Together they trigger the sleep phase.

Running on three cylinders

The study builds on the work of former WSU neuroscientist David Rector who, in 2005, showed that individual cortical columns in the brain go to sleep and wake up at different times. His research confirmed that after a day of unusual exertion certain parts of the brain will continue sleeping the next day. In effect, you really can be "half asleep."

Rector and Krueger also showed that a cortical column could be driven into a sleep-like state by the application of TNF.

Krueger said that although it is late in his 40-year career, his discovery of the neural networks is opening up exciting new fields in sleep research and will help address the elusive mystery of sleep function.

"It is forcing scientists to see sleep as a small network property," he said. "Before, people viewed sleep as a whole-brain phenomenon - using theories that often invoke, "a miracle occurs and then you go to sleep." "In our theory, there is no miracle at all," said Krueger. "Bits and pieces of the brain oscillate between sleep and wake-like states depending on how much activity they had the day before.

"And the reason they do that is because synapses are activity dependent - the more you use them, the better they get," he said. "While our bodies rest, sleep stabilizes the neural network and provides an alternate pattern of stimulation to help preserve our memories."

http://www.eurekalert.org/pub_releases/2015-06/as-lso060515.php

Largest-ever study of parental age and autism finds increased risk with teen moms

Study funded by Autism Speaks also confirms higher risk with older parents

New York, N.Y. - The largest-ever multinational study of parental age and autism risk, funded by Autism Speaks, found increased autism rates among the children of teen moms and among children whose parents have relatively large gaps between their ages. The study also confirmed that older parents are at higher risk of having children with autism. The analysis included more than 5.7 million children in five countries. The study was published today in the journal Molecular Psychiatry.

"Though we've seen research on autism and parental age before, this study is like no other," says co-author Michael Rosanoff, Autism Speaks' director of public health research. "By linking national health registries across five countries, we created the world's largest data set for research into autism's risk factors.

The size allowed us to look at the relationship between parents' age and autism at a much higher resolution - under a microscope, if you will."

"Although parental age is a risk factor for autism," adds co-author Sven Sandin, "it is important to remember that, overall, the majority of children born to older or younger parents will develop normally."

Dr. Sandin, a medical epidemiologist, is affiliated with the Icahn School of Medicine at Mount Sinai, in New York, and Sweden's Karolinska Institutet.

The study builds on the broader research of the International Collaboration for Autism Registry Epidemiology (iCARE).

Autism Speaks, the world's leading autism science and advocacy organization, is a major supporter of iCARE, with its goal of better understanding the factors that predispose or protect against autism.

Though previous studies identified a link between advancing parental age and autism risk, many aspects of the association remained unclear. For example, some studies found increased risk with older dads but not moms. The goal of the new study was to determine whether advancing maternal or paternal ages independently increase autism risk, and to what extent each might do so.

The study looked at autism rates among 5,766,794 children - including more than 30,000 with autism - in Denmark, Israel, Norway, Sweden and Western Australia. The children were born between 1985 and 2004, and the researchers followed up on their development until 2009, checking national health records for autism diagnoses.

Researchers identified and controlled for other age-related influences that might affect autism risk. When separating the influence of mother's versus father's age, they also adjusted for the potential influence of the other parent's age.

"After finding that paternal age, maternal age and parental-age gaps all influence autism risk independently, we calculated which aspect was most important," Dr. Sandin adds. "It turned out to be parental age, though age gaps also contribute significantly."

Key findings:

Autism rates were 66 percent higher among children born to dads over 50 years of age than among those born to dads in their 20s. Autism rates were 28 percent higher when dads were in their 40s versus 20s.

Autism rates were 15 percent higher in children born to mothers in their 40s, compared to those born to moms in their 20s.

Autism rates were 18 percent higher among children born to teen moms than among those born to moms in their 20s.

Autism rates rose still higher when both parents were older, in line with what one would expect if each parent's age contributed to risk.

Autism rates also rose with widening gaps between two parents' ages. These rates were highest when dads were between 35 and 44 and their partners were 10 or more years younger. Conversely, rates were high when moms were in their 30s and their partners were 10 or more years younger.

The higher risk associated with fathers over 50 is consistent with the idea that genetic mutations in sperm increase with a man's age and that these mutations can contribute to the development of autism spectrum disorders (ASD).

By contrast, the risk factors associated with a mother's age remain unexplained, as do those associated with a wide gap between a mother and father's age.

"These results suggest that multiple mechanisms are contributing to the association between parental age and ASD risk," the authors conclude.

"When we first reported that the older age of fathers increases risk for autism, we suggested that mutations might be the cause. Genetic research later showed that this hypothesis was correct," notes co-author Abraham Reichenberg, a neuropsychologist and epidemiologist with the Icahn School of Medicine at Mount Sinai, in New York City. "In this study, we show for the first time that autism risk is associated with disparately aged parents. Future research should look into this to understand the mechanisms."

http://www.eurekalert.org/pub_releases/2015-06/foas-pp060915.php

'Alzheimer's protein' plays role in maintaining eye health and muscle strength

New research in The FASEB Journal shows that the amyloid precursor protein binds to other proteins, FE65 and FE65L1, to facilitate eye and muscle health

Amyloid precursor protein (APP), a key protein implicated in the development Alzheimer's disease, may play an important role in eye and muscle health. In a new report published in the June 2015 issue of The FASEB Journal, scientists have discovered that when proteins that bind to the APP, called FE65 and FE65L1, are deleted, they cause cataracts and muscle weakness in mice. Additionally, this study demonstrates that the expression of laminin, a protein pivotal for the interaction between lens epithelial cells and the lens capsule, is severely altered in mice lenses missing both FE65 and FE65L1 genes. If confirmed in human studies, the FE65 and FE65L1 proteins may become a therapeutic target for cataracts, muscular dystrophy and Alzheimer's disease.

"We hope the discoveries in this study would help to expand our understanding of the normal function of FE65 and APP," said Jaehong Suh, Ph.D., a researcher involved in the work from the Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease at Massachusetts General Hospital in Boston, MA. "From this kind of very basic research, we may be able to find more clues for the causes of, and ultimately to discover effective treatments for related human diseases such as cataract, congenital muscular dystrophies and Alzheimer's disease."

To make their discovery, Suh and colleagues examined and compared the eyes and muscles of four different mouse groups: one without the FE65 protein, one without FE65L1, one without both FE65 and FE65L1, and one that was normal control mice. They found that mice lacking both FE65 and FE65L1 develop severe lens degeneration that may be an extreme manifestation of cataract and muscle weakness. Milder deficits in muscle were found in the mice with only one gene deleted, while no changes were seen in the normal mice. Interestingly, cortical cataracts were observed in old mice lacking the FE65L1 protein.

"It's rare that in any living system, one gene or one protein performs only one function," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. "Although this is a new find, the fact that a protein implicated in Alzheimer's disease has a function in tissues other than the brain should come as no surprise--but APP's function in the eye is unexpected!"

Details: Jaehong Suh, Juliet A. Moncaster, Lirong Wang, Imran Hafeez, Joachim Herz, Rudolph E. Tanzi, Lee E. Goldstein, and Suzanne Y. Guénette. FE65 and FE65L1 amyloid precursor protein-binding protein compound null mice display adult-onset cataract and muscle weakness. FASEB J. June 2015 29:2628-2639; doi:10.1096/fj.14-261453 ; http://www.fasebj.org/content/29/6/2628.abstract

http://www.eurekalert.org/pub_releases/2015-06/esoh-flb060915.php

First live birth after transplantation of ovarian tissue frozen during childhood

A young woman has become the first in the world to give birth to a healthy child after doctors restored her fertility by transplanting ovarian tissue that had been removed and frozen while she was a child.

A report of the case is published today in Human Reproduction [1], one of the world's leading reproductive medicine journals.

While there have been reports of successful pregnancies after ovarian transplantation using tissue that had been removed from patients when they were adults, there have been none using tissue taken from girls before puberty and the ability of such immature ovarian tissue to develop to produce mature eggs is unclear.

The patient, who was born in the Republic of Congo, was diagnosed with sickle-cell anaemia when she was five.

After emigrating to Belgium at the age of 11, doctors decided that her disease was so severe that she should be treated with a bone marrow transplant, and her brother was able to provide the matching tissue.

The procedure requires that the patient's immune system should be disabled before transplantation to prevent rejection of the bone marrow and this is usually done using chemotherapy or radiotherapy, which can destroy the functioning of the ovaries permanently.

Therefore, before treating her with chemotherapy, the Belgian doctors removed the patient's right ovary when she was 13 years and 11 months old and froze tissue fragments. She had not started her periods, although there were signs that she had started puberty with breast development when she was 10.

The bone marrow transplant was successful, although the patient developed graft-versus-host disease and had to continue with immuno-suppressive drugs for 18 months after the transplant. Her remaining ovary failed and when she was 15, doctors gave her hormone replacement therapy to induce the onset of menstruation. Ten years later the patient received counselling after expressing a desire to become pregnant.

In order to restore her fertility, doctors led by Dr Isabelle Demeestere, a gynaecologist and research associate in the Fertility Clinic and Research Laboratory on Human Reproduction at Erasme Hospital, Université Libre de Bruxelles (Brussels, Belgium), stopped the hormone replacement therapy, thawed some, but not all, of the frozen ovarian tissue and grafted four fragments on to the remaining left ovary, and 11 other fragments at other sites in the body.

The transplanted tissue started to respond to her hormones and successfully started growing follicles that contain the maturing eggs. The patient started menstruating five months later and continued having regular menstrual cycles thereafter.

Due to the infertility of her partner, she tried assisted reproduction but stopped when the relationship failed. More than two years after the transplantation she became pregnant naturally with a new partner at the age of 27 and delivered a healthy boy in November 2014, weighing 3140 grams (6.9 pounds).

Dr Demeestere said: "This is an important breakthrough in the field because children are the patients who are most likely to benefit from the procedure in the future.

When they are diagnosed with diseases that require treatment that can destroy ovarian function, freezing ovarian tissue is the only available option for preserving their fertility.

"However, the success of this procedure requires further investigation in very young, pre-pubertal girls, as our patient had already started puberty even although she had not started menstruating.

In addition, the procedure also raises some controversial issues. For instance, because it is an invasive procedure and because the lifespan of the graft is limited, should it be used to induce puberty and menstruation, rather than to restore fertility, when hormone replacement therapy is an efficient, standard, and non-invasive alternative for inducing puberty? Should the procedure only be proposed for patients with a high risk of ovarian failure or for those at low risk as well?

We think, at present, that cryopreserved ovarian tissue should be used only for fertility restoration in patients at high risk of ovarian failure, and not for puberty induction or for restoring menstrual cycles in adults."

The patient's ovary continues to function normally and her doctors say there is no reason why she could not have more babies if she wants to.

"She also has the possibility of undergoing a second transplantation with the remaining frozen tissue if the graft stops working, as we didn't transplant all the ovarian tissue the first time. We have another patient who became pregnant after ovarian transplantation, and she had two babies born after two graft procedures," said Dr Demeestere.

[1] *"Live birth after autograft of ovarian tissue cryopreserved during childhood", by Isabelle Demeestere et al. Human Reproduction journal. doi:10.1093/humrep/dev128*

http://www.bbc.com/news/science-environment-33067582

'Blood cells' found in dino fossils

Researchers have discovered what appear to be the remnants of red blood cells and connective tissue in 75 million-year-old dinosaur fossils.

By Paul Rincon Science editor, BBC News website

The work could shine a light on long-standing questions about dinosaur physiology, including whether specific species were warm- or cold-blooded.

Chemical analysis revealed similarities between blood cells from fossils and those from living emu. The work appears in the journal Nature Communications.

Examining part of a fossilised dinosaur claw, the Imperial College London researchers identified tiny ovoid structures with an inner denser core that resembled red blood cells. And in another fossil fragment, they found fibrous features with a banded structure similar to that seen in modern-day collagen - found in the tendons, skin and ligaments of animals.

It's not the first time such remnants have been found in dinosaur fossils, but co-author Susannah Maidment told BBC News: "All of the previous reports of original components of soft tissues in dinosaur fossils have tended to be in

specimens that are really exceptionally preserved - one-offs, really, that require special pleading to explain how they got preserved."

By contrast, the fossils in this study, which have been lying in the London Natural History Museum collections for more than a century, are largely in a poor state of preservation.

"They're very scrappy, individual broken bones. I can't even tell you what dinosaur they come from," said Dr Maidment, who is from Imperial College London. "If you're finding soft tissues in these kinds of fossils, maybe this kind of preservation might be more common than we realised, and might even be the norm."

The structures appear to be genuine remnants of soft tissue; they are not fossilised.

Using a mass spectrometer, they carried out chemical analysis of the putative collagen protein and the candidate blood cells.

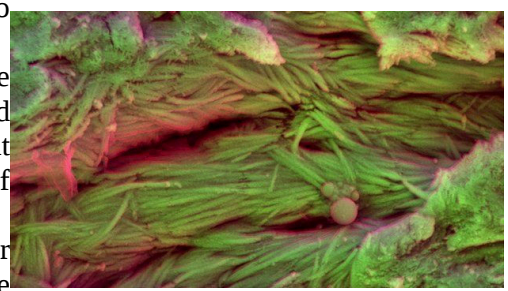
The blood cell structures were found in this claw from a bipedal theropod dinosaur of unknown type

They discovered fragments in the collagen of what look like amino acids - the building blocks of all proteins.

And the chemical profile of the blood cells looked very similar to that obtained from the red blood cells of an emu, which - like all birds - is a direct descendent of dinosaurs.

"There's an extremely well-known relationship within individual vertebrate groups that the smaller the red blood cell, the faster the metabolic rate," said Dr Maidment.

"Animals with fast metabolic rates will tend to be warm blooded, while animals with slower metabolic rates are going to be more cold blooded."



The subject of whether dinosaurs were cold- or warm blooded has preoccupied palaeontologists for decades, because it can provide pointers to the types of lifestyles dinosaurs had.

Were they more bird-like in their behaviour, or more sluggish, like reptiles?

Fibrous structures in the fossils resemble collagen

The red blood cells found in this study were small compared with their counterparts in the emu, but the dinosaur cells will have shrunk and curled up over time.

Furthermore, scientists don't yet understand the relationship between red blood cell size and metabolic rate within dinosaurs, so scientists will need a bigger sample from different species of dinosaur to shed useful light on the debate.

However, said Dr Maidment, "if we can find red blood cells in lots of different dinosaurs and measure them, we might be able to start to understand which dinosaurs had fast metabolic rates, which were approaching warm bloodedness, which were truly warm blooded, and which were cold blooded".

Study of the apparent collagen fibres could shed light on the relationships between different dinosaur species. A technique called collagen fingerprinting is based on the idea that the structure of the collagen molecule is unique to individual animals.

"Most closely related animals will have a more similar collagen structure than more distantly related animals," said Dr Maidment. "If we could extract some of the collagen... and we could find it in lots of different dinosaurs, it could give us a sense of relatedness within the dinosaur family tree."

Co-author Dr Sergio Bertazzo said: "We still need to do more research to confirm what it is that we are imaging in these dinosaur bone fragments.

"If we can confirm that our initial observations are correct, then this could yield fresh insights into how these creatures once lived and evolved."

Prof Mary Schweitzer from North Carolina State University, who was not involved with the latest study, said she appreciated the caution with which the group interpreted their data.

"All in all, I think that papers like these which present data from multiple lines of investigation, and which are cautious in interpretation do much to advance the field, show that fossils are more than 'just rocks', and open the door to the possibility that materials persist in ancient fossils that were not thought possible only a few years ago," she told BBC News.

Prof Schweitzer added: "They did find amino acids consistent with proteins, but the data they presented do not really identify *which* proteins; for that they need additional data.

"But it is a great start, and an exciting paper, particularly in showing what happens when you really *look* at ancient bone and are not bound by the expectation that 'nothing could possibly persist'. If you don't look, you won't find. But if you do, you never know."

On the outside possibility of ever finding DNA in dinosaur remains, Dr Maidment commented: "We haven't found any in our fossils... however, I think it's unwise to say we'll never find any in future."

http://www.eurekalert.org/pub_releases/2015-06/aaon-kmb060915.php

Keeping mind, body active may not protect against underlying signs of Alzheimer's

Though mentally stimulating activities may reduce the risk of Alzheimer's disease, they may not do so by affecting the underlying markers for the disease

MINNEAPOLIS - While participating in physical activities such as bike riding, dancing, walking and gardening and mentally stimulating activities such as crosswords and reading may reduce the risk of Alzheimer's disease, they may not do so by affecting the underlying markers for the disease, according to a study published in the June 10, 2015, online issue of Neurology®, the medical journal of the American Academy of Neurology.

"While a lifelong history of physical and mental activity may support better memory and thinking performance, this relationship may possibly be separate from any protection against the markers of Alzheimer's disease in the brain," said study author Keith A. Johnson, MD, with Harvard Medical School and Massachusetts General Hospital in Boston.

The study involved 186 people with an average age of 74 who were free of memory and thinking problems. Participants reported their physical and mental activity levels over their lives as well as current mental activities. They also wore pedometers for seven days to track current physical activity. The participants had PET and MRI scans to measure the amount of amyloid-beta deposits in the brain, which occurs with Alzheimer's disease. The scans also measured the brain's metabolism and whether the hippocampus area of the brain was shrinking, also signs of Alzheimer's. In addition, participants took tests of their thinking and mental abilities.

The study found that participants who took part in stimulating cognitive activities had significantly higher IQ and better cognitive performance compared those who did not take part in mentally stimulating activities very often. There was no relationship between frequent mental or physical activity and any of the markers of Alzheimer's disease in the brain.

"This suggests that sustaining a lifetime of intellectual engagement may help preserve cognitive function into old age," said Johnson. "In addition, our findings should not discourage people from engaging in physically and mentally stimulating activities, as they have been shown in numerous studies to generally offer many brain benefits," said Johnson. Johnson noted that the study was limited because it did not follow the participants over a long period, but asked them to remember their activities from the past. He said studies that follow people's activities over time are needed to further test the findings.

The study was supported by the National Institute on Aging and the Alzheimer's Association.

http://nyti.ms/1GFTLcR

DNA Deciphers Roots of Modern Europeans

Studies indicate that today's Europeans descend from three groups who moved into Europe at different stages

Carl Zimmer MATTER

A male skeleton associated with the Yamnaya culture near Samara, Russia. **Credit Pavel Kuznetsov**

For centuries, archaeologists have reconstructed the early history of Europe by digging up ancient settlements and examining the items that their inhabitants left behind. More recently, researchers have been scrutinizing something even more revealing than pots, chariots and swords: DNA.

On Wednesday in the journal Nature, two teams of scientists - one based at the University of Copenhagen and one based at Harvard University - presented the largest studies to date of ancient European DNA, extracted from 170 skeletons found in countries from Spain to Russia. Both studies indicate that today's Europeans descend from three groups who moved into Europe at different stages of history.

A Yamnaya skull found near Samara, Russia, colored with ocher. Yamnaya expansion into Europe was most likely relatively peaceful. **Credit Natalia Shishlina**

The first were hunter-gatherers who arrived some 45,000 years ago in Europe. Then came farmers who arrived from the Near East about 8,000 years ago.

Finally, a group of nomadic sheepherders from western Russia called the Yamnaya arrived about 4,500 years ago. The authors of the new studies also suggest that the Yamnaya language may have given rise to many of the languages spoken in Europe today.

Ron Pinhasi, an archaeologist at University College Dublin who was not involved in either study, said that the new studies were "a major game-changer. To me, it marks a new phase in ancient DNA research."

The two teams worked independently, studying different skeletons and using different methods to analyze their DNA. The Harvard team collected DNA from 69 human remains dating back 8,000 years and cataloged the genetic variations at almost 400,000 different points. The Copenhagen team collected DNA from 101 skeletons dating back about 3,400 years and sequenced the entire genomes.

Both teams also compared the newly sequenced DNA to genes retrieved from other ancient Europeans and Asians, and to living humans.

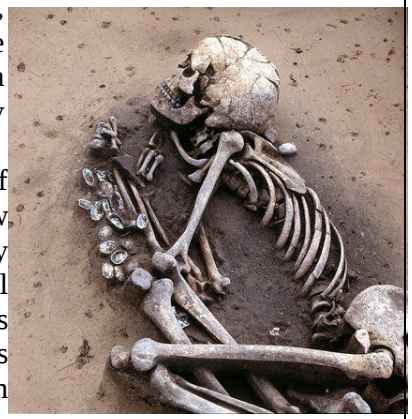
Until about 9,000 years ago, Europe was home to a genetically distinct population of hunter-gatherers, the researchers found. Then, between 9,000 and 7,000 years ago, the genetic profiles of the inhabitants in some parts of Europe abruptly changed, acquiring DNA from Near Eastern populations.

Archaeologists have long known that farming practices spread into Europe at the time from Turkey. But the new evidence shows that it wasn't just the ideas that spread — the farmers did, too.

The hunter-gatherers didn't disappear, however. They managed to survive in pockets across Europe between the farming communities.

"It's an amazing cultural process," said David Reich, a geneticist at Harvard Medical School who led the university's team. "You have groups which are as genetically distinct as Europeans and East Asians. And they're living side by side for thousands of years."

Between 7,000 and 5,000 years ago, however, hunter-gatherer DNA began turning up in the genes of European farmers. "There's a breakdown of these cultural barriers, and they mix," said Dr. Reich.



About 4,500 years ago, the final piece of Europe's genetic puzzle fell into place. A new infusion of DNA arrived - one that is still very common in living Europeans, especially in central and northern Europe. The closest match to this new DNA, both teams of scientists found, comes from skeletons found in Yamnaya graves in western Russia and Ukraine.

A skeleton buried by a Middle Neolithic culture found near Saxony-Anhalt, Germany. A review of DNA from skeletons across Europe indicated that today's Europeans are descended from three groups who moved there at different stages of history. **Credit Juraj Lipták/LDA Sachsen-Anhalt**

Archaeologists have long been fascinated by the Yamnaya, who left behind artifacts on the steppes of western Russia and Ukraine dating from 5,300 to 4,600 years ago. The Yamnaya used horses to manage huge herds of sheep, and followed their livestock across the steppes with wagons full of food and water.

It was an immensely successful way of life, allowing the Yamnaya to build huge funeral mounds for their dead, which they filled with jewelry, weapons and even entire chariots.

David W. Anthony, an archaeologist at Hartwick College and a co-author on the Harvard study, said it was likely that the expansion of Yamnaya into Europe was relatively peaceful. "It wasn't Attila the Hun coming in and killing everybody," he said. Instead, Dr. Anthony thought the most likely scenario was that the Yamnaya "entered into some kind of stable opposition" with the resident Europeans that lasted for a few centuries. But then gradually the barriers between the cultures eroded.

The Copenhagen team's study suggests that the Yamnaya didn't just expand west into Europe, however. The scientists examined DNA from 4,700-year-old skeletons from a Siberian culture called the Afanasievo. It turns out that they inherited Yamnaya DNA, too.

Dr. Anthony was surprised by the possibility that Yamnaya pushed out over a range of about 4,000 miles. "I myself have a hard time wrapping my head around explanations for that," he said.

The two studies also add new fuel to a debate about how languages spread across Europe and Asia. Most European tongues belong to the Indo-European family, which also incudes languages in southern and Central Asia.

For decades, linguists have debated how Indo-European got to Europe. Some favor the idea that the original farmers brought Indo-European into Europe from Turkey. Others think the language came from the Russian steppes thousands of years later.

The new genetic results won't settle the debate, said Eske Willerslev, an evolutionary biologist at Copenhagen University who led the Danish team. But he did think the results were consistent with the idea that the Yamnaya brought Indo-European from the steppes to Europe.

The eastward expansion of Yamnaya, evident in the genetic findings, also supports the theory, Dr. Willerslev said. Linguists have long puzzled over an Indo-European language once spoken in western China called Tocharian. It is only known from 1,200-year-old manuscripts discovered in ancient desert towns. It is possible that Tocharian was a vestige of the eastern spread of the Yamnaya.

"We can just say that the expansion fits very well with the geographical spread of the Indo-European language," said Dr. Willerslev.

Paul Heggarty, a linguist at the Max Planck Institute of Evolutionary Anthropology, said that the new studies were important, but were still too limited

to settle the debate over the origins of Indo-European. “I don’t think we’re there yet,” he said.

Dr. Heggarty noted that the studies showed the arrival of Yamnaya in Central Europe about 4,500 years ago. But Greek is an Indo-European language, and the oldest evidence of writing in Europe shows that Greek had developed about 3,500 years ago. By then, it was distinct from other Indo-European languages in Southern Europe, like Latin.

If the Yamnaya were the source of Indo-European languages, they would have had to get to southern Europe soon after they made it to Central Europe.

Dr. Heggarty speculated instead that early European farmers, the second wave of immigrants, may have brought Indo-European to Europe from the Near East. Then, thousands of years later, the Yamnaya brought the language again to Central Europe.

More ancient DNA could swing the balance of evidence in favor of one theory over the other, Dr. Heggarty said. A stronger case for a steppe origin of Indo-European might emerge, for example, if scientists discovered that Greeks around 4,500 years ago abruptly acquired Yamnaya DNA.

“Let’s see whether they look like the steppe people or not,” he said.

http://www.eurekalert.org/pub_releases/2015-06/kl-spc060915.php

Single protein causes Parkinson's disease and multiple system atrophy

Several neurodegenerative disorders are caused by aggregates of a single protein known as alpha-synuclein.

In collaboration with CNRS and the University of Antwerp, KU Leuven neurobiologists have discovered that the shape of these aggregates - 'cylinders' or 'ribbons' - determines whether a patient develops Parkinson's disease or Multiple System Atrophy, respectively.

Typical of neurodegenerative disorders is the disrupted communication between brain cells together with a loss of cells in specific brain regions. For some brain diseases this phenomenon is linked to a protein known as alpha-synuclein. The exact function of this protein remains unclear, but it may play a role in the communication between brain cells. However, in the case of specific diseases, including Parkinson's disease, Multiple System Atrophy (MSA), and dementia with Lewy bodies (DLB), this protein forms aggregates that cause neurodegeneration.

"When alpha-synuclein aggregates accumulate within a brain cell, they interfere with the normal functioning of the cell. The protein aggregates disrupt the communication between brain cells, resulting in cell death. Up to now, nobody understood how aggregates of this single protein could induce different pathologies," says Professor Veerle Baekelandt from the Research Group for Neurobiology and Gene Therapy.

"You could compare it to the construction of a house," doctoral researcher Wouter Peelaerts explains. "With the same building blocks - in this case the alpha-synuclein protein - you can create many different structures. In 2013, Professor Ronald Melki and his colleagues from CNRS isolated several forms of fibres called 'strains'. The two most important strains were cylinder-shaped fibres reminiscent of spaghetti and broad ribbons that resemble linguini. We injected these fibres separately into the brain and blood stream of rats. We noticed that the rats developed different symptoms: while the 'cylinders' induced Parkinson's disease, the 'ribbons' caused MSA symptoms." This clearly demonstrates that distinct diseases result from alpha-synuclein fibres that are structurally different.

"We are gaining more insight into the differences between the diseases. But we suspect that more fibres with different shapes and effects are waiting to be discovered, apart from the two that we examined in this study. In any case, our findings open up possibilities for the development of new treatments. A drug that counteracts the development of aggregates could be used to treat a whole range of brain diseases."

The full text of the study "Alpha-synuclein strains cause distinct synucleinopathies after local and systemic administration" by W. Peelaerts, L. Bousset, A. Van der Perren, A. Moskalyuk, R. Pulizzi, M. Giugliano, C. Van den Haute, R. Melki, and V. Baekelandt will be published in Nature (DOI 10.1038/nature14547). The paper is scheduled for Advance Online Publication on http://www.nature.com on 10 June 2015 at 7:00 p.m. CEST / 6:00 p.m. London time / 1:00 p.m. US Eastern Time. Alternatively, copies can be obtained from the authors.

http://www.eurekalert.org/pub_releases/2015-06/uom-ndc061015.php

New drug can clear all psoriasis symptoms

New psoriasis drug has resulted in 40 percent of people showing a complete clearance of psoriatic plaques

A University of Manchester led trial of a new psoriasis drug has resulted in 40 percent of people showing a complete clearance of psoriatic plaques after 12 weeks of treatment and over 90 percent showing improvement.

The research tested 2,500 people with psoriasis. Half were given a new drug - ixekizumab - either once every two or four weeks. The other half were given a placebo or a widely used drug for psoriasis called etanercept.

The ixekizumab groups showed quick and extensive improvements in their condition, outperforming the groups on placebo or etanercept. Around half of these patients showed improvement as early as week four of the trial and up to

71% had shown a high level of improvement, as measured using a scale called the Psoriasis Area and Severity Index, by week 12.

Chris Griffiths, Foundation Professor of Dermatology in the University's Faculty of Medical and Human Sciences and Salford Royal NHS Foundation Trust, led the research. He said: "The visible effects of psoriasis can have a major and life-ruining impact on people's confidence and self-esteem.

"What we saw in this trial was not just the physical aspects of the disease clearing up, but people on the new drug also reporting a marked improvement in their quality of life as they felt more confident and suffered less from itching - far more than in the other two groups."

Ixekizumab is a monoclonal antibody - a cloned antibody - which neutralises the inflammatory effects of an interleukin (IL) a protein in the skin which carries signals to cells - known as (IL)-17A. This protein is increasingly becoming recognised as one of the causes of the characteristic red, scaly plaques of psoriasis which affect around 2% of people in the UK.

New treatments are changing the prospects for people with psoriasis according to Professor Griffiths. "The objective for treating psoriasis has been to reduce the visible symptoms," he said. "But new drugs are fast showing us that a realistic goal for all patients should be attaining clear skin and this trial very much sets us on that path."

Paper: Griffiths CEM, Reich K, Lebwohl M, et al. 'Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials'. Published in the Lancet 10 June 2015.

http://www.eurekalert.org/pub_releases/2015-06/hm-har060415.php

Heart attack risk increases 16-21 percent with use of common antacid

Recent studies show increased risk of heart attack for people who use proton pump inhibitors to control GERD and other excess-acid issues

HOUSTON - Adults who use proton pump inhibitors are between 16 and 21 percent more likely to experience a heart attack than people who don't use the commonly prescribed antacid drugs, according to a massive new study by Houston Methodist and Stanford University scientists.

An examination of 16 million clinical documents representing 2.9 million patients also showed that patients who use a different type of antacid drug called an H2 blocker have no increased heart attack risk. The findings, reported in PLOS ONE, follow a Circulation report in 2013 in which scientists showed how -- at a molecular level -- PPIs might cause long-term cardiovascular disease and increase a patient's heart attack risk.

"Our earlier work identified that the PPIs can adversely affect the endothelium, the Teflon-like lining of the blood vessels," said John Cooke, M.D., Ph.D., a senior author of the PLOS ONE report. "That observation led us to hypothesize that anyone taking PPIs may be at greater risk for heart attack. Accordingly, in two large populations of patients, we asked what happened to people that were on PPIs versus other medications for the stomach."

The PLOS ONE study's principal investigator was Stanford vascular medicine specialist Nicholas J. Leeper, M.D.

In the present study, the researchers found a clear and significant association between exposure to PPIs and the occurrences of heart attack.

"By looking at data from people who were given PPI drugs primarily for acid reflux and had no prior history of heart disease, our data-mining pipeline signals an association with a higher rate of heart attacks," said the PLOS ONE report's lead author, Nigam H. Shah, Nigam H. Shah, M.B.B.S., Ph.D., an assistant professor of biomedical informatics at Stanford, where the work was done. "Our results demonstrate that PPIs appear to be associated with elevated risk of heart attack in the general population, and H2 blockers show no such association."

The estimated increase of heart attack risk ranges from 16 to 21 percent, because of uncertainty in the estimation process, Shah said.

The FDA estimates about 1 in 14 Americans has used proton pump inhibitors. In 2009, PPIs were the third-most taken type of drug in the U.S., and are believed to account for $13 billion in annual global sales. Doctors prescribe PPIs to treat a wide range of disorders, including gastro-esophageal reflux disease, or GERD, infection by the ulcer-causing bacterium Helicobacter pylori, Zollinger-Ellison syndrome, and Barrett's esophagus. The drugs can also be purchased over the counter. PPIs come in a variety of slightly different chemical forms, always ending with the suffix "-prazole," for example, omeprazole or lansoprazole. Brand examples of PPIs are Nexium, Prilosec, and PrevAcid.

H2 blockers are another type of antacid drug. They are not believed to be associated with increased risk of heart attack or cardiovascular disease. Examples of the drug are cimetidine and ranitidine. Brand examples of H2 blockers are Zantac and Tagamet.

The researchers collected data from two repositories -- STRIDE (Stanford Translational Research Integrated Database Environment), which contains information about 1.8 million Stanford hospital and clinic patients, and a subset of information for 1.1 million patients from the Web-based electronic medical records company Practice Fusion, Inc. Both sources of patient information were anonymized before the researchers accessed the data.

The group scanned the databases for patients who were prescribed proton pump inhibitors or other drugs, such as H2 blockers, and also looked to see if a given patient had a mention of having experienced a major cardiovascular event, such as myocardial infarction (heart attack), in their medical record. Patients who had used PPIs were found to be at 1.16-1.21-fold-increased risk of heart attack.

Scrutiny of PPIs has only increased with time. Initially it was believed PPIs only posed a risk to a very narrow subset of patients -- those with coronary artery disease who were using the anti-platelet drug clopidogrel to prevent future heart attacks. "Investigators originally assumed this was due to a drug-drug interaction between these compounds, and the FDA went so far as to release a warning about their concomitant use," said Nicholas Leeper.

A 2013 report to Circulation by several of the present report's coauthors, including Cooke, raised the possibility that PPIs could lead to cardiovascular disease in the general population. "This led us to use powerful 'big-data' approaches to try to determine whether PPIs might in fact be associated with risk in 'all comers,' Leeper said. "Our report raises concerns that these drugs -- which are available over the counter and are among the most commonly prescribed drugs in the world -- may not be as safe as we previously assumed."

In the future, the researchers say they hope to conduct a large, prospective, randomized trial to determine whether PPIs are harmful to a broader population of patients.

Also contributing to the PLOS ONE report were co-lead author Paea LePendu, Anna Bauer-Mehren, Srinivasan V. Iyer, and Kevin T. Nead (Stanford University), Yohannes T. Ghebremariam (Houston Methodist), and Jake Marcus (Practice Fusion, Inc.). Research was funded by grants from the National Institutes of Health (U54HG004028, U54LM008748, and 1U01HL100397), the American Heart Association (11IRG5180026), Apixio, Inc., and the Stanford SPARK Translational Research Program.

"Proton pump inhibitor usage and the risk of myocardial infarction in the general population," by Nigam H. Shah et al, PLOS ONE

http://www.eurekalert.org/pub_releases/2015-06/uocd-sbw061015.php

Survival benefit with 'fully human' EGFR antibody necitumumab in squamous NSCLC

Lancet Oncology reports positive phase III clinical trial results of necitumumab in stage IV squamous non-small cell lung cancer

This week, Lancet Oncology reports results of a 1,093-person phase III clinical trial of the drug necitumumab (IMC-11F8) combined with chemotherapies gemcitabine and cisplatin against stage IV squamous non-small cell lung cancer. With addition of necitumumab, median overall survival was 11.5 months compared with median survival of 9.9 months with the two chemotherapies alone.

"We haven't seen any new drug approvals in first-line squamous lung cancer in many, many years. I'm very excited to see a new agent that has survival benefit in this space," says Fred R. Hirsch, MD, PhD, investigator at the University of Colorado Cancer Center, CEO of the International Association for the Study of Lung Cancer, and one of the trial's co-principal investigators.

The study, known as SQUIRE, included 184 investigative sites in 26 countries. Patients with stage IV squamous non-small cell lung cancer were eligible for the study, regardless of EGFR mutation status. Additionally, the CU Cancer Center performed biomarker analysis of tissue samples, evaluating patient tumor samples for amplification of the EGFR gene. The efficacy of the drug specifically in the population of patients with EGFR amplification will be released during the 16th World Conference on Lung Cancer, September 6-9, 2015 in Denver, Colo.

Notably, necitumumab uses a novel approach to activate the immune system against tumor tissue. Some cancers mutate in ways that let them over-express epidermal growth factor receptor (EGFR). These cells, coated with EGFR, "trap" more epidermal growth factor, signaling these cells to continuously grow and divide in a cancerous way. Thus coated with EGFR, these cancer cells are also marked as different than the surrounding, healthy tissue. The goal of immunotherapies directed at EGFR is to teach the immune system to specifically attack these cells marked by the overabundance of EGFR.

These drugs are generally based on monoclonal antibodies (thus the "m.a.b." at the end of immunotherapy drugs like bevacizumab, necitumumab and cetuximab). Produced by the immune system, a monoclonal antibody binds to a specific protein and marks the cell that holds that protein for attack by the immune system. It's as if the monoclonal antibody is the sighting system that guides the missiles of the immune system.

Researchers can manufacture monoclonal antibodies specific to proteins - again, if a protein is over-expressed on a tumor, introducing the corresponding monoclonal antibody will tell the immune system to attack tumor cells that express this protein. "As we've seen, this is a very promising approach," Hirsch says. "If you discover a protein that is uniquely expressed or over-expressed by a tumor, in this case EGFR, we can use monoclonal antibodies targeting that protein to inhibit the physiological consequences of EGFR activation, which, without therapy, would otherwise lead to cancer progression."

However, due to technical challenges of manufacturing monoclonal antibodies, most existing monoclonal antibodies are "chimeric" - produced using the combination of mouse and human DNA. (Cetuximab is one of these chimeric monoclonal antibodies, targeting EGFR.) There can be challenges with drugs based on chimeric monoclonal antibodies, most notably the immune system's

habit of recognizing the monoclonal antibodies themselves as threats and eliminating them from the body immediately (and also the side effect of undesirable, system-wide immune response).

Necitumumab uses "fully human" antibodies, which are produced without the hybridization with mouse DNA. This approach (described in a 1995 paper in the journal International Reviews in Immunology), though technically challenging, may help patients treated with necitumumab avoid some of the side effects associated with drugs based on chimeric antibodies.

"While we saw more side effects in the group treated with necitumumab in combination with the two chemotherapies, we found that the safety profile of necitumumab plus gemcitabine and cisplatin was acceptable and in line with expectations," Hirsch says.

Non-small cell lung cancers (NSCLC) comprise 85-90 percent of all lung cancers, with squamous cell lung cancers accounting for 25-30 percent of NSCLC. Worldwide, lung cancer results in more than 1.5 million deaths per year, about 20 percent of all deaths caused by cancer, and is the leading cause of cancer mortality. Due in part to the lack of new, targeted therapies for squamous NSCLC, this form of the disease has a poorer prognosis than non-squamous NSCLC.

Regulatory submission of necitumumab for FDA approval is completed, with a decision expected soon.

"This is an improvement. Based on this large prospective study in first-line therapy of squamous lung cancer, a subtype of lung cancer where there is an urgent unmet need for treatment improvement, the drug warrants approval," Hirsch says.

http://www.bbc.com/news/health-33079846

Scientists find CJD resistance gene

Researchers have identified a gene that might make people resistant to the brain eating disease CJD.

By Pallab Ghosh Science correspondent, BBC News

The study is part of an effort to find ways of combating a possible epidemic caused by eating BSE infected beef in the 1980s.

It is claimed that the findings could give important insight into other human brain diseases that lead to dementia.

The results have been published in the journal Nature.

Creutzfeldt-Jakob disease (CJD) is a rare but fatal brain disorder.

There are three forms of the disease: sporadic which occurs naturally in the human population; variant CJD (vCJD) caused by eating BSE infected beef and kuru which was once widespread in a remote area Papua New Guinea and was caused by the practice among a particular tribal community called the Fore of eating human brains.

They would eat their dead as a mark of respect at mortuary feasts. This led to a major epidemic of kuru which, at its height in the late 1950's, caused the death of up to 2% of the population each year.

Prof John Collinge at the Medical Research Council's Prion Unit at University College London has been studying kuru for more than 20 years in order to find a treatment for other forms of CJD. He was particularly interested in those people in the Fore who seemed to be resistant to kuru.

Protection

Prof Collinge and his team found that they had a change in one of their genes, called the prion protein gene which he believed might be protecting people against the disease.

To test this, he bred mice with the suspected protective gene. To his surprise he found that the mice were resistant not only to kuru but also to all forms of CJD.

According to Prof Collinge if scientists can now understand how this gene works they could find a way to prevent not only CJD, but other dementias.

"This could provide great insights into how the disease works and ultimately how to stop it," he told BBC News.

There had been fears that tens of thousands of people would die following the emergence of a new form of vCJD in the 1990s from eating BSE infected beef. So far 177 people are thought to have died from the disease in the UK although one in 2,000 people are thought to be carrying the infection.

But according to Prof Collinge, "It is important that we don't drop our guard".

"Thirty thousand people are silently carrying the disease and we don't know whether they will carry on carrying the disease without developing symptoms or go on to develop the disease".

Those with kuru take 50 years to develop the disease after they have become infected. If the same is true of vCJD, says Prof Collinge, it could be several decades before we will know the full extent of BSE exposure"

http://www.bbc.com/news/health-33076815

Nuts 'protect against early death'

Eating half a handful of nuts every day could substantially lower the risk of early death, a Dutch study suggests.

Previous studies had already indicated a link with cardiovascular health, but this is the first to look at specific nuts and diseases.

Maastricht University researchers found a 23% lower chance of death during the 10-year study in people eating at least 10g (0.3oz) of nuts or peanuts a day.

There was no benefit for peanut butter, which is high in salt and trans fats.

What's in a nut?

monounsaturated and polyunsaturated fatty acids
various vitamins
fibre
antioxidants
other bioactive compounds

More than 120,000 Dutch 55-to-69-year-old men and women provided dietary and lifestyle information in 1986, and then their mortality rate was looked at 10 years later. The premature mortality risk due to cancer, diabetes, respiratory and neurodegenerative diseases was lower among the nut consumers.

There was an average 23% lower risk of 10-year mortality across all diseases, with a decrease of:

45% for neurodegenerative disease
39% for respiratory disease
30% for diabetes

Prof Piet van den Brandt, who led the study, published in the International Journal of Epidemiology, said: "It was remarkable that substantially lower mortality was already observed at consumption levels of 15g of nuts or peanuts on average per day."

The researchers had taken into account the mitigating factor that nut consumers ate more fruit and vegetables and that women who ate nuts were often leaner, and adjusted the results accordingly, Prof Van den Brandt told the BBC.

http://www.eurekalert.org/pub_releases/2015-06/varc-lsd061115.php

Lab study: Daily aspirin could block growth of breast, other cancers

Drug appears to affect cancer stem cells

"Take two aspirin and call me in the morning" has been the punchline for countless jokes. Could it also be good advice for cancer patients?

A lab study to appear in the July 2015 issue of Laboratory Investigation found that a daily dose of aspirin was effective at blocking breast tumor growth. Previous studies have already shown a similar effect on colon, gastrointestinal, prostate, and other cancers.

The trick, says Dr. Sushanta Banerjee, research director of the Cancer Research Unit at the Kansas City (Mo.) Veterans Affairs Medical Center, is to ensure conditions around cancer stem cells aren't conducive for reproduction, something aspirin seems able to do.

"In cancer, when you treat the patient, initially the tumor will hopefully shrink," says Banerjee. "The problem comes 5 or 10 years down the road when the disease relapses." Cancer has stem cells, or residual cells. These cells have already survived chemotherapy or other cancer treatment and they go dormant until conditions in the body are more favorable for them to again reproduce.

"When they reappear they can be very aggressive, nasty tumors," he says.

To test his theory that aspirin could alter the molecular signature in breast cancer cells enough that they wouldn't spread, Banerjee, also a professor at the University of Kansas Medical Center, used both incubated cells and mouse models.

For the cell test, breast cancer cells were placed in 96 separate plates and then incubated. Just over half the cultures were exposed to differing doses of acetylsalicylic acid, commonly known as aspirin.

According to Banerjee, exposure to aspirin dramatically increased the rate of cell death in the test. For those cells that did not die off, many were left unable to grow.

The second part of his study involved studying 20 mice with aggressive tumors. For 15 days, half the mice were given the human equivalent of 75 milligrams of aspirin per day, which is considered a low dose. At the end of the study period, the tumors were weighed. Mice that received aspirin had tumors that were, on average, 47 percent smaller.

To show that aspirin could also prevent cancer, the researchers gave an additional group of mice aspirin for 10 days before exposing them to cancer cells.

After 15 days, those mice had significantly less cancerous growth than the control group.

"We found aspirin caused these residual cancer cells to lose their self-renewal properties," says Banerjee.

"Basically, they couldn't grow or reproduce. So there are two parts here. We could give aspirin after chemotherapy to prevent relapse and keep the pressure on, which we saw was effective in both the laboratory and the mouse model, and we could use it preventatively."

Experts suggest patients consult with a doctor before starting a daily aspirin regimen. The drug is known to thin the blood and increase the risk of gastrointestinal bleeding.

"Of course there is a risk," says Banerjee, "but you have to weigh that against the risks of cancer. It's true this is relatively new and we don't know all the side effects yet, but this was a very low dose."

Nevertheless, Banerjee is taking his own medicine. For three years he has been on a daily aspirin regimen with, he says, no ill effects. Each person, he stresses, should of course check with his or her own health care provider before doing the same.

http://www.eurekalert.org/pub_releases/2015-06/aaft-gsd060815.php

Genetic switch determines egg or sperm

Fox13 gene appears to be the switch that determines germ cell sex

This news release is available in Japanese.

New experiments in the Japanese rice fish show that the fox13 gene appears to be the switch that determines whether a germ cell becomes an egg or sperm cell. The finding could help researchers learn more about how the sexual fate of germ cells is determined during vertebrate development. Toshiya Nishimura and colleagues demonstrated that fox13, which is expressed in germ cells but not in the surrounding cells of the fish's reproductive organs, provides a molecular cue that prevents the start of sperm formation. When the researchers disrupted fox13 in adult fish with two X chromosomes (the female state), sperm formed in the female ovary. These sperm were functional and could fertilize eggs normally. The results indicate that germ cells in these fish -- and potentially other vertebrates -- do not need to be in the environment of the male reproductive organ to begin their switch into sperm.

Article #28: "foxl3 is a germ cell-intrinsic factor involved in sperm-egg fate decision in medaka," by T. Nishimura; Y. Yamamoto; I. Watakabe; S. Kobayashi; M. Tanaka at National Institute for Basic Biology in Okazaki, Japan; T. Nishimura; S. Kobayashi; M. Tanaka at The Graduate University for Advanced Studies (SOKENDAI) in Okazaki, Japan; T. Sato; Y. Ohkawa; M. Suyama at Kyushu University in Fukuoka, Japan; T. Sato; Y. Ohkawa; M. Suyama at Japan Science and Technology Agency in Fukuoka, Japan.

http://www.eurekalert.org/pub_releases/2015-06/cwru-ndt060915.php

New drug triggers tissue regeneration: Faster regrowth and healing of damaged tissues

Research focuses on select tissues injured through disease, surgery and transplants, but early findings indicate potential for broad applications

The concept sounds like the stuff of science fiction: take a pill, and suddenly new tissues grow to replace damaged ones.

Researchers at Case Western Reserve and UT Southwestern Medical Center this week announced that they have taken significant steps toward turning this once-improbable idea into a vivid reality. In a study published in the June 12 edition of Science, they detail how a new drug repaired damage to the colon, liver and bone marrow in animal models -- even going so far as to save the lives of mice who otherwise would have died in a bone marrow transplantation model.

"We are very excited," said Sanford Markowitz, MD, PhD, the Ingalls Professor of Cancer Genetics at the university's School of Medicine and a medical oncologist at University Hospitals Case Medical Center's Seidman Cancer Center. "We have developed a drug that acts like a vitamin for tissue stem cells, stimulating their ability to repair tissues more quickly. The drug heals damage in multiple tissues, which suggests to us that it may have applications in treating many diseases."

The institutions collaborating on this work next hope to develop the drug -- now known as "SW033291" -- for use in human patients. Because of the areas of initial success, they first would focus on individuals who are receiving bone marrow transplants, individuals with ulcerative colitis, and individuals having liver surgery. The goal for each is the same: to increase dramatically the chances of a more rapid and successful recovery.

The key to the drug's potential involves a molecule the body produces that is known as prostaglandin E2, or PGE2. It is well established that PGE2 supports proliferation of many types of tissue stem cells. Markowitz and University of Kentucky Professor Hsin-Hsiung Tai earlier had demonstrated that a gene product found in all humans, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), degrades and reduces the amount of PGE2 in the body.

Markowitz, also a Harrington Discovery Institute Scholar-Innovator, and James K.V. Willson, MD, a former Case Western Reserve colleague now at UT-Southwestern, hypothesized that inhibiting 15-PGDH would increase PGE2 in tissues. In so doing, it would promote and speed tissue healing. When experiments on mice genetically engineered to lack 15-PGDH proved them correct, the pair began searching for a way to inactivate 15-PGDH on a short-term basis.

The preliminary work began in test tubes. Yongyou Zhang, PhD, a Case Western Reserve research associate in Markowitz's lab and a lead author on the study, developed a test where cells glowed when 15-PGDH levels changed. Zhang then traveled to UT Southwestern's Harold C. Simmons Comprehensive Cancer Center, where Willson serves as director. Zhang and UT Southwestern researchers Bruce Posner, PhD, and Joseph Ready, PhD, collaborated to comb through the center's library of 230,000 different chemicals. Ultimately they identified one chemical that they found inactivated 15-PGDH.

"The chemical, SW033291, acts in an incredibly potent way," Markowitz said. "It can inactivate 15-PGDH when added at one part in 10 billion into a reaction mixture, which means it has promise to work as a drug."

A series of experiments showed that SW033291 could inactivate 15-PGDH in a test tube and inside a cell, and, most importantly, when injected into animal models. The third finding came through collaboration between Markowitz and Stanton L. Gerson, MD, director of the Case Comprehensive Cancer Center, UH Seidman Cancer Center, and the National Center for Regenerative Medicine, as well as the Asa and Patricia Shiverick-Jane Shiverick (Tripp) Professor of Hematological Oncology.

Case Western Reserve research associate Amar Desai, PhD, worked between the Markowitz and Gerson laboratories to determine the effect of SW033291 on mice that had received lethal doses of radiation and then received a partial bone marrow transplant. Without SW033291, the animals died. With it, they recovered.

From there, more detailed studies showed that mice given SW033291 recovered normal blood counts six days faster than mice that were transplanted without receiving SW033291. In addition, SW033291-treated mice showed faster recovery of neutrophils, platelets and red blood cells. Neutrophils battle infection, platelets prevent bleeding, and red blood cells deliver oxygen throughout the body. In addition, Desai's work showed that when SW033291 increases PGE2 in bone marrow, the body also begins to produce other materials that bone marrow stem cells need to survive. Finally, these benefits emerged without any adverse side effects, even at SW033291 doses much higher than would be required for 15-PGDH inhibition.

When investigators treated mice with other diseases, the SW033291 drug again accelerated tissue recovery. For example, the investigators teamed with Fabio Cominelli, MD, PhD, a Case Western Reserve Professor and Chief of the Division of Gastroenterology and Liver Disease, to study a mouse model of ulcerative colitis. SW033291 healed virtually all the ulcers in the animals' colons and prevented colitis symptoms. In mice where two-thirds of their livers had been removed surgically, SW033291 accelerated regrowth of new liver nearly twice as fast as normally happens without medication.

Because bone marrow, colon, and liver are significantly different tissues, the investigators believe the pathway by which SW033291 speeds tissue regeneration is likely to work as well for treating diseases of many other tissues of the body. However, the next stages of the research will concentrate on three diseases where SW033291 already shows promise to provide dramatic improvement.

In bone marrow transplants, for example, effects of SW033291 in accelerating tissue growth would provide the body the cells required to fight off the two most common and sometimes fatal complications, infection and bleeding. For those suffering the debilitating impact of colitis, accelerating tissue growth could heal colon ulcers more quickly, which in turn could allow patients to take lower dosages of other medications that treat colitis -- some of which have serious side effects. Finally, the promise of tissue growth could increase survival rates for patients with liver cancer; in some cases today, physicians are unable to perform surgery because the amount of the liver to be removed would be so great as to pose severe risk to the patient. But having a drug to accelerate the liver's regrowth could make surgery a viable option.

The team's next step will be to complete studies showing safety of SW033291-related compounds in larger animals, a required part of the pathway to secure approval from the U.S. Food and Drug Administration for trials in humans. If the drugs prove safe and effective in those clinical trials, they could then become available for general use by physicians. Investigators hope to partner with pharmaceutical companies to be able to start human trials within three years.

"These are thrilling times for us as researchers, and it is also an exciting time for Case Western Reserve," Markowitz said. "In Cleveland, there has been a major effort in the last two to three years to figure out how all our institutions can together work to develop drugs. This discovery is really something we should celebrate. It helps put us on the map as a place where new drugs get invented."

Markowitz added that this research received crucial financial assistance from Case Western Reserve University School of Medicine's Council to Advance Human Health (CAHH), from the Harrington Discovery Institute at University Hospitals, and from multiple National Institutes of Health grants that included the Case GI SPORE, led by Markowitz, and the National Center for Accelerating Innovation at the Cleveland Clinic. Additional support was received from the Marguerite Wilson Foundation; the Welch Foundation; the Cancer Prevention & Research Institute of Texas; Inje University; and the Korean National Research Foundation. Generous major gifts also came from the Leonard and Joan Horvitz Foundation and the Richard Horvitz and Erica Hartman-Horvitz Foundation.

Markowitz said the authors' contributions to this research are truly a tribute to the powers of collaboration. Senior authors Hsin-Hsiung Tai, Stanton L. Gerson, Joseph M. Ready, Bruce Posner, James K.V. Willson and Markowitz provided substantial leadership. Markowitz and Willson, former director of the Case Comprehensive Cancer Center and now director of the Simmons Cancer Center at UT Southwestern, initiated the project to study the potential of inhibiting 15-PGDH as a tissue-healing treatment strategy. Tai, at the University of Kentucky, Lexington, originally discovered 15-PGDH and tested SW033291 as a 15-PGDH inhibitor. Gerson and Markowitz partnered to show the SW033291 drug is effective for regenerating bone marrow in mice. Ready, a UT Southwestern chemist, synthesized SW033291 for the studies and has made multiple other highly promising derivatives of the compound. Posner, also a chemist from UT Southwestern, oversaw the search through the 230,000 compounds in the UT Southwestern chemical library.

Lead authors Yongyou Zhang, Amar Desai, Sung Yeun Yang, Ki Beom Bae, Monika I. Antczak, Stephen P. Fink and Shruiti Tiwari contributed equally to the scientific investigation. Zhang, Case Western Reserve, led the experiments that identified the drug. Desai, Case Western Reserve, performed experiments that

showed that SW033291 works in bone marrow transplantation in mice. Yang and Bae, now at Inje University in Korea, worked in the Markowitz laboratory on studies of colitis (Yang) and on liver regrowth after surgery (Bae). Antczak worked in the Ready lab at UT Southwestern on the chemical synthesis of SW033291. Fink and Tiwari, both of Case Western Reserve, completed the work on the colitis mouse model.

Markowitz also cited important collaboration of two Case Western Reserve participating authors -- gastroenterologist Fabio Cominelli, who played a role in the success of the colitis experiments in mice, and Mark Chance, who contributed proteomics expertise for studies that showed how SW033291 works. Other participating investigators also contributed substantially: Joseph E. Willis, Dawn M. Dawson, David Wald, Wei-Dong Chen, Zhenghe Wang, Lakshmi Kasturi, Gretchen A. Larusch, Lucy He, Luca Di Martino, Juan Sanabria, Chris Dealwis, and Debra Mikkola, all of Case Western Reserve; Zora Djuric, University of Michigan, Ann Arbor; Ginger L. Milne, Vanderbilt University, Nashville; and Noelle S. Williams, Jacinth Naidoo, and Shuguang Wei, all at UT-Southwestern, Dallas.

"An impressive number of individuals contributed to the discovery of this 15-PGDH inhibitor drug," Markowitz said. "Each one of them has done something absolutely remarkable and indispensable to the success of the study."

http://www.eurekalert.org/pub_releases/2015-06/uoh-ldo061115.php

Large doses of antioxidants may be harmful to neuronal stem cells

Stem cells are especially sensitive to oxygen radicals and antioxidants

Stem cells are especially sensitive to oxygen radicals and antioxidants shows new research from the group of Anu Wartiovaara in the Molecular Neurology Research Program of University of Helsinki. The research led by researcher Riikka Martikainen was published in Cell Reports -journal May 28th 2015.

Mitochondria are cellular power plants that use oxygen to produce energy. As a by-product they produce reactive oxygen. Excessive oxygen radicals may cause damage to cells but they are needed in small quantities as important cellular signaling molecules. One of their main functions is to control function of stem cells. Antioxidants are widely used to block the damage caused by reactive oxygen. To enhance their effect some new antioxidants are targeted to accumulate into mitochondria.

The current research showed that a small increase in oxygen radicals did not directly lead to cellular damage but disrupted intracellular signaling in stem cells and lead to decrease in their stemness properties. Treatment with antioxidants was able to improve the stemness properties in these cells. However, surprisingly, the researchers found that an antioxidant targeted to mitochondria showed dose-dependent toxic effects especially on neural stem cells.

The use of antioxidants as dietary supplements is common, but little is known of their effects on stem cells. This new research shows that large doses of antioxidants may be harmful to neural stem cells. Additional research on stem cells should be done to assess safety of mitochondria targeted antioxidants.

Article: Hämäläinen RH, Ahlqvist KJ, Ellonen P, Lepistö M, Logan A, Otonkoski T, Murphy MP, Suomalainen A. MtDNA Mutagenesis Disrupts Pluripotent Stem Cell Function by Altering Redox Signaling. Cell Reports 2015

http://www.eurekalert.org/pub_releases/2015-06/ki-sid061115.php

Swift intervention doubles survival rate from cardiac arrest

A team of Swedish researchers finds that early cardiopulmonary resuscitation more than doubles the chance of survival for patients suffering out-of-hospital cardiac arrest.

The percentage of patients who receive life-saving resuscitation has also increased substantially thanks to so-called SMS Lifesavers. These results are published simultaneously in two studies in the highly reputed New England Journal of Medicine.

The two studies were conducted by researchers at the Center for Resuscitation Science at Karolinska Institutet and Södersjukhuset (Stockholm South General Hospital) in collaboration with University of Borås, Danderyd Hospital and Sahlgrenska Academy, all in Sweden.

"Both these studies clearly show that cardiopulmonary resuscitation is an effective, life-saving treatment, and that further encouragement must be given to respond swiftly on suspected cardiac arrest," says Dr Jacob Hollenberg, Cardiologist and Head of Research at the Center for Resuscitation Science.

In one of the two articles, the researchers have analysed over 30,000 cases of out-of-hospital cardiac arrest in Sweden. The results show that cardiopulmonary resuscitation performed before the arrival of the ambulance is associated with over a two-fold increase in the chance of survival. This powerful effect is independent of age, sex, place, cause, ECG pattern, and time period. According to the researchers, this study unique in several ways. Aside from its main results, is the number of cases analysed, the fact that data is reproducible for three decades and that the material was subjected to thorough correction for sources of error and bias.

In the other article, the researchers have evaluated a new method of dispatching CPR trained volunteers, known as SMS Lifesavers to cardiac arrests. Their results show that these volunteers have caused a 30 % increase in the number of patients who receive cardiopulmonary resuscitation before the arrival of paramedics, the

rescue services or the police. The study involved 10,000 civilian volunteers in Stockholm County who were alerted by mobile phone text message to the cardiac arrest in order to administer cardiopulmonary resuscitation if they were within a range of 500 metres.

"Traditional methods such as mass public training, which are now used throughout the world, are important but have not shown any evidence of a similar increase," says Dr Hollenberg. "The new mobile phone text-message alert system shows convincingly that new technology can be used to ensure that more people receive life-saving treatment as they wait for an ambulance."

This research was financed by grants from the Heart-Lung Foundation, Stockholm County Council, the Swedish Association of Local Authorities and Regions and the Laerdal Foundation for Acute Medicine in Norway.

Facts about cardiac arrest:

About 10,000 Swedes suffer out-of-hospital cardiac arrest every year. In the USA, more than 300 000 persons suffer out-of-hospital cardiac arrest each year.

Only 1 in 10 victims survive.

Cardiac arrest is often caused by acute myocardial infarction.

The delay between onset and treatment in the form of cardiopulmonary resuscitation and defibrillation is decisive for survival.

More than 3 Million Swedes (out of a population of 10 Million inhabitants) have been trained in CPR

More about Swedish SMS Lifesavers: http://www.SMSlivraddare.se/english

Publications:

'Early Cardiopulmonary Resuscitation in Out-of-Hospital Cardiac Arrest', Ingela Hasselqvist-Ax, Gabriel Riva, Johan Herlitz, Marten Rosenqvist, Jacob Hollenberg, Per Nordberg, Mattias Ringh, Martin Jonsson, Christer Axelsson, Jonny Lindqvist, Thomas Karlsson, and Leif Svensson, NEJM 2015; 372:2307-15, online 11 June 2015.

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http://www.bbc.com/news/world-africa-33103294

First penile transplant recipient 'to become father'

The South African recipient of the world's first penile transplant is to become a father, a surgeon who performed the operation has told the BBC.

His girlfriend has reported that she is about four months pregnant, and this showed that the "transplant worked", said Andre van der Merwe. The 21-year-old recipient, whose identify is being protected, lost his penis in a botched circumcision.

The operation took place in December. Surgeons at Stellenbosch University and Tygerberg Hospital performed a nine-hour operation to attach a donated penis. Dr Van der Merwe said he was "very pleased" when he heard that the man's girlfriend was pregnant, and had not asked for a paternity test as there was no reason not to believe the couple.

Further transplants

"This is what we intended, that he should be able to stand up and be able to urinate and have intercourse, so it is a milestone for him," Dr Van der Merwe told the BBC. He had not expected the man to be infertile, as he had an issue with his penis, not his testicles, the surgeon added.

Dr Van der Merwe said the surgical team is yet to review the success of the operation, and may then carry out further transplants.

The boy had been left with just 1cm of his original penis as a result of the botched circumcision. He was 18 and sexually active at the time. When attaching the donated penis, the surgical team used some of the techniques that had been developed to perform the first face transplants in order to connect the tiny blood vessels and nerves.

There have been attempts at penis transplants before, including one in China. Accounts suggested the operation went well, but the penis was later rejected.

Doctors say South Africa has some of the greatest need for penis transplants in the world. Dozens, some say hundreds, of boys are maimed or die each year during traditional initiation ceremonies.

http://www.bbc.com/news/health-33095945

Deadly dish: the dinner that can give you cancer

A local delicacy in north-east Thailand, made from raw fish, has been found to be behind a high incidence of liver cancer in the area, and doctors are trying to educate people about the risk.

By Jonathan Head South East Asia correspondent

The Isaan plateau of north-eastern Thailand is poor, dry, and far from the sea. Home to around one third of the country's population, most of them ethnic Lao in origin, it is renowned for its spicy and inventive cuisine, using whatever ingredients are available.

Where there are rivers or lakes, they use the smaller fish they catch in a pungent dish called koi plaa. The fish are chopped up finely, and mixed by hand with local herbs, lime juice and live red ants, and served up raw. It is very popular, but also dangerous.

For decades, certain populations in the north-east have been known to have abnormally high levels of liver cancer. In men it comprises more than half of all cancer cases, compared to an average of less than 10% worldwide. The high prevalence has long been linked to infection by liver flukes, a kind of parasite, found in raw fish.

But it is only in the last decade that a serious effort has been made to get people to change their eating habits, by cooking koi plaa to kill the flukes before they eat it.

Fluke infestation

Liver fluke eggs are excreted into the water system by infected people.

Dr. Banchob Sripa at the Tropical Disease Research Laboratory in Khon Kaen University is the man largely responsible for this effort. "We have been studying this link in our labs for over 30 years", he said. "We found that the liver fluke can make a chemical that stimulates a host immune response - inflammation - and after many years, this becomes chronic inflammation, which then becomes cancer."

His team found that in some communities up to 80% of people were infected by the fluke, some as young as four years-old, but that the cancer rarely developed before people reached 50. Once it does, though, there is little hope for patients.

At the university hospital they receive around 2,000 patients a year with a specific form of liver cancer called cholangiocarcinoma. Only around 200 of those can be treated, usually by surgery, cutting out the tumour from the liver. The others are given palliative care, easing their discomfort, usually by draining bile ducts, until they die.

The only effective remedy is prevention. So Dr. Banchob and his team are running a community-based health education programme in the villages along the great wetland, known as Lawa Lake, south of Khon Kaen, where liver fluke infection rates are highest.

Changing perceptions

They started by using the most effective methods for this region; recruiting respected community leaders to do most of the talking, and injecting plenty of north-eastern music and humour, which can be as pungent as the local cooking.

They have composed songs that press home easily understood information about the life-cycle of the fluke.

The larvae, embedded in the fish's flesh, are consumed and grow into an adult flukes inside the liver. The eggs are then excreted, passing back into the water system where they are eaten by a particular snail, before the larvae move back to the fish again. They also take a portable ultrasound machine around the villages to screen people for liver fluke infection.

It is striking how many older people have high levels, indicating that they still eat their koi plaa raw. "Sometimes I cook it, but sometimes I forget," said 61-year-old Jongluck Laonongkwa after his screening. His liver was infested with flukes.

Although liver fluke infestation can start young, liver cancer usually appears in later life.

"I think 60% do understand the causes of the liver cancer" said Dr. Banchob, "they are aware of the liver fluke. "But 10% are still eating raw fish. I believe that 10% probably cannot change. So we should change the environment, make the fish cleaner, to get fewer infections."

Part of the education campaign focuses on getting people to use proper toilets, and not defecate in the lake, which reduces the number of fluke eggs. In the villages where the campaign has been running, infection rates are coming down sharply, to below 10% in some. It will take more time for liver cancer rates to fall significantly, but the attitude of younger people is encouraging.

Kamphan Sapsombat, 71, is being treated in hospital for an inoperable tumour. He is jaundiced, with yellow eyes which is a clear sign of a blocked bile duct.

His daughter, Rattana, said her father had eaten raw fish all his life. But the rest of her family had stopped it years ago, she said. They understood all too well that the risk of ending up like her father was not worth it.

http://www.bbc.com/news/world-asia-33125659

South Korea hospital 'is source of many Mers cases'

A hospital has suspended most of its services after being identified as the source of almost half the cases in the South Korean outbreak of Middle East Respiratory Syndrome (Mers).

The president of the Samsung Medical Center in the capital Seoul issued a public apology on Sunday. Health officials have reported seven new cases bringing the total to 145. Fifteen people are known to have died. Meanwhile, a South Korean man in Slovakia is being tested for the virus. The man reportedly works for a subcontractor of South Korean car maker Kia.

Visitors banned

Samsung Medical Center president Song Jae-hoon told reporters that the hospital would stop treating outpatients and admitting new patients to prevent further infections among patients and medical staff. He said no visitors would be allowed, and non-urgent surgery was being stopped. "We apologise for causing great concern as Samsung Medical Center became the centre of the spread of Mers," he said.

"This is entirely our responsibility and failing, as we did not properly manage emergency-room staff." Mr Song said he would review the suspension on services on 24 June.

More than 70 cases have been traced back to the hospital, authorities say. Among them was an emergency ward orderly who worked for days after developing symptoms and came into contact with more than 200 people, officials said.

It is believed the orderly picked up the virus from an infected person who waited for days in various parts of the emergency ward, potentially exposing the virus to

an estimated 900 staff, patients and visitors. South Korea reported seven new cases on Sunday and the 15th victim died in the city of Busan.

The World Health Organization (WHO) has warned that the outbreak is "large and complex" with further cases expected, although it does not expect the outbreak to spread among the wider community. The outbreak is the largest outside Saudi Arabia, where the disease was first identified in humans in 2012.

Middle East Respiratory Syndrome (Mers)

Mers is caused by a coronavirus, a type of virus which includes the common cold and Sars (severe acute respiratory syndrome).

First cases emerged in the Middle East in 2012, and the first death in Saudi Arabia in June that year.

It is not known for certain how it is transmitted. It is possible the virus is spread in droplets when an infected person coughs or sneezes.

Patients have a fever, cough and breathing difficulties, but Mers can also cause pneumonia and kidney failure.

Approximately 36% of reported patients with Mers have died - there is no vaccine or specific treatment.

http://bbc.in/1dEIkF4

Philae comet lander wakes up, says European Space Agency

The European Space Agency (Esa) says its comet lander, Philae, has woken up and contacted Earth.

Philae, the first spacecraft to land on a comet, was dropped on to the surface of Comet 67P by its mothership, Rosetta, last November. It worked for 60 hours before its solar-powered battery ran flat.

The comet has since moved nearer to the Sun and Philae has enough power to work again, says the BBC's science correspondent Jonathan Amos. An account linked to the probe tweeted the message, "Hello Earth! Can you hear me?"

On its blog, Esa said Philae had contacted Earth, via Rosetta, for 85 seconds on Saturday in the first contact since going into hibernation in November. "Philae is doing very well. It has an operating temperature of -35C and has 24 watts available," said Philae project manager Stephan Ulamec. Scientists say they now waiting for the next contact.

ESA scientist Mark McCaughrean told the BBC: "It's been a long seven months, and to be quite honest we weren't sure it would happen - there are a lot of very happy people around Europe at the moment."

Philae was carrying large amounts of data that scientists hoped to download once they made contact again, he said. "I think we're optimistic now that it's awake that we'll have several months of scientific data to pore over," he added.

This is one of the most astonishing moments in space exploration and the grins on the faces of the scientists and engineers are totally justified, says BBC science editor David Shukman. For the first time, we will have a hitchhiker riding on a comet and describing what happens to a comet as it heats up on its journey through space, he adds.

Analysis: Jonathan Amos, BBC science correspondent

When Philae first sent back images of its landing location, researchers could see it was in a dark ditch. The Sun was obscured by a high wall, limiting the amount of light that could reach the robot's solar panels.

Scientists knew they only had a limited amount of time - about 60 hours - to gather data before the robot's battery ran flat.

But the calculations also indicated that Philae's mission might not be over for good when the juice did eventually run dry. The comet is currently moving in towards the Sun, and the intensity of light falling on Philae, engineers suggested, could be sufficient in time to re-boot the machine.

And so it has proved. There is some relief also, because the very low temperatures endured by the lander in recent months could have done irreparable damage to some of the circuitry.

The fact that both the computer and transmitter have fired up indicate that the engineering has stood up remarkably well to what must have been really quite extreme conditions. Scientists must now hope they can get enough power into Philae to carry out a full range of experiments.

One ambition not fulfilled before the robot went to sleep was to try to drill into the comet, to examine its chemical make-up. One attempt was made last year, and it failed. A second attempt will now become a priority.

Philae is designed to analyse the ice and rocky fragments that make up the comet.

The Rosetta probe took 10 years to reach 67P, and the lander - about the size of a washing-machine - bounced at least a kilometre when it touched down.

Before it lost power, Philae sent back images of its surroundings that showed it was in a dark location with high walls blocking sunlight from reaching its solar panels. Its exact location on the duck-shaped comet has since been a mystery.

Esa had a good idea of where it was likely to be, down to a few tens of metres, but could not get Rosetta close enough to the comet to acquire conclusive pictures.

Continued radio contact should now allow precise coordinates to be determined, correspondents say.

Comet 67P is currently 205 million km (127 million miles) from the Sun, and getting closer. It is due in August to get as close as 186 million km, before then sweeping back out into the outer Solar System.

As it nears the sun, the comet will warm and its ices will melt. This process will throw out a huge shroud of gas and dust, and if Philae can continue to keep working it will provide scientists with an extraordinary view of what is happening right at the surface of 67P.

http://www.bbc.com/news/science-environment-33127357

Philae comet lander: The plucky robot is back

When Philae first sent back images of its landing location on Comet 67P, researchers could see it was in a dark ditch.

By Jonathan Amos BBC Science Correspondent

The Sun was obscured by a high wall, limiting the amount of light that could reach the robot's solar panels.

Scientists knew they only had a short amount of time - about 60 hours - to gather data before the lander's battery ran flat.

But the calculations also indicated that Philae's mission might not be over for good when the voltages did eventually flat-line.

67P is currently moving in towards the Sun, and engineers suggested that the intensity of light falling on Philae could be sufficient in time to re-boot the machine. And so it has proved.

The plucky robot that enthralled the world is back.

The sense of relief in the mission team must be immense. Many people had worried that the very low temperatures endured by the lander on the icy comet could have done irreparable damage to its electronic circuitry.

The fact that both its computer and transmitter have fired up to contact home indicates that the engineering has stood up remarkably well in what must have been really quite challenging conditions these past seven months.

Scientists must now hope they can get enough power into Philae to carry out the full range of experiments.

One ambition not fulfilled before the robot went to sleep in November was to try to drill into 67P, to examine its chemical make-up.

Philae is designed to analyse the ice and rocky fragments on the comet

An attempt was made last year, but it did not appear to work. Either the tool picked up nothing, or for some reason the gathered sample did not make it into the on-board laboratories.

Either way, a second bid to drill the surface will now become a priority.

But some experiments will be more power-hungry than others, and drilling is one of these.

Engineers must establish what they can, and cannot, accomplish with the revitalised Philae.

The robot could yet turn out to be one of the biggest good-luck stories in the history of space exploration.

Had Philae landed precisely where it was targeted back in November, it would have been sitting on an open plain. Solar generation conditions would have been perfect from the outset.

But even if it had succeeded, death would have come relatively soon. Indeed, the pre-landing analysis was that Philae would succumb to overheating on the plain after perhaps a couple of months.

As it was, the robot bounced into its shaded ditch and went into hibernation. And that long slumber means it has now come back to life at a far more interesting time on Comet 67P - just as it nears perihelion, the closest point to the Sun.

If you had to pick a time to have a robot on the surface, it would be right now. 67P's ices are being energised, and are throwing huge jets of gas and dust into space.

A fully recovered Philae promises a scientific extravaganza beyond what anyone dared believe was possible when it first touched down.