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How fasting helps fight fatty liver disease

Upon fasting a certain protein is produced that adjusts the metabolism in the liver

Neuherberg, Germany - Scientists at Helmholtz Zentrum München have new information on what happens at the molecular level when we go hungry. Working with the Deutsches Zentrum für Diabetesforschung (German Center for Diabetes Research - DZD) and the Deutsches Krebsforschungszentrum (German Cancer Research Center - DKFZ) they were able to show that upon deprivation of food a certain protein is produced that adjusts the metabolism in the liver. The results are published in the Open Access Journal EMBO Molecular Medicine.

The growing number of overweight people has long been one of modern society's pressing issues. In particular the resulting metabolic diseases such as type 2 diabetes and corresponding secondary conditions can have serious consequences for health. A reduced intake of calories, such as in the framework of an intermittent fasting diet, can help to whip the metabolism back into shape - but why does this happen?

This is the question that Prof. Dr. Stephan Herzig, Director of the Institute for Diabetes and Cancer (IDC) at the Helmholtz Zentrum München, and Dr. Adam J. Rose, head of the 'Protein metabolism in health and disease' research group at the DKFZ in Heidelberg, wanted to answer. "Once we understand how fasting influences our metabolism we can attempt to bring about this effect therapeutically," Herzig states.

Stress molecule reduces the absorption of fatty acids in the liver

In the current study, the scientists looked for liver cell genetic activity differences that were caused by fasting. With the help of so-called transcript arrays, they were able to show that especially the gene for the protein GADD45β was often read differently depending on the diet: the greater the hunger, the more frequently the cells produced the molecule, whose name stands for 'Growth Arrest and DNA Damage-inducible'. As the name says, the molecule was previously associated with the repair of damage to the genetic information and the cell cycle, rather than with metabolic biology.

Subsequent simulation tests showed that GADD45β is responsible for controlling the absorption of fatty acids in the liver. Mice who lacked the corresponding gene were more likely to develop fatty liver disease. However when the protein was restored, the fat content of the liver normalized and also sugar metabolism improved. The scientists were able to confirm the result also in humans: a low GADD45β level was accompanied by increased fat accumulation in the liver and an elevated blood sugar level.

"The stress on the liver cells caused by fasting consequently appears to stimulate GADD45β production, which then adjusts the metabolism to the low food intake," Herzig summarizes. The researchers now want to use the new findings for therapeutic intervention in the fat and sugar metabolism so that the positive effects of food deprivation might be translated for treatment.

Background: Researchers at the Deutsches Institut für Ernährungsforschung in Potsdam-Rehbrücke (German Institute of Human Nutrition - DIfE), also a DZD member, already made similar observations a year ago. They also succeeded in detecting a change in the liver's fat content and a reduction in particularly the quantity of those fats suspected of promoting insulin resistance. They attributed this to a modified composition of the protein molecules bound to the fat droplets. Improved energy metabolism was also observed as a result of the fasting. Further examinations are necessary, however, in order to further explain this molecular correlation. This was the starting point of the current study by Prof. Herzig's team.

Original publication: Fuhrmeister, J. et al. (2016). Fasting-induced liver GADD45β restrains hepatic fatty acid uptake and improves metabolic health, EMBO Molecular Medicine, DOI: 10.15252/emmm.201505801

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Human nature: Behavioral economists create model of our desire to make sense of it all

'We are 'informavores' as much as we are omnivores,' CMU's George Loewenstein says

Researchers have identified a powerful human motive that has not been adequately appreciated by social and behavioral scientists: the drive to make sense of our lives and the world around us. Published in the Journal of Economic Behavior & Organization, Carnegie Mellon University's George Loewenstein and Warwick Business School's Nick Chater developed a theoretical model of the drive for sense-making and how it is traded off against other goals.

They show that the drive for sense-making can help to make sense of a wide range of disparate phenomena, including curiosity, boredom, confirmation bias and information avoidance, esthetics (in both art and science), caring about other's beliefs, the importance of narrative and the role of "the good life" in decision-making.

"The mind is a sense-making machine; we are informavores as much as we are omnivores," said Loewenstein, the Herbert A. Simon University Professor of Economics and Psychology in the Dietrich College of Humanities and Social Sciences.

Most drives are extensions of autonomous internal processes. For example, when our body temperature drops, without any conscious planning our bodies work to keep us warm: we shiver, get goose bumps, and blood flow to our extremities is reduced. But autonomous processes are not always sufficient; sometimes our

conscious mind needs to take control. The conscious experience of feeling cold, and the conscious "drive" to warm ourselves, prompt us to put on a sweater, or turn up the thermostat.

In the same way that it regulates our internal temperature, our brain is constantly, and autonomously, engaged in sense-making and simplification, distilling sensory inputs to make it possible for us to make sense of our environment and our lives.

In some situations, however, internal processes are not up to the task; our conscious mind needs to be recruited to help us make sense of the world around us. We feel conscious drives, such as curiosity that can motivate us to seek out more information (whether by scrutinizing an old photo, searching the Internet or conducting a scientific experiment). Our drive for sense-making, like our drives to avoid cold and hunger, can intrude on, and direct, our conscious attention.

The sense-making drive also helps to explain the appeal of religion as well as conspiracy theories, although these two forms of explanation satisfy the drive in different ways. Religion provides simple answers, like "God decides everything," to daunting questions, but simple answers fail to predict specific facts, experiences or events. Conspiracy theories, by contrast, aim to explain a plethora of specific facts by using explanations that are generally complicated and convoluted.

"We make a particular sense of our lives and of our world that allows us to process and retain information and to decide what to do," said Chater, professor of behavioural science at Warwick Business School. "Our drive for sense-making can make us hostile to alternative points of view that might suggest that our world, and even our lives, makes less sense than we thought,"

The model has novel implications both for when people choose to obtain or avoid information, and it sheds light on phenomena, such as political polarization and emotionally charged beliefs relating to topics like the cause of autism and the reality of climate change. "There is an irony to the paper," Loewenstein added. "It is an attempt to make sense of our desire to make sense of the world."

Read "The Under-Appreciated Drive for Sense-Making" at http://www.sciencedirect.com/science/article/pii/S0167268115002838.

http://www.eurekalert.org/pub_releases/2016-05/tjnj-pel050516.php

Pesticide exposure linked to increased risk of ALS

Cumulative pesticide exposure associated with increased risk of ALS

Survey data suggest reported cumulative pesticide exposure was associated with increased risk of amyotrophic lateral sclerosis (ALS), a progressive and fatal neurodegenerative disease, according to an article published online by JAMA Neurology.

Eva L. Feldman, M.D., Ph.D., of the University of Michigan, Ann Arbor, and coauthors examined occupational exposures and environmental factors on the risk of developing ALS in Michigan. The authors evaluated assessments of environmental pollutants in the blood and detailed exposure reporting through a survey. The study recruited 156 patients with ALS and 128 control patients for comparison; 101 patients with ALS and 110 controls had complete demographic and pollutant data. Pesticide exposure was associated with increased risk of ALS in survey data and by blood measurements, according to the results.

"Finally, as environmental factors that affect the susceptibility, triggering and progression of ALS remain largely unknown, we contend future studies are needed to evaluate longitudinal trends in exposure measurements, assess newer and nonpersistent chemicals, consider pathogenic mechanisms, and assess phenotypic variations," the study conclude. To read the full study and a related editorial by Jacquelyn J. Cragg, Ph.D., of the Harvard T.H. Chan School of Public Health, Boston, please visit the For The Media website.

JAMA Neurol. Published online May 9, 2016. doi:10.1001/jamaneurol.2016.0594. Available pre-embargo to the media at http://media.jamanetwork.com.

http://www.eurekalert.org/pub_releases/2016-05/qumc-ayf050616.php

A yellow fever epidemic: A new global health emergency?

Mounting evidence that the current outbreak of yellow fever is becoming the latest global health emergency

WASHINGTON -- Evidence is mounting that the current outbreak of yellow fever is becoming the latest global health emergency, say two Georgetown University professors who call on the World Health Organization to convene an emergency committee under the International Health Regulations. In addition, with frequent emerging epidemics, they call for the creation of a "standing emergency committee" to be prepared for future health emergencies.

In their JAMA Viewpoint published online May 9, Daniel Lucey, MD, MPH, and Lawrence O. Gostin, JD, of the O'Neill Institute for National and Global Health Law at Georgetown, explain that the ongoing spread, and potential future spread, of yellow fever coupled with a limited vaccine supply should compel the WHO to "urgently convene an emergency committee to mobilize funds, coordinate an international response, and spearhead a surge in vaccine production."

An epidemic of yellow fever, first reported in January, has been spreading rapidly in Angola. As of last month, the country had 2,023 suspected yellow fever cases and 258 deaths. The Pan American Health Organization (PAHO) declared an epidemiological alert on April 22 for yellow fever in Latin America, where the Aedes aegypti mosquito vector is also actively transmitting Zika and dengue viruses.

Vaccine "supply shortages could spark a health security crisis," say the professors, pointing out that spread of yellow fever has already taken place in Kenya and the Democratic Republic of Congo, where efforts to vaccinate two million people are planned. "Acting proactively to address the evolving yellow fever epidemic is imperative," they say.

Gostin and Lucey point out that an emergency committee meeting would allow its members to advise the Director-General on the epidemic and trigger discussions about a surge in vaccine production even if a public health emergency of international concern (PHEIC) is not declared.

Finally, the professors say time has come to consider a more efficient way to manage potential public health emergencies.

"The complexities and apparent increased frequency of emerging infectious disease threats, and the catastrophic consequences of delays in the international response, make it no longer tenable to place sole responsibility and authority with the Director-General to convene currently ad hoc emergency committees," Lucey and Gostin write. Instead, they support establishing a "standing emergency committee" that would meet regularly to advise the Director-General.

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Placental RNA may help protect embryo from viruses, Penn study finds

The human placenta is an organ unlike any other. During the course of nine months it is formed by the embryo, sustains life and then is shed.

"What that means," said Montserrat Anguera, an assistant professor in the University of Pennsylvania School of Veterinary Medicine, "is it has to make very specialized cells, it has to form structures to support itself and the baby, it has to sense cues from the mom and from the environment and it has to do all of these things really, really fast."

In a new study, Anguera and colleagues have identified a long non-coding RNA, or lncRNA, that contributes to a crucial function of the placenta: protecting the unborn baby from invading pathogens. The work, published in the journal Molecular and Cellular Biology, is the first to identify a lncRNA in the placenta involved in regulating the immune response.

Further study of this and other lncRNAs could shed light on how the placenta protects against pathogens, even at the earliest stage of embryotic development. Long-term, the researchers say, it's possible that this lncRNA could even present a target for priming the placenta to resist viruses or other infectious agents. Anguera collaborated on the work with lead author Ian Penkala, Jianle Wang, Camille M. Syrett and Carolina B. López of Penn Vet and Laura Goetzl of Temple University.

Knowledge about lncRNAs is fast-evolving, and it's an area that Anguera has been part of since her time as a postdoctoral researcher. As their name suggests, lncRNAs are RNA transcripts greater than 200 nucleotides in length that do not code for proteins. Many of them are known to regulate gene expression and to do so in a rapid manner.

Other researchers have identified lncRNAs in later-term placentas involved in regulating functions such as growth, but Anguera wanted to look at the earliest stages of placental formation to see how lncRNAs might be influencing development.

Using data from an earlier paper by a Chinese group that had sequenced RNA in various stages of early human development, Anguera's team zeroed on a lncRNA called lncRHOXF1, located on the X chromosome, that was present at high levels in trophectoderm cells, from which the placenta arises, and barely detectable in the cells that give rise to the embryo. Not only was it present in trophectoderm cells, it was one of the most abundant lncRNAs in that cell type.

They then went about characterizing lncRHOXF1. Using computer models, they confirmed that it was unlikely to code for a protein and, because it had strong matches to non-human primate genomes, as well as those of elephants and dogs but not for mice, it was likely a recently evolved lncRNA.

Using an in vitro model, they found that levels of the lncRNA were highest two days after embryotic stem cells began to differentiate, the same time point at which these cells begin to express markers that distinguish them as placental precursor cells. The researchers also confirmed the presence of the molecule in various cell types, at low levels in human first-trimester placenta and placenta cell lines and at higher levels in extravillous cytotrophoblasts, or the precursors of the portion of the placenta that implants in the maternal uterus, and at the highest levels in their in vitro system, the human embryotic stem cells. The findings suggested that lncRHOXF1 appears to play an important role very early in placental development.

Next they determined where in the cell the lncRNA was expressed and were surprised to find it at high levels dispersed throughout the nucleus and the cytoplasm, suggesting it may regulate the expression of genes that are distant from it.

"It was all over the place," Anguera said. "That was a good thing for us in studying it, because if you can detect it easily it's more likely to have a robust phenotype that you're going to pick up on."

The subsequent experiments were designed to reveal what that phenotype, or function, was. Overexpressing it in undifferentiated human embryonic stem cells caused cells to grow more slowly and tend toward differentiation. When the team

looked at how gene expression was altered with overexpression of the lncRNA, they found an influence on about 150 genes, many involved in DNA synthesis, packaging and replication, as well as metabolism.

When they repressed expression of the lncRNA in their in vitro system, they again found that the expression of many genes was altered, with a noticeable emphasis on genes involved in viral and immune responses.

The findings intrigued Anguera, and Penkala, currently a V.M.D.-Ph.D. student who presented them at a Penn Vet Student Research Day. López, a virologist, was in the audience and was likewise intrigued. She and Anguera struck up a collaboration which led to the final set of investigations of this study.

In these, the researchers took cells in which lncRHOXF1 expression had been disrupted and infected them with Sendai virus. They found that cells in which the lncRNA had been blocked expressed less viral RNA, indicating a less severe infection. They also observed that lncRHOXF1 levels increased in these cells after viral infection.

"The lncRNA seems to be sensing and modulating its expression based on the virus being there," Anguera said. "People have found other examples of lncRNAs being important in regulating the innate immune response, but no one has looked in the placenta early in development."

Anguera and colleagues will be further studying this lncRNA to see if it is also responsive to different types of virus or perhaps even other types of pathogens. They would also like to gain a better understanding of how the presence of virus is translated into a message to increase levels of this lncRNA and to induce the corresponding changes in expression of genes involved in viral response.

"What we are really excited about is to pretreat or prime these placental cells by inhibiting lncRHOXF1 and see if they will be less resistant to viral infections," Anguera said. "Especially with so much current interest in Zika, it could be really interesting to see whether different viruses elicit the same type of response."

The study was supported in part by the Pennsylvania Health Research Formula Fund, the National Institute of Health and Penn's Abramson Cancer Center.

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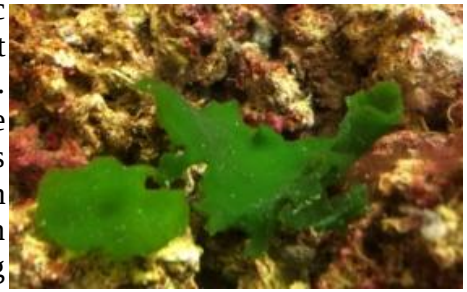
Strange Seaweed Rewrites the History of Green Plants

An ancient alga developed large size and complex structure independently of other plants

By Emma Marris, Nature magazine on May 9, 2016

A mysterious deep-ocean seaweed diverged from the rest of the green-plant family around 540 million years ago, developing a large body with a complex structure independently from all other sea or land plants. All of the seaweed's close relatives are unicellular plankton.

The finding, published today in Scientific Reports, upends conventional wisdom about the early evolution of the plant kingdom. "People have always assumed that within the green-plant lineage, all the early branches were unicellular," says Frederik Leliaert, an evolutionary biologist at Ghent University in Belgium. "It is quite surprising that among those, a macroscopic seaweed pops up."



Seaweed in the order Palmophyllales, such as the specimen shown here, live at great depth. **Suzanne Fredericq**

There are only a few described species in this odd order of sea life, known as the Palmophyllales. All live at great depth, usually more than 80 metres below the surface. Five years ago, Leliaert was one of the team that first investigated the order's genetics. But even though it looked superficially like many green algae, the seaweed turned out to be only very distantly related to any other macroscopic green algae or land plant. At this point, the scientists could do little more than show that the species was very different.

Now the researchers have mapped the strange seaweed's place in the tree of life, using a specimen dredged from the Gulf of Mexico after the 2010 Deepwater Horizon oil spill. The work became more feasible as next-generation sequencing technologies dropped the price for a detailed look at the genome of Palmophyllales' chloroplast—the energy-producing structure in a plant cell—to roughly US$8,000.

Green genes

With more genes in hand, the scientists could better compare Palmophyllales to an ever-growing collection of green algae. It also allowed the researchers to use phylogenetic software to pinpoint when Palmophyllales branched off from related plant species.

It turns out that the group diverged from the rest just after the green plants themselves split into their two main lineages, back when such plants were newfangled upstarts.

Brent Mishler, a botanist at the University of California, Berkeley, finds the new work to be convincing. "It nails down the relationships," he says. "The green plants are one of the most diverse branches on the tree of life, with a half million species that range in size from planktonic unicells to redwood trees. This paper makes a huge contribution to unravelling how this enormous and important lineage got started."

But although Palmophyllales split off early from other plants, its macroscopic size might not have developed until later in its evolution. And Leliaert says that he's wary of calling the seaweed "multicellular" because its cells are undifferentiated and suspended in a stiff gel. Still, he says, the whole plant has a distinct structure that includes a root-like holdfast, a stem, and blades. How the cells of the plant communicate with one another remains unknown.

For Charles Delwiche, a molecular systematist at the University of Maryland in College Park, and one of the principal investigators of the Assembling the Green Algal Tree of Life project that supported the work, the result shows how little is known about green algae, despite the fact that they gave rise to all land plants.

"We still need to do a lot more sampling of those lineages," says Delwiche. "I think the tree of life will become a lot more shrubby."

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Intravenous ketamine may rapidly reduce suicidal thinking in depressed patients

Repeat ketamine infusions decreased -- and for some, eliminated -- suicidal thoughts in outpatients with treatment-resistant depression

Repeat intravenous treatment with low doses of the anesthetic drug ketamine quickly reduced suicidal thoughts in a small group of patients with treatment-resistant depression. In their report receiving Online First publication in the Journal of Clinical Psychiatry, a team of Massachusetts General Hospital (MGH) investigators report the results of their study in depressed outpatients who had been experiencing suicidal thought for three months or longer.

"Our finding that low doses of ketamine, when added on to current antidepressant medications, quickly decreased suicidal thinking in depressed patients is critically important because we don't have many safe, effective, and easily available treatments for these patients," says Dawn Ionescu, MD, of the Depression Clinical and Research Program in the MGH Department of Psychiatry, lead and corresponding author of the paper. "While several previous studies have shown that ketamine quickly decreases symptoms of depression in patients with treatment-resistant depression, many of them excluded patients with current suicidal thinking."

It is well known that having suicidal thoughts increases the risk that patients will attempt suicide, and the risk for suicide attempts is 20 times higher in patients with depression than the general population. The medications currently used to treat patients with suicidal thinking -- including lithium and clozapine -- can have serious side effects, requiring careful monitoring of blood levels; and while electroconvulsive therapy also can reduce suicidal thinking, its availability is limited and it can have significant side effects, including memory loss.

Primarily used as a general anesthetic, ketamine has been shown in several studies to provide rapid relief of symptoms of depression. In addition to excluding patients who reported current suicidal thinking, many of those studies involved only a single ketamine dose. The current study was designed not only to examine the antidepressant and antisuicidal effects of repeat, low-dose ketamine infusions in depressed outpatients with suicidal thinking that persisted in spite of antidepressant treatment, but also to examine the safety of increased ketamine dosage.

The study enrolled 14 patients with moderate to severe treatment-resistant depression who had suicidal thoughts for three months or longer. After meeting with the research team three times to insure that they met study criteria and were receiving stable antidepressant treatment, participants received two weekly ketamine infusions over a three-week period. The initial dosage administered was 0.5 mg/kg over a 45 minute period -- about five times less than a typical anesthetic dose -- and after the first three doses, it was increased to 0.75 mg/kg. During the three-month follow-up phase after the ketamine infusions, participants were assessed every other week.

The same assessment tools were used at each visit before, during and after the active treatment phase. At the treatment visits they were administered about 4 hours after the infusions were completed. The assessments included validated measures of suicidal thinking, in which patients were directly asked to rank whether they had specific suicide-related thoughts, their frequency and intensity.

While only 12 of the 14 enrolled participants completed all treatment visits -- one dropped out because of ketamine side effects and one had a scheduling conflict -- most of them experienced a decrease in suicidal thinking, and seven achieved complete remission of suicidal thoughts at the end of the treatment period. Of those seven participants, two maintained remission from both suicidal thinking and depression symptoms throughout the follow-up period. While there were no serious adverse events at either dose and no major differences in side effects between the two dosage levels, additional studies in larger groups of patients are required before any conclusions can be drawn.

"In order to qualify for this study, patients had to have suicidal thinking for at least three months, along with persistent depression, so the fact that they experienced any reduction in suicidal thinking, let alone remission, is very exciting," says Ionescu, who is an instructor in Psychiatry at Harvard Medical School. "We only studied intravenous ketamine, but this result opens the

possibility for studying oral and intranasal doses, which may ease administration for patients in suicidal crises."

She adds, "One main limitation of our study was that all participants knew they were receiving ketamine. We are now finishing up a placebo-controlled study that we hope to have results for soon. Looking towards the future, studies that aim to understand the mechanism by which ketamine and its metabolites work for people with suicidal thinking and depression may help us discover areas of the brain to target with new, even better therapeutic drugs."

Additional co-authors of the Journal of Clinical Psychiatry paper are Michaela Swee, Kara Pavone, Lee Baer, PhD, Maren Nyer, PhD, Paolo Cassano, MD, David Mischoulon, MD, PhD, Jonathan Alpert, MD, PhD, Maurizio Fava, MD, and Cristina Cusin, MD, Depression and Clinical Research Program, MGH Psychiatry; Norman Taylor, MD, Oluwaseun Akeju, MD, and Emery Brown, MD, PhD, MGH Department of Anesthesia, Critical Care and Pain Medicine; and Matthew K. Nock, PhD, Harvard University Department of Psychology. Support for the study includes National Center for Advancing Translational Science grant 8UL1TR000170-05 to the Harvard Clinical and Translational Science Center.

http://www.eurekalert.org/pub_releases/2016-05/uom-rdf050516.php

Researchers discover first safe way to deliver drugs to the placenta

Method to selectively deliver drugs to a pregnant woman's placenta without harming the foetus

For the first time, researchers have devised a method to selectively deliver drugs to a pregnant woman's placenta without harming the foetus, in a development which could help prevent some premature births and treat conditions such as pre-eclampsia.

The University of Manchester scientists, writing in the journal Science Advances, have demonstrated that two peptides - chains of amino acids - originally used to target tumours selectively, will perform the same function on a placenta, delivering drugs which improve placental function and benefit the growing baby without causing it harm.

Many pregnancy complications are caused by the placenta not growing or functioning correctly. But currently there are no drugs that can be used to treat pregnancy complications, such as pre-eclampsia or foetal growth restriction, which affect more than ten percent of pregnant women.

Instead doctors have to induce early delivery of the baby. Premature babies are at increased risk of developing infections and cerebral palsy and throughout their lives have an increased risk of heart disease and diabetes.

The Manchester research has the potential to avoid these problems by treating the baby inside the mother and avoiding induced labour. Dr Lynda Harris, the lead researcher explained: "Placentas behave like well-controlled tumours," she said. "They grow quickly, produce growth hormones and evade the immune system.

"A lot of cancer research focuses on finding ways of delivering drugs to kill the tumour without affecting the rest of the body. We had the idea that if we could selectively target the placenta in the same way, we could deliver other drugs which help improve placental function and therefore treat pregnancy complications."

As a result the researchers have demonstrated that in mice a growth hormone can be delivered to placentas, which has no effect on normal-sized foetuses, but helps undersized ones to grow, proving that there is potential for this method to be used in humans.

There were no signs that these drugs built up in the mouse's organs, instead passing out of the body, and there were no drugs found in the mouse foetuses. The paper acknowledges that there may be harmful effects in mothers who have undiagnosed cancers, because the drugs will also target their tumours, but the authors suggest a screening programme would overcome these difficulties.

Dr Harris added: "Only one drug for use during pregnancy has been licensed in the last twenty years. By developing this platform we have opened up the possibility of any number of new drugs which can be adapted and then used safely to treat common and serious pregnancy complications."

Professor Melanie Welham, BBSRC Chief Executive, said: "This research demonstrates the value of novel approaches to drug delivery that could help us lead healthier, longer lives. The findings could help develop therapies that can help both the mother and particularly the unborn baby."

The paper, 'Tumour homing peptides as tools for targeted delivery of payloads to the placenta', will be published in the journal Science Advances and was funded by the Biotechnology and Biological Sciences Research Council (BBSRC).

http://nyti.ms/1TBZOQh

Kepler Finds 1,284 New Planets

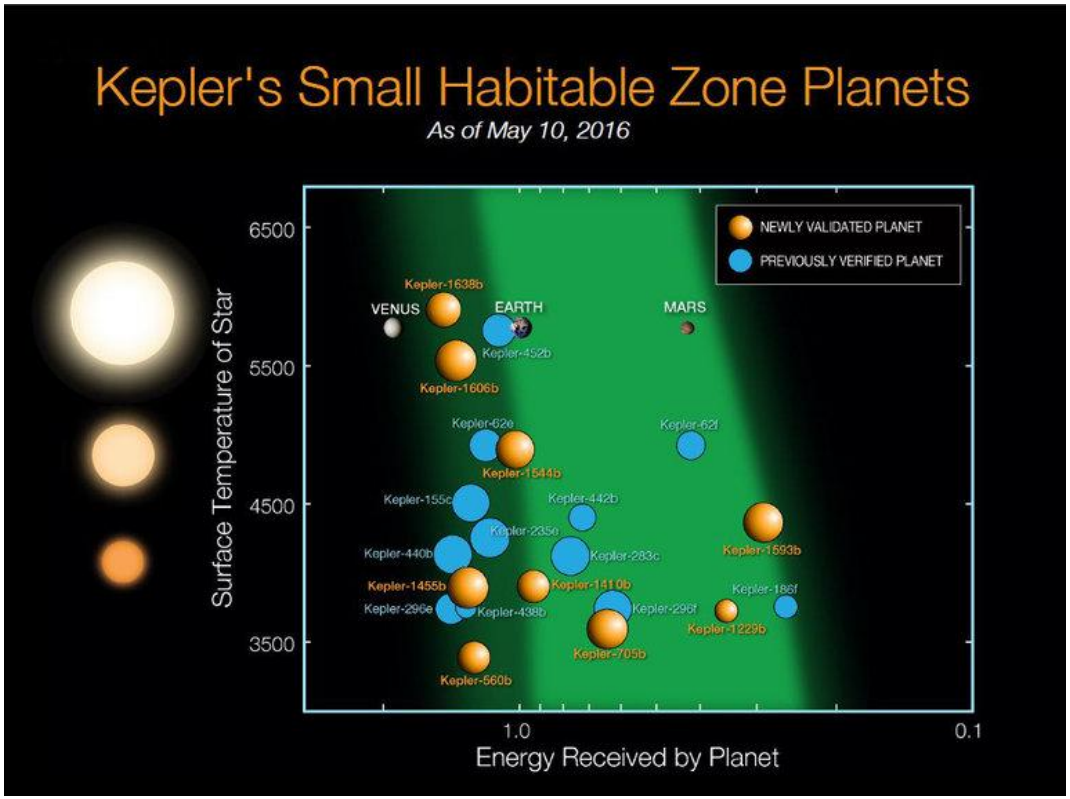
Planets keep falling out of the sky for the Kepler spacecraft. And as their number grows, so grows the age-old dream of ending human cosmic loneliness.

By DENNIS OVERBYE MAY 10, 2016

Astronomers operating NASA's planet-finding spacecraft announced Tuesday that they had validated the planethood of 1,284 new candidates from Kepler's voluminous catalog of potential exoplanets, the largest collection of new planets announced at one time. It brings the total of actual planets Kepler has discovered to more than 2,000.

All of them orbit stars in a patch of sky on the Cygnus-Lyra border, where Kepler, launched in 2009, spent four years staring at 150,000 stars looking for the

characteristic dimming when planets crossed their faces, until its pointing system broke down and the team had to develop a new observing strategy. Since then, Kepler has identified some 4,700 possible planets, and more keep being found.



Planets found so far by the Kepler spacecraft that are in the "Goldilocks" zone where water and life might be possible. Earth, Venus and Mars are included for reference. **N. Batalha and W. Stenzel/NASA Ames**

In the past, it took lengthy and arduous ground-based telescopic observations to winnow impostors like double stars and other pretenders from the planet list. But the numbers have grown too large, the cosmos too verdant, for this case-by-case analysis.

The new results rely on a statistical technique developed by Timothy Morton, an astronomer at Princeton University, to vet the potential candidates in bulk, by analyzing the shape of the dips they make in starlight and taking into account how common the various types of impostors are and assigning a reliability score to each one.

"Planet candidates can be thought of like bread crumbs," said Dr. Morton in a NASA teleconference on Tuesday. "If you drop a few large crumbs on the floor, you can pick them up one by one. But if you spill a whole bag of tiny crumbs, you're going to need a broom. This statistical analysis is our broom."

So far, two dozen of the planets found and confirmed by Kepler occupy the so-called Goldilocks zones of their stars where liquid water and perhaps "Life as We Think We Know It" could exist.

Extrapolating these results to the entire galaxy, Natalie Batalha, Kepler mission scientist from the Ames Research Center, said there could be 10 billion roughly Earth-size planets in the galaxy within their stars' habitable zones. The nearest habitable planet, she estimated, could be as close as 11 light-years. In the cosmic scheme of things, that is next door and reachable in our lifetimes with current or near-future technology. Last month, scientists announced a plan to try to send smartphone-like spacecraft to Alpha Centauri, which is 4.4 light-years away.

Kepler was conceived as a mission to determine how common Earth-size planets, possible habitable rocks, are in the universe. The Kepler team, Dr. Batalha said, is now approaching in the next year or two the closeout of that mission, one that has helped change humanity's view of how friendly the cosmos might be to life, and has made exoplanets one of the most explosive fields in astronomy.

That quest will go on. Kepler will be passing the baton to future missions like NASA's TESS, which will search for planets around nearby bright stars, starting in 2017.

http://www.eurekalert.org/pub_releases/2016-05/hm-cal050616.php

Common antacid linked to accelerated vascular aging

Research supports observations of increased risk for heart disease, dementia and kidney disease

Chronic use of some drugs for heartburn and gastroesophageal reflux (GERD) speeds up the aging of blood vessels, according to a published paper in Circulation Research (early online), an American Heart Association journal. This accelerated aging in humans could lead to increased cardiovascular disease, vascular dementia and renal failure.

These findings by a Houston Methodist Research Institute team are a progression of the work that John Cooke, M.D., Ph.D., began more than five years ago, and support recent epidemiological and retrospective studies that observed associations between the long-term use of proton pump inhibitors (PPIs) and an increased risk of heart attack, renal failure and dementia.

PPIs like esomeprazole (Nexium) are widely used for the treatment of GERD. These medications are sold over-the-counter in the United States so medical supervision is not required. While these drugs are effective when taken as prescribed, they were not approved for long-term use and evidence suggests that up to 70 percent of PPI use may be inappropriate.

Cooke, the paper's senior author, and team showed that chronic exposure to PPIs accelerated biological aging in human endothelial cells which line the inside of blood vessels. When healthy, human endothelial cells create a Teflon-like coating that prevents blood from sticking. When older and diseased, the endothelium becomes more like Velcro, with blood elements sticking to the vessel to form blockages.

"When we exposed human endothelial cells over a period of time to these PPIs, we observed accelerated aging of the cells," Cooke said. "The PPIs also reduce acidity in lysosomes of the endothelial cell. The lysosomes are like cellular garbage disposals and need acid to work properly. We observed cellular garbage accumulating in the endothelial cells, which sped up the aging process."

Cooke suspects that this may be the unifying mechanism that explains the increased risk of heart attack, renal failure and dementia observed in long-term PPI users.

"These drugs do not seem to adversely affect the heart and blood vessels when taken for a few weeks. However, we urgently need studies to assess the impact of long-term use of these drugs on vascular health in a broad patient population. We also need to consider if these drugs should be so accessible without medical supervision."

Cooke's earlier work identified at a molecular level that PPIs might cause long-term cardiovascular disease and increase a patient's heart attack risk. That work led to a collaborative study with Stanford University colleagues (PLOS ONE, June 2015) to show that in two large populations of patients, adults who used PPIs were between 16 to 21 percent more likely to experience a heart attack than people who didn't use the commonly prescribed antacid drugs.

Cooke, who holds the Joseph C. "Rusty" Walter and Carole Walter Looke Presidential Distinguished Chair in Cardiovascular Disease Research, said while PPIs were shown to affect vascular aging, H2 blockers like ranitidine did not adversely affect the endothelium. Brand examples of H2 blockers are Zantac and Tagamet.

The FDA estimates about 1 in 14 Americans have used a PPI. 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. In addition to GERD and heartburn, PPIs treat a wide range of disorders, including infection by the ulcer-causing bacterium Helicobacter pylori, Zollinger-Ellison syndrome, and Barrett's esophagus. PPIs come in a variety of forms, always ending with the suffix "-prazole," and other brand examples include Prilosec and PrevAcid.

Additional researchers who collaborated with Cooke on the Circulation Research paper were: Gautham Yepuri, Roman Sukhovershin, Timo Z. Nazari-Shafti (Houston Methodist Research Institute, Houston, TX); Yohannes T. Ghebre (Baylor College of Medicine); and Michael Petrascheck (The Scripps Research Institute, La Jolla, CA).

This research was supported by grants from National Institutes of Health (U01HL100397 and K01HL118683) and the Swiss National Science Foundation (P2FRP3_151676).

http://www.eurekalert.org/pub_releases/2016-05/anu-afw050916.php

Archaeologists find world's oldest axe in Australia

Archaeologists from the Australian National University have unearthed fragments from the edge of the world's oldest-known axe, found in the Kimberley region of Western Australia

Archaeologists from The Australian National University (ANU) have unearthed fragments from the edge of the world's oldest-known axe, found in the Kimberley region of Western Australia.

Lead archeologist Professor Sue O'Connor said the axe dates back between 46,000 and 49,000 years, around the time people first arrived on the continent.

"This is the earliest evidence of hafted axes in the world. Nowhere else in the world do you get axes at this date," said Professor O'Connor from the ANU School of Culture, History and Language. "In Japan such axes appear about 35,000 years ago. But in most countries in the world they arrive with agriculture after 10,000 years ago."

Professor O'Connor said this discovery showed early Aboriginal technology was not as simple as has been previously suggested. A hafted axe is an axe with a handle attached.

"Australian stone artefacts have often been characterised as being simple. But clearly that's not the case when you have these hafted axes earlier in Australia than anywhere else in the world," she said.

Examples of the type of axes the blade fragments would have been from. **Stuart Hay, ANU**

Professor O'Connor said evidence suggests the technology was developed in Australia after people arrived around 50,000 years ago. "We know that they didn't have axes where they came from. There's no axes in the islands to our north. They arrived in Australia and innovated axes," she said.

Once unearthed, the flakes were then analysed by Professor Peter Hiscock from the University of Sydney. "Since there are no known axes in Southeast Asia during the Ice Age, this discovery shows us that when humans arrived in Australia

they began to experiment with new technologies, inventing ways to exploit the resources they encountered," Professor Hiscock said. "The question of when axes were invented has been pursued for decades, since archaeologists discovered that in Australia axes were older than in many other places. Now we have a discovery that appears to answer the question," Professor Hiscock said.

Professor Hiscock said although humans spread across Australia, axe technology did not spread with them. "Axes were only made in the tropical north. These differences between northern Australia, where axes were always used, and southern Australia, where they were not, originated around the time of colonisation and persisted until the last few thousand years when axes began to be made in most southern parts of mainland Australia," Professor Hiscock said

The axe fragment was initially excavated in the early 1990s by Professor O'Connor at Carpenter's Gap 1, a large rock shelter in Windjana Gorge National Park in the Kimberley region of WA.

New studies of the fragment have revealed that it comes from an axe made of basalt that had been shaped and polished by grinding it against a softer rock like sandstone.

This type of axe would have been very useful for a variety of tasks including making spears and chopping down or taking the bark off trees.

This work resulted from an Australian Research Council Linkage grant awarded to Professor O'Connor and Professor Jane Balme of The University of Western Australia. An article on the discovery has been published in in the journal Australian Archaeology.

http://www.eurekalert.org/pub_releases/2016-05/uomm-nsh051016.php

New study: Has HDL, the 'good' cholesterol, been hyped?

New study shows for the first time that HDL's protection depends on the levels of two other blood lipids

Baltimore, Md. - For years, physicians have told patients that HDL (high-density lipoprotein cholesterol) helps protect them from cardiovascular disease (CVD). And the higher the number, the more the protection. HDL, often considered an independent predictor of heart disease, has been dubbed the "good" cholesterol, thanks to its protective effects. But a new study shows for the first time that HDL's protection depends on the levels of two other blood fats or lipids associated with heart disease. If these fats are not within normal ranges, even a high HDL may not be protective.

The new research analyzes nearly 25 years of data from the Framingham Heart Study's Offspring Cohort. It focuses on the roles HDL, LDL (low-density lipoprotein cholesterol) and triglycerides (TG) play in increasing or decreasing the risk of heart disease. The study, published online in Circulation: Cardiovascular Quality and Outcomes, followed 3,590 men and women without known cardiovascular disease between 1987 and 2011.

"There's no question that HDL does have a protective role, as we also confirm in the study, but HDL has been hyped-up," says senior author Michael Miller, MD, professor of cardiovascular medicine at the University of Maryland School of Medicine and preventive cardiologist at the University of Maryland Medical Center. "HDL really should be viewed as a third priority, with LDL on top and TG second."

The questions:

Can the level of HDL by itself determine the risk of a person developing heart disease?

What happens to the risk if LDL and TG are abnormal?

The method:

The researchers looked at study participants with both low and high HDL levels, and Those who also had normal and high levels of LDL and TG

"Nobody has really looked at an isolated low and isolated high HDL, and whether or not other factors, such as triglycerides and LDL, make a difference in the risk of cardiovascular disease," says Dr. Miller.

The conclusions:

HDL was not uniformly predictive of cardiovascular risk

TG and LDL modified the incidence of CVD in both low- and high-level HDL

Compared with isolated low HDL, the CVD risk was 30-60 percent higher in the presence of high levels of LDL, TG or both

High HDL was not associated with reduced CVD risk if TG and LDL were above 100 mg/dL

Dr. Miller is available for interviews on study details and implications for patient care

Bartlett J, Predazzi IM, Williams SM, Bush, WS, Kim Y, Havas S, Toth PP, Fazio S, Miller M. "Is isolated low high-density lipoprotein cholesterol a cardiovascular disease risk factor? New insights from the Framingham Offspring Study." Circulation: Cardiovascular Quality and Outcomes. Online: May 10, 2016. doi: 10.1161/CIRCOUTCOMES.115.002436

http://www.eurekalert.org/pub_releases/2016-05/tu-ssb051016.php

Silk stabilizes blood samples for months at high temperatures

New technology could improve clinical care & research for underserved groups

Medford/Somerville, Mass. - Researchers at Tufts University have stabilized blood samples for long periods of time without refrigeration and at high temperatures by encapsulating them in air-dried silk protein. The technique, which is published online this week in the Proceedings of the National Academy of Sciences, has broad applications for clinical care and research that rely on accurate analysis of blood and other biofluids.

Blood contains proteins, enzymes, lipids, metabolites, and peptides that serve as biomarkers for health screening, monitoring and diagnostics. Both research and clinical care often require blood to be collected outside a laboratory. However, unless stored at controlled temperatures, these biomarkers rapidly deteriorate, jeopardizing the accuracy of subsequent laboratory analysis. Existing alternative collection and storage solutions, such as drying blood on paper cards, still fail to effectively protect biomarkers from heat and humidity.

The Tufts scientists successfully mixed a solution or a powder of purified silk fibroin protein extracted from silkworm cocoons with blood or plasma and air-dried the mixture. The air-dried silk films were stored at temperatures between 22 and 45 degrees C (71.6 to 113 degrees F). At set intervals, encapsulated blood samples were recovered by dissolving the films in water and analyzed.

"This approach should facilitate outpatient blood collection for disease screening and monitoring, particularly for underserved populations, and also serve needs of researchers and clinicians without access to centralized testing facilities. For example, this could support large-scale epidemiologic studies or remote pharmacological trials," said senior and corresponding author David L. Kaplan, Ph.D., Stern Family Professor in the Department of Biomedical Engineering at Tufts School of Engineering.

"We found that biomarkers could be successfully analyzed even after storage for 84 days at temperatures up to 113 degrees F. Encapsulation of samples in silk provided better protection than the traditional approach of drying on paper, especially at these elevated temperatures which a shipment might encounter during overseas or summer transport," said the paper's co-first author Jonathan A. Kluge, who earned both his Ph.D. and B.S. from Tufts School of Engineering and was a postdoctoral associate in the Kaplan lab when the research was done.

The paper noted that the silk-based technique requires accurate starting volumes of the blood or other specimens to be known, and salts or other buffers are needed to reconstitute samples for accurate testing of certain markers.

Kaplan, whose specialty is biopolymer engineering, has studied the unique properties and applications of silk for more than 20 years. He and his collaborators have successfully demonstrated silk's ability to stabilize a variety of bioactive materials including antibiotics, vaccines, enzymes and monoclonal antibiotics with numerous biomedical and biomaterial applications. He also holds Tufts faculty appointments in the Department of Chemical and Biological Engineering, School of Medicine, School of Dental Medicine and Department of Chemistry in the School of Arts and Sciences.

Other authors on the paper were Adrian B. Li, Ph.D., scientist at Vaxess Laboratories and a former doctoral student in Tufts' Department of Chemical and Biological Engineering; Brooke Kahn, B.S., research associate at Cocoon Biotech and former intern in the Kaplan laboratory; Dominique S. Michaud, Sc.D., Tufts University School of Medicine, and Fiorenzo G. Omenetto, Ph.D., Frank C. Doble Professor in the Department of Biomedical Engineering.

The work was supported by National Science Foundation Award IIP-1521898, Air Force Office of Scientific Research Grant FA9550-14-1-0015, Defense Threat Reduction Agency Grant HDTRA1-14-1-0061, National Institutes of Health Grant P41EB002520 and Defense Advanced Research Projects Agency Program SB112-005.

"Silk-based blood stabilization for diagnostics," by Jonathan A. Kluge et al. http://www.pnas.org/cgi/doi/10.1073/pnas.1602493113.

http://www.eurekalert.org/pub_releases/2016-05/tjnj-isi050616.php

Increase seen in the BMI associated with lowest risk of death

BMI value associated with the lowest all-cause mortality increased over the past decades

In a study appearing in the May 10, 2016 issue of JAMA, Børge G. Nordestgaard, M.D., D.M.Sc., of Copenhagen University Hospital, Herlev, Denmark and colleagues examined whether the body mass index (BMI) value that is associated with the lowest all-cause mortality has increased in the general population over a period of 3 decades.

Previous findings indicate that while average BMI has increased over time in most countries, the prevalence of cardiovascular risk factors may be decreasing among obese individuals. Thus, the BMI associated with lowest all-cause mortality may have changed over time. This study included three groups from the same general population enrolled at different times: the Copenhagen City Heart Study in 1976-1978 (n = 13,704) and 1991-1994 (n = 9,482) and the Copenhagen General Population Study in 2003-2013 (n = 97,362). All participants were followed up from inclusion in the studies to November 2014, emigration, or death, whichever came first.

The researchers found that the BMI value associated with the lowest all-cause mortality has increased by 3.3 over 3 decades from 1976-1978 to 2003-2013, from 23.7 to 27. In addition, the risk for all-cause mortality that was associated with BMI of 30 or greater vs BMI of 18.5 to 24.9 decreased from an adjusted hazard ratio of 1.3 to 1.0 over this 30-year period. "These latter findings were robust in analyses stratified by age, sex, smoking status, and history of cardiovascular disease or cancer."

The authors write that an interesting finding in this study is that the optimal BMI in relation to mortality is placed in the overweight category in the most recent 2003-2013 cohort. "This finding was consistent in both the whole population sample (optimal BMI, 27), and in a subgroup of never-smokers without history of cardiovascular disease or cancer (optimal BMI, 26.1). If this finding is confirmed

in other studies, it would indicate a need to revise the WHO categories presently used to define overweight, which are based on data from before the 1990s."

Regarding the increase in the BMI value associated with the lowest all-cause mortality, the researchers write that "further investigation is needed to understand the reason for this change and its implications."

doi:10.1001/jama.2016.4666; this study is available pre-embargo at the For The Media website

http://bit.ly/1R10TiG

How 'fatigue amnesia' makes some doctors so tired they can't remember saving patients' lives

Fatigued doctors lose all memory of providing medical care within hours of scrubbing out.

One late night, in a hospital in South West England, a neurologist retreated to the on-call room to get some shuteye. Soon after falling asleep, she was awoken to manage a patient who'd gone into cardiac arrest. The neurologist proceeded as usual: She resuscitated the patient and wrote up case notes. The next morning, someone told her that the patient was doing well and had eaten breakfast. The neurologist might have been pleased had she not been so surprised — she had no recollection of the patient or the time she'd spent shocking his heart into rhythm.

The neurologist suffered a bout of what two UK researchers have dubbed "fatigue amnesia," defined as "transient amnesia in the context of prolonged activity and sleep deprivation." In other words, it occurs when someone is so sleep deprived they have no memory of certain tasks. A new paper, published in the journal Cortex, describes four instances where doctors lost all memory of providing medical care within hours of scrubbing out.

Fleeting memory loss is by no means absent from the medical literature. It's well-documented, for example, that injuries, stroke, drug use and migraines can trigger brief amnesia episodes. But, until now, fatigue amnesia hasn't been recognized, according to study co-author Adam Zeman, a cognitive neurologist at the University of Exeter Medical School. Zeman has a history of homing in on un-named medical phenomena. In 2010, he published the first-ever case study of Aphantasia, which describes an inability to visualize images.

Six years later, Zeman's adding another mysterious, and perhaps quite rare, condition to the annals of huh-inducing medicine. But, unlike Aphantasia, fatigue amnesia is less a biological quirk than a situational affliction of the overworked and underslept. Or that's what the paper suggests. Two of the other cases involved a geriatrician who lost all recollection of a late-night patient by morning rounds and a microbiologist with a similar tale.

The three forgetful physicians' amnesia episodes share several features. For starters, they occurred toward the end of long shifts during which the doctors likely caught minimal, scattered Zzzs. (The UK, study authors noted, has since updated policies regarding medical shift limits.) And, their accounts bear a similar pattern of memory loss. The doctors saw patients, furnished critical care and held onto the experiences long enough to jot down accurate, thorough case notes after the fact. Across the board, the doctors responded to wake-up calls appropriately and did their jobs competently — they just had no idea any of it happened.

Their memories didn't fail off the bat. The fact that they entered case notes, Zeman and co-author Sonali Dharia wrote, suggests that they successfully "encoded" their patient interactions, meaning they absorbed and retained what happened. Something misfired, however, during memory consolidation, the process of converting newly learned information and experiences into long-term memories. Researchers interpreted the phenomenon as a "novel form of accelerated long-term forgetting, whereby a memory for events is acquired normally but then decays more rapidly than usual."

What's most striking, researchers wrote, is that the doctors could entirely forget such attention-demanding tasks — documented in writing — within a few hours.

At this point, Zeman and Dharia can only speculate as to the brain glitch underlying fatigue amnesia. But, they offer insights from neuroscience and memory research. One well-regarded theory says the primary neurobiological function of sleep is "renormalization." During the day, we absorb all sorts of facts and faces and feelings. Or, in a word, we learn.

Let's back up. The concept of plasticity tells us that brains change through experience. Learning increases brainpower, so to speak. When we learn new information and skills, we strengthen synapses (the connections between neurons that transmit chemical messages). We even build new synapses, a process called neurogenesis. But, our brains need breaks between periods of active learning to clean shop and dispose of weak synapses (unnecessary garbage thoughts). That way, we can lock in the most important information. And we lock in that info by consolidating it into a long-term memory. This happens, of course, during deep sleep.

When doctors work a 24-hour shift on scant rest, constantly challenging themselves to hit the right arteries and make sense of diagnostic riddles, they exhaust their synaptic plasticity, researchers posited. The overworked MDs basically hit their capacity for jamming in information without getting enough time to clear their neural decks. As a result, the important memories — say, the details of a four-hour-old heart transplant — don't get consolidated.

Of course, it's hard to discuss fatigue amnesia without mentioning the ongoing debate over devising optimal shifts for hospital workers. Among other concerns, hospital administrators (and other healthcare experts) want to minimize on-the-job mistakes. Some research suggests that more patient-care errors occur during "hand-offs," when doctors and nurses switch shifts and take on new, unfamiliar caseloads, than when they're tired but well-versed in their appendectomy patient's drug allergies.

But, the cases of fatigue amnesia before us don't concern mistakes, per se. The doctors sprung into action and went to work as they were supposed to. This may not be surprising; research suggests that doctors work on autopilot even when they're alert and well-slept. The idea here is that they subconsciously use mental shortcuts called heuristics to make decisions. So, let's say a doctor needs to revive a trauma victim.

Rather than logically think through each step of the process, weighing all the information available, they make gut-level choices that, based on their experience and knowledge, have a high probability of being correct. Then again, doctors need experience to fuel heuristic decision-making. If yesterday's "House, M.D."-level diagnosis doesn't become a consolidated memory, then how can it inform medical sleuthing going forward?

http://www.eurekalert.org/pub_releases/2016-05/mu-cdr051016.php

Cosmic dust reveals Earth's ancient atmosphere

Using the oldest fossil micrometeorites - space dust - ever found, Monash University-led research has made a surprising discovery about the chemistry of Earth's atmosphere 2.7 billion years ago.

The findings of a new study published today in the journal Nature - led by Dr Andrew Tomkins and a team from the School of Earth, Atmosphere and Environment at Monash, along with scientists from the Australian Synchrotron and Imperial College, London - challenge the accepted view that Earth's ancient atmosphere was oxygen-poor.

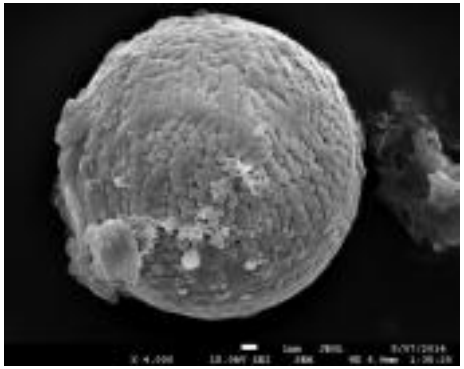
The findings indicate instead that the ancient Earth's upper atmosphere contained about the same amount of oxygen as today, and that a methane haze layer separated this oxygen-rich upper layer from the oxygen-starved lower atmosphere.

Dr Tomkins explained how the team extracted micrometeorites from samples of ancient limestone collected in the Pilbara region in Western Australia and examined them at the Monash Centre for Electron Microscopy (MCEM) and the Australian Synchrotron.

"Using cutting-edge microscopes we found that most of the micrometeorites had once been particles of metallic iron - common in meteorites - that had been turned into iron oxide minerals in the upper atmosphere, indicating higher concentrations of oxygen than expected," Dr Tomkins said.

"This was an exciting result because it is the first time anyone has found a way to sample the chemistry of the ancient Earth's upper atmosphere," Dr Tomkins said.

Imperial College researcher Dr Matthew Genge - an expert in modern cosmic dust - performed calculations that showed oxygen concentrations in the upper atmosphere would need to be close to modern day levels to explain the observations.



This is one of 60 micrometeorites extracted from 2.7 billion year old limestone, from the Pilbara region in Western Australia. These micrometeorites consist of iron oxide minerals that formed when dust particles of meteoritic iron metal were oxidised as they entered Earth's atmosphere, indicating that the ancient upper atmosphere was surprisingly oxygen-rich. **Andrew Tomkins**

"This was a surprise because it has been firmly established that the Earth's lower atmosphere was very poor in oxygen 2.7 billion years ago; how the upper atmosphere could contain so much oxygen before the appearance of photosynthetic organisms was a real puzzle," Dr Genge said.

Dr Tomkins explained that the new results suggest the Earth at this time may have had a layered atmosphere with little vertical mixing, and higher levels of oxygen in the upper atmosphere produced by the breakdown of CO 2 by ultraviolet light.

"A possible explanation for this layered atmosphere might have involved a methane haze layer at middle levels of the atmosphere. The methane in such a layer would absorb UV light, releasing heat and creating a warm zone in the atmosphere that would inhibit vertical mixing," Dr Tomkins said.

"It is incredible to think that by studying fossilised particles of space dust the width of a human hair, we can gain new insights into the chemical makeup of Earth's upper atmosphere, billions of years ago." Dr Tomkins said.

Dr Tomkins outlined next steps in the research.

"The next stage of our research will be to extract micrometeorites from a series of rocks covering over a billion years of Earth's history in order to learn more about changes in atmospheric chemistry and structure across geological time. We will focus particularly on the great oxidation event, which happened 2.4 billion years ago when there was a sudden jump in oxygen concentration in the lower atmosphere."

http://www.eurekalert.org/pub_releases/2016-05/jhub-tmf050916.php

Too much folate in pregnant women increases risk for autism, study suggests

Researchers say that while folate deficiency is bad for developing fetus, excessive amounts could also be harmful

Women who plan on becoming pregnant are told they need enough of the nutrient folate to ensure proper neurodevelopment of their babies, but new research from the Johns Hopkins Bloomberg School of Public Health suggests there could be serious risks in having far too much of the same nutrient.

The researchers found that if a new mother has a very high level of folate right after giving birth - more than four times what is considered adequate - the risk that her child will develop an autism spectrum disorder doubles. Very high vitamin B12 levels in new moms are also potentially harmful, tripling the risk that her offspring will develop an autism spectrum disorder. If both levels are extremely high, the risk that a child develops the disorder increases 17.6 times. Folate, a B vitamin, is found naturally in fruits and vegetables, while the synthetic version, folic acid, is used to fortify cereals and breads in the United States and in vitamin supplements.

The preliminary findings will be presented May 13 at the 2016 International Meeting for Autism Research in Baltimore. A press conference is scheduled for 10 a.m. on May 11 at the at the Baltimore Convention Center, Room 302-303.

"Adequate supplementation is protective: That's still the story with folic acid," says one of the study's senior authors M. Daniele Fallin, PhD, director of the Bloomberg School's Wendy Klag Center for Autism and Developmental Disabilities. "We have long known that a folate deficiency in pregnant mothers is detrimental to her child's development. But what this tells us is that excessive amounts may also cause harm. We must aim for optimal levels of this important nutrient."

Folate is essential in cell growth and promotes neurodevelopmental growth. Deficiencies early in pregnancy have been linked to birth defects and to an increased risk of developing an autism spectrum disorder. And despite this push to ensure women get adequate folate, some women still don't get enough or their bodies aren't properly absorbing it, leading to deficiencies. The Centers for Disease Control and Prevention says that one in four women of reproductive age in the U.S. have insufficient folate levels. Levels are not routinely monitored during pregnancy.

Autism spectrum disorder is a neurodevelopmental condition characterized by social impairment, abnormal communication and repetitive or unusual behavior. One in 68 children in the U.S. have the disorder, with boys five times more likely than girls to have it. The causes remain unclear but research suggests the factors are a combination of genes and the environment.

For the study, researchers analyzed data from 1,391 mother-child pairs in the Boston Birth Cohort, a predominantly low-income minority population.

The mothers were recruited at the time of their child's birth between 1998 and 2013 and followed for several years, with the mother's blood folate levels checked once within the first one to three days of delivery. The researchers found that one in 10 of the women had what is considered an excess amount of folate (more than 59 nanomoles per liter) and six percent had an excess amount of vitamin B12 (more than 600 picomoles per liter).

The World Health Organization says that between 13.5 and 45.3 nanomoles per liter is an adequate amount of folate for a woman in her first trimester of pregnancy. Unlike with folate, there are not well-established thresholds for adequate vitamin B12 levels.

A large majority of the mothers in the study reported having taken multivitamins - which would include folic acid and vitamin B12 - throughout pregnancy. But the researchers say they don't know exactly why some of the women had such high levels in their blood. It could be that they consumed too many folic acid-fortified foods or took too many supplements. Or, they say, it could be that some women are genetically predisposed to absorbing greater quantities of folate or metabolizing it slower, leading to the excess. Or it could be a combination of the two.

More research is needed, the scientists say, in order to determine just how much folic acid a woman should consume during pregnancy to have the best chance that she will have optimal blood folate levels to ensure her offspring's health.

With many types of vitamin supplements, the conventional wisdom has been that too much is not harmful, that the body will flush out the excess. That may not be the case with folic acid and vitamin B12.

"This research suggests that this could be the case of too much of a good thing," says study lead author Ramkripa Raghavan, MPH, MSc, a DrPH candidate in the Department of Population, Family and Reproductive Health at the Bloomberg School. "We tell women to be sure to get folate early in pregnancy. What we need to figure out now is whether there should be additional recommendations about just what an optimal dose is throughout pregnancy."

Other researchers involved in the study include Anne Riley; Heather Volk; Deanna Caruso; Kari Hironaka; Laura Sices; Xiumei Hong; Guoying Wang; Bolanle Ajao; Jing Zhang; Yuelong Ji; Mengying Li; Huan He; Anastacia Wahl; Tom Stivers; Elizabeth Stuart; Rebecca Landa and Xiaobin Wang.

This study is part of an ongoing prospective birth cohort study on early life determinants of autism in the Boston Birth Cohort, co-led by Fallin and Wang, MD, MPH, ScD, Zanvyl Krieger Professor, Director, Center on the Early Life Origins of Disease at Bloomberg School, and is supported by the Maternal and Child Health Bureau (R40MC27443). Raghavan is supported by a student research grant from the Wendy Klag Center for Autism and Developmental Disorders; the Bloomberg School and the John and Alice Chenoweth-Pate Fellowship.

http://www.eurekalert.org/pub_releases/2016-05/tuom-hfh051216.php

Hay fever's hidden supporting substances

Non-allergenic substances in pollen heighten the immune response

Up to now, research into pollen allergies has largely focused on allergens - those components of pollen that trigger hypersensitivity reactions. When it comes into contact with the nasal mucous membrane, however, pollen releases a host of other substances in addition to allergens. In a pilot study, a team of researchers from the Technical University of Munich (TUM) and the Helmholtz Zentrum München investigated for the first time the effects of these substances on allergy sufferers. It emerged that the non-allergenic components of pollen have a significant influence on the way the body reacts. The results of the study suggest that it may be time to rethink the current methods of treating allergies.

In April and May, birch pollen makes life miserable for many people. The body's defense mechanism is primarily triggered by a protein called Bet v 1, which is the main allergen of birch pollen. For a team of researchers under Prof. Claudia Traidl-Hoffmann from TUM, however, this allergen is not the focus of their interest. Instead, their study involved filtering the metabolic products of birch pollen so that only non-allergenic low molecular substances remained in the extract - that is, substances with particularly small molecules.

One part of the experiment saw the researchers performing a skin prick test on hay fever sufferers with various combinations of allergens and low molecular substances. They also administered some of the mixtures through the nasal passages of the study participants.

The results were clear: In both the skin prick test and the nasal inhalation approach, the reactions were much stronger when the low molecular substances were administered along with the allergen. In cases where both were injected under the skin, extremely pronounced reddening and swelling occurred. When the mixture was administered through the nose, the study participants experienced a strong build-up of mucus and their immune systems produced a large number of antibodies.

No effect was discernible, however, when the low molecular substances were administered by themselves to the allergy sufferers.

Reaction not limited to those allergic to birch pollen

The researchers noticed that the birch pollen extract did not just have an effect on the test subjects who react to Bet v 1. The effect was also evident in those who are allergic to grass pollen and who were nasally administered the corresponding allergen in combination with the birch pollen extract. The explanation behind this is that many of the low molecular substances also occur in other plant pollens. "The inflammatory effect of the low molecular components is non-specific, i.e. it is not connected to any one allergen" explains Claudia Traidl-Hoffmann. "We suspect that effects could even be noticed in people who do not suffer from allergies."

The birch pollen extract contains as many as 1,000 different low molecular substances. The researchers were able to identify some of the components that heighten allergic reactions in earlier studies - components like adenosine and various fatty acids.

Irrespective of the fact that scientists do not yet understand how all of these components work, it seems that the interaction between different substances also plays an important role in the occurrence and effects of allergies. "The human organism is a complex system. We can hardly expect to pinpoint the cause of allergies to one single substance," comments Traidl-Hoffmann.

Negative effects on immunotherapy

The finding that non-allergenic substances in pollen have a major influence on the body's response could have a lasting impact on the medical treatment of allergies. During specific immunotherapy (hypo-sensitization), doctors currently administer a pollen extract in liquid form containing all the components of pollen. This means that components like the low molecular substances investigated in this particular study also make their way into the human organism.

"At present, only 60 to 70 percent of hypo-sensitization therapies work," points out Traidl-Hoffmann. One reason for this might be the presence of non-allergenic but pro-inflammatory contents that could have a negative impact on treatment. A more helpful way to treat allergy sufferers could be vaccination with recombinant proteins, which are derived from biotechnology. This would allow selective administration of the allergen by itself so that the body can become accustomed to its effects. To date, recombinant protein therapy has only been developed for people with an allergy to wasp and bee venom.

S. Gilles-Stein, I. Beck, A. Chaker, M. Bas, M. McIntyre, L. Cifuentes, A. Petersen, J. Gutermuth, C. Schmidt-Weber, H.Behrendt, C. Traidl-Hoffmann, Pollen derived low molecular compounds enhance the human allergen specific immune response in vivo, Clinical and Experimental Allergy, DOI: 10.1111/cea.12739

http://bit.ly/1qjeSdR

World War Zero brought down mystery civilisation of 'sea people'

The Trojan War was a grander event than even Homer would have us believe.

By Colin Barras

The famous conflict may have been one of the final acts in what one archaeologist has controversially dubbed "World War Zero" – an event he claims brought the eastern Mediterranean Bronze Age world crashing down 3200 years ago.

And the catalyst for the war? A mysterious and arguably powerful civilisation almost entirely overlooked by archaeologists: the Luwians.

By the second millennium BC, civilisation had taken hold throughout the eastern Mediterranean. The Egyptian New Kingdom coexisted with the Hittites of central Anatolia and the Mycenaeans of mainland Greece, among others.

In little more than a single generation, they had all collapsed. Was the culprit climate change? Some sort of earthquake storm? Social unrest? Archaeologists can't seem to agree.

Eberhard Zangger, head of international non-profit, Luwian Studies, based in Zurich, Switzerland, says that's because one crucial piece of the puzzle is missing. Another powerful civilisation in western Anatolia played a crucial role in the downfall.

His investigations of the published literature show that western Anatolia is extraordinarily rich in mineral and metal ore deposits, meaning it's likely to have been an important region in antiquity.

Through studies of satellite imagery, Zangger has also found that the area was densely populated during the Late Bronze Age. Only a handful of the 340 large city-like sites he has identified have been excavated.

"Some of these sites are so large you can see them from space," says Zangger. "There's so much waiting to be found it's really just mind-boggling."

Hittite texts talk of several petty kingdoms in western Anatolia speaking versions of a common language – Luwian. According to Zangger, that means we can legitimately talk of them as forming a Luwian civilisation in their own right.

We know from Hittite texts that the Luwian kingdoms sometimes formed coalitions powerful enough to attack the Hittite empire. Zangger thinks that 3200 years ago the Luwians did just that and destroyed the Hittite Empire (see map, above).

Shortly after the demise of the Hittites, Egyptian texts document an attack force they termed the "Sea People". Zangger says it makes sense to view these Sea People as the Luwians, continuing their campaign for wealth and power and, in the process, weakening and destabilising the Egyptian New Kingdom.

The Mycenaeans, perhaps anticipating an attack on their territory, formed a grand coalition of their own, says Zangger. They sailed across the Aegean and attacked the Luwians, bringing down their civilisation and destroying its key cities like Troy – events immortalised in Homer's *Iliad*.

On returning to Greece, however, and in the sudden absence of any other threat, Zangger believes the Mycenaeans squabbled and fell into civil war – events hinted at in Homer's *Odyssey*. Their civilisation was the last in the area to collapse.

Zangger says that only such a sequence of events fits with the evidence documented in ancient texts across the eastern Mediterranean, and also explains why the archaeological record shows that almost every large city in the region was destroyed in warfare at the end of the Bronze Age. He sets out his ideas in a new book, and on a website that launches in English today.

Bombastic storytelling – but is it true?

So what do other archaeologists make of this idea of a lost Luwian civilisation? Many stopped trying to impose this sort of monolithic cultural identity on ancient peoples decades ago, says Christoph Bachhuber at the University of Oxford.

"Archaeologists will need to discover similar examples of monumental art and architecture across western Anatolia and ideally texts from the same sites to support Zangger's claim of a civilisation," he says.

The textual evidence available is mainly from post-Bronze age and it paints a slightly confusing picture, which could be seen as both supporting and undermining Zangger's theory, says Ilya Yakubovich, a historical linguist at the Philipp University of Marburg, Germany.

Zangger's broader "World War Zero" narrative is also debatable. "He's bringing in this idea of ancient international warfare," says Michael Galaty at Mississippi State University. "Most archaeologists would balk at using such terminology."

Bachhuber calls it "big bombastic storytelling" and points out that today, archaeologists are sceptical that ancient narratives like Homer's approximate historical truth.

Zangger, however, says there are several other ancient accounts of the Trojan War that all tell a similar story to Homer. One, written in the first century AD, even refers to now-lost Egyptian monuments that documented the conflict.

Despite these criticisms, though, there is near-universal praise for the fact that Zangger's ideas will raise the profile of Late Bronze Age archaeological research in long-neglected western Anatolia, which can only benefit the scientific community.

"He's really getting the ball rolling to do larger holistic studies of the area," says Bachhuber. "I'm actually quite excited that he's bringing attention to this region."

http://nyti.ms/23Sh21f

An Old Idea, Revived: Starve Cancer to Death

In the early 20th century, the German biochemist Otto Warburg believed that tumors could be treated by disrupting their source of energy. His idea was dismissed for decades — until now.

By SAM APPLE MAY 12, 2016

The story of modern cancer research begins, somewhat improbably, with the sea urchin. In the first decade of the 20th century, the German biologist Theodor Boveri discovered that if he fertilized sea-urchin eggs with two sperm rather than one, some of the cells would end up with the wrong number of chromosomes and fail to develop properly. It was the era before modern genetics, but Boveri was aware that cancer cells, like the deformed sea urchin cells, had abnormal chromosomes; whatever caused cancer, he surmised, had something to do with chromosomes.

Today Boveri is celebrated for discovering the origins of cancer, but another German scientist, Otto Warburg, was studying sea-urchin eggs around the same time as Boveri. His research, too, was hailed as a major breakthrough in our understanding of cancer. But in the following decades, Warburg's discovery would largely disappear from the cancer narrative, his contributions considered so negligible that they were left out of textbooks altogether.

Unlike Boveri, Warburg wasn't interested in the chromosomes of sea-urchin eggs. Rather, Warburg was focused on energy, specifically on how the eggs fueled their growth. By the time Warburg turned his attention from sea-urchin cells to the cells of a rat tumor, in 1923, he knew that sea-urchin eggs increased their oxygen consumption significantly as they grew, so he expected to see a similar need for extra oxygen in the rat tumor. Instead, the cancer cells fueled their growth by swallowing up enormous amounts of glucose (blood sugar) and breaking it down without oxygen. The result made no sense. Oxygen-fueled reactions are a much more efficient way of turning food into energy, and there was plenty of oxygen available for the cancer cells to use. But when Warburg tested additional tumors, including ones from humans, he saw the same effect every time. The cancer cells were ravenous for glucose.

Warburg's discovery, later named the Warburg effect, is estimated to occur in up to 80 percent of cancers. It is so fundamental to most cancers that a positron emission tomography (PET) scan, which has emerged as an important tool in the staging and diagnosis of cancer, works simply by revealing the places in the body where cells are consuming extra glucose. In many cases, the more glucose a tumor consumes, the worse a patient's prognosis.

In the years following his breakthrough, Warburg became convinced that the Warburg effect occurs because cells are unable to use oxygen properly and that this damaged respiration is, in effect, the starting point of cancer. Well into the 1950s, this theory — which Warburg believed in until his death in 1970 but never proved — remained an important subject of debate within the field. And then, more quickly than anyone could have anticipated, the debate ended. In 1953, James Watson and Francis Crick pieced together the structure of the DNA molecule and set the stage for the triumph of molecular biology's gene-centered approach to cancer. In the following decades, scientists came to regard cancer as a disease governed by mutated genes, which drive cells into a state of relentless division and proliferation. The metabolic catalysts that Warburg spent his career analyzing began to be referred to as "housekeeping enzymes" — necessary to keep a cell going but largely irrelevant to the deeper story of cancer.

"It was a stampede," says Thomas Seyfried, a biologist at Boston College, of the move to molecular biology. "Warburg was dropped like a hot potato." There was every reason to think that Warburg would remain at best a footnote in the history of cancer research. (As Dominic D'Agostino, an associate professor at the University of South Florida Morsani College of Medicine, told me, "The book

that my students have to use for their cancer biology course has no mention of cancer metabolism.") But over the past decade, and the past five years in particular, something unexpected happened: Those housekeeping enzymes have again become one of the most promising areas of cancer research. Scientists now wonder if metabolism could prove to be the long-sought "Achilles' heel" of cancer, a common weak point in a disease that manifests itself in so many different forms.

There are typically many mutations in a single cancer. But there are a limited number of ways that the body can produce energy and support rapid growth. Cancer cells rely on these fuels in a way that healthy cells don't. The hope of scientists at the forefront of the Warburg revival is that they will be able to slow — or even stop — tumors by disrupting one or more of the many chemical reactions a cell uses to proliferate, and, in the process, starve cancer cells of the nutrients they desperately need to grow.

Even James Watson, one of the fathers of molecular biology, is convinced that targeting metabolism is a more promising avenue in current cancer research than gene-centered approaches. At his office at the Cold Spring Harbor Laboratory in Long Island, Watson, 88, sat beneath one of the original sketches of the DNA molecule and told me that locating the genes that cause cancer has been "remarkably unhelpful" — the belief that sequencing your DNA is going to extend your life "a cruel illusion." If he were going into cancer research today, Watson said, he would study biochemistry rather than molecular biology.

"I never thought, until about two months ago, I'd ever have to learn the Krebs cycle," he said, referring to the reactions, familiar to most high-school biology students, by which a cell powers itself. "Now I realize I have to."

Born in 1883 into the illustrious Warburg family, Otto Warburg was raised to be a science prodigy. His father, Emil, was one of Germany's leading physicists, and many of the world's greatest physicists and chemists, including Albert Einstein and Max Planck, were friends of the family. (When Warburg enlisted in the military during World War I, Einstein sent him a letter urging him to come home for the sake of science.) Those men had explained the mysteries of the universe with a handful of fundamental laws, and the young Warburg came to believe he could bring that same elegant simplicity and clarity to the workings of life. Long before his death, Warburg was considered perhaps the greatest biochemist of the 20th century, a man whose research was vital to our understanding not only of cancer but also of respiration and photosynthesis. In 1931 he won the Nobel Prize for his work on respiration, and he was considered for the award on two other occasions — each time for a different discovery. Records indicate that he would have won in 1944, had the Nazis not forbidden the acceptance of the Nobel by German citizens.

That Warburg was able to live in Germany and continue his research throughout World War II, despite having Jewish ancestry and most likely being gay, speaks to the German obsession with cancer in the first half of the 20th century. At the time, cancer was more prevalent in Germany than in almost any other nation. According to the Stanford historian Robert Proctor, by the 1920s Germany's escalating cancer rates had become a "major scandal." A number of top Nazis, including Hitler, are believed to have harbored a particular dread of the disease; Hitler and Joseph Goebbels took the time to discuss new advances in cancer research in the hours leading up to the Nazi invasion of the Soviet Union. Whether Hitler was personally aware of Warburg's research is unknown, but one of Warburg's former colleagues wrote that several sources told him that "Hitler's entourage" became convinced that "Warburg was the only scientist who offered a serious hope of producing a cure for cancer one day."

Although many Jewish scientists fled Germany during the 1930s, Warburg chose to remain. According to his biographer, the Nobel Prize-winning biochemist Hans Krebs, who worked in Warburg's lab, "science was the dominant emotion" of Warburg's adult life, "virtually subjugating all other emotions." In Krebs's telling, Warburg spent years building a small team of specially trained technicians who knew how to run his experiments, and he feared that his mission to defeat cancer would be set back significantly if he had to start over. But after the war, Warburg fired all the technicians, suspecting that they had reported his criticisms of the Third Reich to the Gestapo. Warburg's reckless decision to stay in Nazi Germany most likely came down to his astonishing ego. (Upon learning he had won the Nobel Prize, Warburg's response was, "It's high time.")

"Modesty was not a virtue of Otto Warburg," says George Klein, a 90-year-old cancer researcher at the Karolinska Institute in Sweden. As a young man, Klein was asked to send cancer cells to Warburg's lab. A number of years later, Klein's boss approached Warburg for a recommendation on Klein's behalf. "George Klein has made a very important contribution to cancer research," Warburg wrote. "He has sent me the cells with which I have solved the cancer problem." Klein also recalls the lecture Warburg gave in Stockholm in 1950 at the 50th anniversary of the Nobel Prize. Warburg drew four diagrams on a blackboard explaining the Warburg effect, and then told the members of the audience that they represented all that they needed to know about the biochemistry of cancer.

Warburg was so monumentally stubborn that he refused to use the word "mitochondria," even after it had been widely accepted as the name for the tiny structures that power cells. Instead Warburg persisted in calling them "grana," the

term he came up with when he identified those structures as the site of cellular respiration. Few things would have been more upsetting to him than the thought of Nazi thugs chasing him out of the beautiful Berlin institute, modeled after a country manor and built specifically for him. After the war, the Russians approached Warburg and offered to erect a new institute in Moscow. Klein recalls that Warburg told them with great pride that both Hitler and Stalin had failed to move him. As Warburg explained to his sister: "***Ich war vor Hitler da***" — "I was here before Hitler."

Imagine two engines, the one being driven by complete and the other by incomplete combustion of coal," Warburg wrote in 1956, responding to a criticism of his hypothesis that cancer is a problem of energy. "A man who knows nothing at all about engines, their structure and their purpose may discover the difference. He may, for example, smell it."

The "complete combustion," in Warburg's analogy, is respiration. The "incomplete combustion," turning nutrients into energy without oxygen, is known as fermentation. Fermentation provides a useful backup when oxygen can't reach cells quickly enough to keep up with demand. (Our muscle cells turn to fermentation during intense exercise.) Warburg thought that defects prevent cancer cells from being able to use respiration, but scientists now widely agree that this is wrong. A growing tumor can be thought of as a construction site, and as today's researchers explain it, the Warburg effect opens the gates for more and more trucks to deliver building materials (in the form of glucose molecules) to make "daughter" cells.

If this theory can explain the "why" of the Warburg effect, it still leaves the more pressing question of what, exactly, sets a cell on the path to the Warburg effect and cancer. Scientists at several of the nation's top cancer hospitals have spearheaded the Warburg revival, in hopes of finding the answer. These researchers, typically molecular biologists by training, have turned to metabolism and the Warburg effect because their own research led each of them to the same conclusion: A number of the cancer-causing genes that have long been known for their role in cell division also regulate cells' consumption of nutrients.

Craig Thompson, the president and chief executive of the Memorial Sloan Kettering Cancer Center, has been among the most outspoken proponents of this renewed focus on metabolism. In Thompson's analogy, the Warburg effect can be thought of as a social failure: a breakdown of the nutrient-sharing agreement that single-celled organisms signed when they joined forces to become multicellular organisms. His research showed that cells need to receive instructions from other cells to eat, just as they require instructions from other cells to divide. Thompson hypothesized that if he could identify the mutations that lead a cell to eat more glucose than it should, it would go a long way toward explaining how the Warburg effect and cancer begin. But Thompson's search for those mutations didn't lead to an entirely new discovery. Instead, it led him to AKT, a gene already well known to molecular biologists for its role in promoting cell division. Thompson now believes AKT plays an even more fundamental role in metabolism.

The protein created by AKT is part of a chain of signaling proteins that is mutated in up to 80 percent of all cancers. Thompson says that once these proteins go into overdrive, a cell no longer worries about signals from other cells to eat; it instead stuffs itself with glucose. Thompson discovered he could induce the "full Warburg effect" simply by placing an activated AKT protein into a normal cell. When that happens, Thompson says, the cells begin to do what every single-celled organism will do in the presence of food: eat as much as it can and make as many copies of itself as possible. When Thompson presents his research to high-school students, he shows them a slide of mold spreading across a piece of bread. The slide's heading — "Everyone's first cancer experiment" — recalls Warburg's observation that cancer cells will carry out fermentation at almost the same rate of wildly growing yeasts.

Just as Thompson has redefined the role of AKT, Chi Van Dang, director of the Abramson Cancer Center at the University of Pennsylvania, has helped lead the cancer world to an appreciation of how one widely studied gene can profoundly influence a tumor's metabolism. In 1997, Dang became one of the first scientists to connect molecular biology to the science of cellular metabolism when he demonstrated that MYC — a so-called regulator gene well known for its role in cell proliferation — directly targets an enzyme that can turn on the Warburg effect. Dang recalls that other researchers were skeptical of his interest in a housekeeping enzyme, but he stuck with it because he came to appreciate something critical: Cancer cells can't stop eating.

Unlike healthy cells, growing cancer cells are missing the internal feedback loops that are designed to conserve resources when food isn't available. They're "addicted to nutrients," Dang says; when they can't consume enough, they begin to die. The addiction to nutrients explains why changes to metabolic pathways are so common and tend to arise first as a cell progresses toward cancer: It's not that other types of alterations can't arise first, but rather that, when they do, the incipient tumors lack the access to the nutrients they need to grow. Dang uses the analogy of a work crew trying to put up a building. "If you don't have enough cement, and you try to put a lot of bricks together, you're going to collapse," he says.

Metabolism-centered therapies have produced some tantalizing successes. Agios Pharmaceuticals, a company co-founded by Thompson, is now testing a drug that treats cases of acute myelogenous leukemia that have been resistant to other therapies by inhibiting the mutated versions of the metabolic enzyme IDH 2. In clinical trials of the Agios drug, nearly 40 percent of patients who carry these mutations are experiencing at least partial remissions.

Researchers working in a lab run by Peter Pedersen, a professor of biochemistry at Johns Hopkins, discovered that a compound known as 3-bromopyruvate can block energy production in cancer cells and, at least in rats and rabbits, wipe out advanced liver cancer. (Trials of the drug have yet to begin.) At Penn, Dang and his colleagues are now trying to block multiple metabolic pathways at the same time. In mice, this two-pronged approach has been able to shrink some tumors without debilitating side effects. Dang says the hope is not necessarily to find a cure but rather to keep cancer at bay in a "smoldering quiet state," much as patients treat their hypertension.

Warburg, too, appreciated that a tumor's dependence upon a steady flow of nutrients might eventually prove to be its fatal weakness. Long after his initial discovery of the Warburg effect, he continued to research the enzymes involved in fermentation and to explore the possibility of blocking the process in cancer cells. The challenge Warburg faced then is the same one that metabolism researchers face today: Cancer is an incredibly persistent foe. Blocking one metabolic pathway has been shown to slow down and even stop tumor growth in some cases, but tumors tend to find another way. "You block glucose, they use glutamine," Dang says, in reference to another primary fuel used by cancers. "You block glucose and glutamine, they might be able to use fatty acids. We don't know yet."

Given Warburg's own story of historical neglect, it's fitting that what may turn out to be one of the most promising cancer metabolism drugs has been sitting in plain sight for decades. That drug, metformin, is already widely prescribed to decrease the glucose in the blood of diabetics (76.9 million metformin prescriptions were filled in the United States in 2014). In the years ahead, it's likely to be used to treat — or at least to prevent — some cancers. Because metformin can influence a number of metabolic pathways, the precise mechanism by which it achieves its anticancer effects remains a source of debate. But the results of numerous epidemiological studies have been striking. Diabetics taking metformin seem to be significantly less likely to develop cancer than diabetics who don't — and significantly less likely to die from the disease when they do.

Near the end of his life, Warburg grew obsessed with his diet. He believed that most cancer was preventable and thought that chemicals added to food and used in agriculture could cause tumors by interfering with respiration. He stopped eating bread unless it was baked in his own home. He would drink milk only if it came from a special herd of cows, and used a centrifuge at his lab to make his cream and butter.

Warburg's personal diet is unlikely to become a path to prevention. But the Warburg revival has allowed researchers to develop a hypothesis for how the diets that are linked to our obesity and diabetes epidemics — specifically, sugar-heavy diets that can result in permanently elevated levels of the hormone insulin — may also be driving cells to the Warburg effect and cancer.

The insulin hypothesis can be traced to the research of Lewis Cantley, the director of the Meyer Cancer Center at Weill Cornell Medical College. In the 1980s, Cantley discovered how insulin, which is released by the pancreas and tells cells to take up glucose, influences what happens inside a cell. Cantley now refers to insulin and a closely related hormone, IGF-1 (insulinlike growth factor 1), as "the champion" activators of metabolic proteins linked to cancer. He's beginning to see evidence, he says, that in some cases, "it really is insulin itself that's getting the tumor started." One way to think about the Warburg effect, says Cantley, is as the insulin, or IGF-1, signaling pathway "gone awry — it's cells behaving as though insulin were telling it to take up glucose all the time and to grow." Cantley, who avoids eating sugar as much as he can, is currently studying the effects of diet on mice that have the mutations that are commonly found in colorectal and other cancers. He says that the effects of a sugary diet on colorectal, breast and other cancer models "looks very impressive" and "rather scary."

Elevated insulin is also strongly associated with obesity, which is expected soon to overtake smoking as the leading cause of preventable cancer. Cancers linked to obesity and diabetes have more receptors for insulin and IGF-1, and people with defective IGF-1 receptors appear to be nearly immune to cancer. Retrospective studies, which look back at patient histories, suggest that many people who develop colorectal, pancreatic or breast cancer have elevated insulin levels before diagnosis. It's perhaps not entirely surprising, then, that when researchers want to grow breast-cancer cells in the lab, they add insulin to the tissue culture. When they remove the insulin, the cancer cells die.

"I think there's no doubt that insulin is pro-cancer," Watson says, with respect to the link between obesity, diabetes and cancer. "It's as good a hypothesis as we have now." Watson takes metformin for cancer prevention; among its many effects, metformin works to lower insulin levels. Not every cancer researcher, however, is convinced of the role of insulin and IGF-1 in cancer. Robert Weinberg, a researcher at M.I.T.'s Whitehead Institute who pioneered the discovery of cancer-causing genes in the '80s, has remained somewhat cool to certain aspects of the cancer-metabolism revival. Weinberg says that there isn't

yet enough evidence to know whether the levels of insulin and IGF-1 present in obese people are sufficient to trigger the Warburg effect. “It’s a hypothesis,” Weinberg says. “I don’t know if it’s right or wrong.”

During Warburg’s lifetime, insulin’s effects on metabolic pathways were even less well understood. But given his ego, it’s highly unlikely that he would have considered the possibility that anything other than damaged respiration could cause cancer. He died sure that he was right about the disease. Warburg framed a quote from Max Planck and hung it above his desk: “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die.”

http://bit.ly/1rN5Y9N

Guest Blog

It's Time to Retire Premed

The existing system of premedical education is broken, and needs to be fixed

By Nathaniel P. Morris on May 12, 2016

During my junior year of college, I waited in line with classmates to use a chemistry lab scale. We held fragile containers with an unknown white powder and had to identify the mystery powder using techniques like chromatography, distillation, and recrystallization. It was the most important lab of the year in organic chemistry.

Suddenly the girl next to me dropped her container. Her grade, her future, her hopes depended on that powder falling to her feet. When the container hit the floor, sending white dust across the floor, a nearby classmate pumped his fist and blurted out, “Yes!”

This is what it’s like to be pre-med.

Next month, students around the country will begin submitting their applications to medical schools. When we talk about the rigors of becoming a physician, we tend to focus on some classic rites of passage, like anatomy lab or intern year. But pre-med can be one of the most brutal and dehumanizing parts of medical training.

Medical school applicants generally have to complete a series of basic science courses, including biology, chemistry, organic chemistry, and physics. These requirements came to be after 1910, when the educator Abraham Flexner wrote a report on medical education for the Carnegie Foundation. Back then, medical schools had lax admissions standards and inconsistent, nonscientific curricula. But Flexner argued that medical training should be science-based and that applicants should complete undergraduate coursework in basic sciences in order to apply.

His recommendations were transformative. Since Flexner’s report, basic science classes have formed the foundation of how we screen aspiring doctors in the United States. Medical schools across the country have since required applicants to complete some variation of these core classes, and the Medical College Admission Test (MCAT) has largely focused on these subjects.

But this system of pre-med is outdated and broken. It has to be fixed.

The first issue is that the required basic science classes have become largely irrelevant to modern medicine. Ask any medical student or physician how much they use knowledge from their pre-med classes. They’ll probably laugh at you.

Do primary care doctors use atomic orbital theory or SN2 reactions in clinic? Do surgeons need to know black body radiation or Schrodinger’s time-independent equation to care for patients?

Of course, physics can help future doctors understand blood flow, and chemistry can teach students about drug receptors. But virtually every college class, from financial planning to gender studies, has some relevance to medical practice. The question is which core classes will best identify and prepare future doctors.

Instead these basic science classes have turned into factories of cutthroat competition. At many colleges and universities, these classes have become the gateways to medical school and fill up with hundreds of anxious pre-meds. For example, in 2009, my introductory chemistry class at Cornell had over 820 students, all of us trying to distinguish ourselves from the heap.

Making matters worse, professors frequently grade students on a curve. In other words, students’ grades don’t depend on their own performance, but rather the comparison to their peers. That’s why my classmate pumped his fist when the other student dropped her powder sample in chemistry lab. He literally benefited from her misfortune.

These classes have come to be known as “weed out” courses for their role in culling the students who can’t cut it. Indeed I know plenty of classmates who would have made fantastic doctors, but fell victim to this brutal process.

I remember once studying with a brilliant classmate before one of these exams. He hoped to be a doctor, but became discouraged by pre-med coursework and eventually switched career tracks. That night, as we sat at a library table, surrounded by textbooks and papers, he looked up at me and asked, “Why do we have to do this to help patients?”

I’m not sure. We all want compassionate, well-rounded physicians to care for us. We want doctors who can work in teams and who put patients’ interests first. Yet our current pre-med system bears little relationship to the practice of medicine and encourages students to focus on their own success above all else.

We should look for budding doctors who dream of caring for patients and spend their college years developing diverse passions. Students who study the injustices of socioeconomic disparities, the intricacies of music theory or the beauty of poetry can also make great physicians.

Research backs this up. Since 1987, the Icahn School of Medicine at Mt. Sinai has run a Humanities and Medicine Program (HuMed) that admits non-traditional applicants who haven't taken the usual pre-med requirements. In 2010, faculty there published a study of hundreds of students and found HuMed students and traditional pre-med students performed at virtually the same level in medical school.

Mt. Sinai has since expanded this program, and more medical schools have followed suit. Last year, the American Association of Medical Colleges released a new version of the MCAT that includes sections on social sciences and psychology. These are encouraging reforms, but we need to do more.

More than a century ago, Abraham Flexner recognized that medical education should be science-based. But we've since taken his recommendations too far. Today we "weed out" potentially wonderful doctors through a demoralizing maze of basic sciences that more often resembles the Hunger Games than a sensible recruitment process.

It's time for a new Flexner report. It's time to reconsider what we value in our physicians.

http://www.eurekalert.org/pub_releases/2016-05/cp-ste050516.php

Surprise! This eukaryote completely lacks mitochondria

Eukaryote that contains no trace of mitochondria

Mitochondria are membrane-bound components within cells that are often described as the cells' powerhouses. They've long been considered as essential components for life in eukaryotes, the group including plants, fungi, animals, and unicellular protists, if for no other reason than that every known eukaryote had them. But researchers reporting in the Cell Press journal Current Biology on May 12, 2016 now challenge this notion. They've discovered a eukaryote that contains absolutely no trace of mitochondria at all.

"In low-oxygen environments, eukaryotes often possess a reduced form of the mitochondrion, but it was believed that some of the mitochondrial functions are so essential that these organelles are indispensable for their life," says Anna Karnkowska, a former post-doctoral fellow at Charles University in Prague who is now at the University of British Columbia in Vancouver, Canada. "We have characterized a eukaryotic microbe which indeed possesses no mitochondrion at all."

Organisms from the genus Monocercomonoides have been recognized for more than 80 years. They are related to the human pathogens Giardia and Trichomonas, all of which belong to a group known as Metamonada, which lives exclusively in low-oxygen environments.

In the new study, Karnkowska and Vladimir Hampl at Charles University in Prague and BIOCEV, along with colleagues from the Czech Republic and Canada, sequenced the Monocercomonoides genome. They were surprised to find that this organism lacks all mitochondrial proteins.

Monocercomonoides seems to have gotten by without mitochondria thanks to a cytosolic sulfur mobilization system (SUF) that they acquired from bacteria and that appears to substitute for essential mitochondrial functions. Through a unique combination of events including the loss of many mitochondrial functions and the acquisition of this essential machinery from prokaryotes, "this organism has evolved beyond the known limits that biologists circumscribed," Karnkowska says.

Researchers have been looking for organisms lacking mitochondria for decades. As the years went by, it seemed more and more unlikely that a eukaryote that truly lacked mitochondria would ever be found. Nevertheless, Karnkowska, Hampl, and their colleagues now say there may be others.

"This amazing organism is a striking example of a cell which refuses to adhere to the standard cell biology text book, and we believe there may be many more similar examples in the so far hidden diversity in the world of microbial eukaryotes--the protists," Karnkowska says.

The researchers say they'd now like to learn more about how these organisms function. They'd also like to better characterize Monocercomonoides and its relatives to understand their discovery in a broader, evolutionary context.

"It is very likely that the mitochondrion is absent in the whole group called oxymonads," senior author Vladimir Hampl says. "We would like to know how long ago the mitochondria were lost."

Current Biology, Karnkowska et al.: "A Eukaryote without a Mitochondrial Organelle" *http://www.cell.com/current-biology/fulltext/S0960-9822(16)30263-9*

http://www.medscape.com/viewarticle/862961

Should Parents Be Allowed to Withhold Lifesaving Treatment?

What should be done for children whose parents reject the idea of providing them with potentially life-saving medical treatment?

Brandon Cohen May 12, 2016

In a recent article on Medscape, noted ethicist Arthur Caplan related the story of a 19-month-old Canadian infant who died of bacterial meningitis while his parents treated him with alternative remedies such as maple syrup, hot peppers, garlic, and horseradish. The parents elected not to take him to a medical doctor, even after a nurse acquaintance warned them of the severity of the child's condition. The parents were later found guilty of "failing to provide the necessaries of

life."[1] This heartbreaking story spurred passionate debate among healthcare professionals.

Unsurprisingly, most of those responding felt strongly that a seriously ill child must be seen and treated by mainstream medical professionals regardless of the parents' beliefs. (Some quotes have been edited for clarity.)

A surgeon kicked things off:

This is a serious problem: people who ignore the results of decades of research and development. I have been advised that because I am a medical school graduate, I am a member of a conspiracy against the sick and injured. This is so sad when it results in the loss of a life. Use intelligence and discernment!

A pathologist linked this kind of behavior with more commonly condemned forms of child abuse:

Child abuse can be actions of commission or omission. An example of an action of commission is beating a child. An example of an action of omission is not seeking medical care when absolutely needed. This tragic case would be classified in the latter category (a fatal omission). Society has the moral obligation to protect children because children cannot protect themselves.

A pediatrician advocated stronger legislation, asking,

"Would it be reasonable as a society to amend the Constitution to state that children must not be denied life-saving care, regardless of the belief system of the parent?"

But a dermatologist questioned the feasibility of the plan, asking in return,

"Do you mean to say the Constitution should be amended to require the federal government to fund 100% of the healthcare costs of children? How else will your proposal be realized?"

A pathologist who had been down this path offered a dose of reality:

More than 20 years ago, on behalf of our state medical association, I presented this issue to our legislative leadership. They were very empathetic but described the solid opposition within some of our faith-based community. This past session, the question again arose, and the corrective legislation again died. We need help, and perhaps different communication strategies, in presenting this issue to the public.

But some professionals saw valid options when it came to serious childhood illness. One physician wrote,

"How about we each live our own life and make our own decisions? Life is full of difficult decisions."

An internist shot back.

"This is a free country, and adults are certainly free to believe any sort of nonsense they wish, but they do not have the right to inflict their stupidity on their helpless children."

A health administrator thought it was counterproductive to take a hard line against those who did not seek mainstream medicine:

It is not a good idea to force people to take their loved ones to a hospital. These parents care the most about their child. If some people don't believe in medicine, we need to improve trust with medicine and the trustworthiness of those who practice it.

But a pediatrician was not buying this line of reasoning:

If you were talking about taking a dog or cat to a veterinarian, I would agree with you. But when you are saying parents have the right to eschew allopathic medicine due to a religious or philosophic concern, then you are condoning child abuse.

A registered nurse saw dangers in modern medicine that many other professionals were likely to dismiss:

Centers for Disease Control and Prevention statistics claim that more than 400,000 hospital-caused deaths occur every year. Doctors, hospitals, pharmaceuticals, and the medical insurance industry have set themselves up to prosper by treating symptoms and diseases and not to work intensively with patients on preventing morbidity with lifestyle changes. We provide lip service to prevention, but our livelihood is about the fix.

The final word goes to a nurse practitioner who offered a unique view on the complexity of the issue:

There have been times when I have encountered such parental opposition in the treatment of premature babies. What often happens is the neonatologist gets a court order to administer a treatment that the parents have declined, such as a blood transfusion. We have often found that parents cannot actually approve the transfusion but are okay as long as someone else takes the decision out of their hands. The parents aren't upset but are actually relieved when this approach is used. Their baby receives what is needed and they remain in good standing with their faith.

The full discussion of the topic is available on Medscape.

[1] *Graveland B. Alberta parents found guilty in son's death from meningitis. The Toronto Sun. April 26, 2016. http://www.torontosun.com/2016/04/26/alberta-parents-found-guilty-in-sons-death-from-meningitis Accessed May 2, 2016.*

http://bit.ly/1NuLEUm

Building blocks of life's first self-replicator recreated in lab

One of the hardest steps in the origin of life on Earth may be easier than chemists thought.

By Bob Holmes

RNA, or something very like it, has long been a strong candidate as the first self-replicating molecule in the origin of life. This is because it can both catalyse chemical reactions and carry genetic information. But chemists first needed to explain how a large, complex molecule like RNA could form spontaneously to begin the process. They had done so for some, but not all, components of the RNA molecule.

The biggest sticking point was that until now, no one had identified a plausible way to generate the two purine nucleosides, adenosine and guanosine – A and G

in the genetic code. Now a team led by Thomas Carell, an organic chemist at the Ludwig Maximilian University of Munich in Germany, may have found a method.

Previous efforts made the parts of a nucleoside separately and then linked them together – a stepwise process that generally yields a useless mess of many possible configurations.

Instead, Carell's team started with even simpler precursors and let the whole process unfold at once, under mildly acidic conditions that mimicked early Earth. Their approach worked, producing high yields of adenosine. Guanosine can then easily be made from this. Better yet, Carell's starting points – formic acid and molecules called aminopyrimidines – or their precursors have been found on comets, and thus were probably available at the origin of life.

Path of life

"We now have a pathway that would allow us to use simple molecules that were likely present on the early Earth," says Carell. The next step is to link the bases into a full-length RNA strand, he says.

Carell's discovery removes one of the key stumbling blocks to RNA-based scenarios of the origin of life, whether they involve RNA alone or in concert with primitive proteins, says Nicholas Hud, a chemist at the Georgia Institute of Technology in Atlanta. Moreover, Carell's chemical reaction should work equally well with more primitive, RNA-like molecules, making it an excellent candidate for the prebiotic world, says Hud.

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http://bit.ly/1selCLe

Students are using 'smart' spy technology to cheat in exams

Students are using smart technology to try to beat the exam system.

Ritesh Chugh

Students at a medical college in Thailand have been caught using spy cameras linked to smartwatches to cheat during exams. They used wireless spycams in eyeglasses to capture exam questions, transmit them to associates elsewhere and receive responses through linked smartwatches. But the entrance exam in question was cancelled after the plot was discovered and Arthit Ourairat, the rector of Rangsit University, posted pictures of the hi-tech cheating equipment on his Facebook page.

The cheating attempt has already been compared to Hollywood's classic spy dramas but it shows how easily such high-tech devices are available to those who seek to gain an unfair advantage in educational pursuits.

Unfortunately, it's a problem that will only get worse when devices such as smartglasses become cheaper and more readily available. Smartglasses such as Google Glass have the capability to take photos, send information and also display information on the lens itself, eliminating the need to connect to a smartwatch.

Smartwatch ban

It was around this time last year that universities globally started banning, or at least exploring a ban on, smartwatches in exams. Smartwatches are considered an aid to cheating in exams because they give easy access to stored text and images, language translation, mathematical calculations and internet access. Subsequent bans on smartwatches were also introduced by school boards for Year 12 exams in Australia.

But a blanket ban on all watches – traditional or smart – could be on the horizon, especially because it is difficult and impractical for exam invigilators to differentiate between the two in an exam environment.

Other gadgets

It's not just smartwatches we need to worry about. A plethora of hi-tech cheating gadgets exist that would also not look out of place in a James Bond or Mission Impossible film. These are devices such as special glasses with a built-in transmitter and a separate wireless earpiece, aimed at establishing a two-way secretive audio communication between people during exams.

There is a device marketed as a Cheating Watch that can store PDF, Word and other documents. But it also has a super-fast emergency button that locks other buttons and displays only the time when approached by any suspecting exam invigilator.

Many other devices are offered for covert cheating in exams through wireless audio transmission. There is even an Invisible Watch that appears to display nothing when the watch is switched on. But when viewed with special glasses sold with the watch, the screen becomes visible and you can see any uploaded content, such as your exam cheat notes.

An open market

Before you criticise me for giving away details of these devices, I should point out that there is a very open marketplace where they are being spruiked and sold as gadgets to aid cheating in exams. They are not hard to find. Similar devices are also being sold on Amazon and eBay, companies that appear to claim no ethical responsibility for what is being sold on their platforms. Prices range from as little as A$40 up to A$600, depending on the features. Although these devices could be used for legitimate purposes, the marketing of such gadgets to students for cheating in exams is an issue that is plaguing educational institutions.

Globally, educational institutions abhor the erosion of academic integrity and want students who are smart with gadgetry – not smart-cheaters. The dilemma facing exam administrators is deciding which devices to ban and how.

Similar to the ban on mobile phones in exams, any devices capable of storing, transmitting, receiving and displaying digital information should also be banned.

So, as a starting point, a ban on watches – traditional and smart – for now is the way forward.

In order to eliminate the problem of differentiating between watches in an exam environment, some Australian universities have already implemented bans on all wristwatches. Others across Australia and the world should follow suit.

As newer surreptitious technologies emerge, educational institutions will have to come up with better plans to combat these new ways of cheating, and devise solutions that could range from banning devices to scanning for radio signals as was done using drones in an exam in China!

http://www.medscape.com/viewarticle/862975

Vinegar and Diabetes: Dos and Don'ts

Question: What should patients know before taking vinegar to help lower their blood sugar levels?

Response from Andrea G. Scott,
PharmD, MPH Pharmacist, StoneSprings Hospital Center, Dulles, Virginia

Vinegar has been used for millennia as a food, drink, medicinal, preservative, and disinfectant. Fruit juices are fermented with yeast into wine, which is further fermented by acetic acid bacteria into vinegar. Various types of vinegar are made from apples (cider vinegar), grapes (wine vinegar, balsamic vinegar), cereals such as barley (malt vinegar), sugar, and other products. Distilled vinegar (white vinegar) is made from dilute distilled alcohol.

The US Food and Drug administration requires products labelled "vinegar" to contain at least 4% acetic acid. Cider and wine vinegars contain 5% to 6% acetic acid; white vinegar ranges from 4% to 7%.[1,2]

Vinegar has been used as a folk remedy for various conditions, including hypertension, weight loss, leg cramps, osteoarthritis, cancer prevention, jelly fish stings, and warts.[1] Before the availability of pharmacologic glucose-lowering therapy, vinegar was used as a home remedy for diabetes.[3]

Research to support the potential use of vinegar to lower blood sugar dates to 1988 when Japanese researchers showed that vinegar containing 5% acetic acid reduced insulin response in seven healthy volunteers.[4] In 1995, research in five healthy study participants who ate lettuce salad with white vinegar (5% acetic acid) as a salad dressing ingredient and white bread showed a reduced glycemic response. Salad dressings prepared with vinegar neutralized with sodium bicarbonate or a salt solution did not significantly affect the glycemic response.[5]

Other research in small numbers of healthy subjects (N ≤ 14) also showed postprandial antihyperglycemic effects.[6-8] The proposed mechanism for this effect is delayed gastric emptying.[5,6]

Two studies of patients with type 1 diabetes are available. In a study of 10 patients with type 1 diabetes and diabetic gastroparesis, ingestion of 30 mL apple cider vinegar in 200 mL of water further delayed gastric emptying.[9] In the second study, which was a randomized controlled crossover trial published as a research letter, 10 men with type 1 diabetes drank vinegar (30 mL vinegar plus 20 mL water) or placebo (50 mL water) 5 minutes before a meal of bread, cheese, turkey ham, orange juice, butter, and a cereal bar. Rapid-acting insulin was given on the basis of each patient's insulin-to-carbohydrate ratio. Vinegar reduced blood glucose by 20% compared with placebo.[10]

Most research on vinegar for hypoglycemic effects has focused on type 2 diabetes and prediabetes (insulin resistance). Several small studies[11-14] involving eight to 16 patients have shown mixed results of the effects of vinegar on glucose in patients with prediabetes and type 2 diabetes. In patients with type 2 diabetes controlled with metformin or diet, vinegar appears to lower postprandial glucose following a high-glycemic, but not a low-glycemic, meal.[11] In studies of patients with type 2 diabetes or prediabetes, vinegar reduced postprandial insulin levels and increased muscle glucose intake following a meal of bread, cheese, turkey ham, orange juice, butter, and a cereal bar.[12,13] Contrary to the positive results found with vinegar given before a meal, administration of vinegar before a 75-g glucose beverage did not affect blood glucose.[14]

The limited available research suggests that vinegar taken before a meal may lower blood glucose from 20% to 33%.[10,12] The response may depend on the type of glucose load—that is, a more pronounced response with a high-glycemic vs low-glycemic meal or glucose-containing beverage.[11,14]

Large amounts of vinegar can be irritating to the stomach and may cause nausea.[15] Hypokalemia (theoretically through renal potassium loss that occurs with bicarbonate production from acetate in vinegar) has been reported with long-term ingestion of 250 mL of vinegar per day.[16] Erosion of dental enamel also has been reported.[17] Patients should limit consumption to a maximum of 1-2 tablespoons of vinegar diluted with water twice daily. Drinking through a straw may increase palatability and reduce contact with the teeth. A more palatable way to consume vinegar is to combine it with olive oil as a salad dressing.

Vinegar tablets also are available, but they may contain varying amounts of acetic acid. Patients should avoid very concentrated vinegar tablets; concentrations of nonneutralized acetic acid greater than 20% can damage the esophagus.[18]

For patients who want to add vinegar to their daily diet, blood glucose should be checked more frequently and medication regimens may need to be adjusted

accordingly. Vinegar could reduce postprandial hyperglycemia and delay gastric emptying, so the dose of preprandial, short-acting insulin may require an adjustment. In patients with insulin-dependent diabetes and gastroparesis, blood glucose must be monitored more frequently to prevent hypoglycemia.

It should be emphasized to patients that the use of vinegar should not replace healthy eating habits, exercise, or any glucose-lowering medications.

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http://nyti.ms/1ThU1BQ

Scientists Talk Privately About Creating a Synthetic Human Genome

Scientists are now contemplating the fabrication of a human genome, meaning they would use chemicals to manufacture all the DNA contained in human chromosomes.

By ANDREW POLLACK MAY 13, 2016

The prospect is spurring both intrigue and concern in the life sciences community because it might be possible, such as through cloning, to use a synthetic genome to create human beings without biological parents.

While the project is still in the idea phase, and also involves efforts to improve DNA synthesis in general, it was discussed at a closed-door meeting on Tuesday at Harvard Medical School in Boston. The nearly 150 attendees were told not to contact the news media or to post on Twitter during the meeting.

Organizers said the project could have a big scientific payoff and would be a follow-up to the original Human Genome Project, which was aimed at reading the sequence of the three billion chemical letters in the DNA blueprint of human life. The new project, by contrast, would involve not reading, but rather writing the human genome — synthesizing all three billion units from chemicals.

But such an attempt would raise numerous ethical issues. Could scientists create humans with certain kinds of traits, perhaps people born and bred to be soldiers? Or might it be possible to make copies of specific people?

“Would it be O.K., for example, to sequence and then synthesize Einstein’s genome?” Drew Endy, a bioengineer at Stanford, and Laurie Zoloth, a bioethicist at Northwestern University, wrote in an essay criticizing the proposed project.

“If so how many Einstein genomes should be made and installed in cells, and who would get to make them?”

Dr. Endy, though invited, said he deliberately did not attend the meeting at Harvard because it was not being opened to enough people and was not giving enough thought to the ethical implications of the work.

George Church, a professor of genetics at Harvard Medical School and an organizer of the proposed project, said there had been a misunderstanding.

The project was not aimed at creating people, just cells, and would not be restricted to human genomes, he said. Rather it would aim to improve the ability to synthesize DNA in general, which co
ld be applied to various animals, plants and microbes.

“They’re painting a picture which I don’t think represents the project,” Dr. Church said in an interview.

He said the meeting was closed to the news media, and people were asked not to tweet because the project organizers, in an attempt to be transparent, had submitted a paper to a scientific journal.

They were therefore not supposed to discuss the idea publicly before publication. He and other organizers said ethical aspects have been amply discussed since the beginning.

The project was initially called HGP2: The Human Genome Synthesis Project, with HGP referring to the Human Genome Project. An invitation to the meeting at Harvard said that the primary goal “would be to synthesize a complete human genome in a cell line within a period of 10 years.”

But by the time the meeting was held, the name had been changed to “HGP-Write: Testing Large Synthetic Genomes in Cells.”

The project does not yet have funding, Dr. Church said, though various companies and foundations would be invited to contribute, and some have indicated interest. The federal government will also be asked.

A spokeswoman for the National Institutes of Health declined to comment, saying the project was in too early a stage.

Besides Dr. Church, the organizers include Jef Boeke, director of the institute for systems genetics at NYU Langone Medical Center, and Andrew Hessel, a self-described futurist who works at the Bay Area software company Autodesk and who first proposed such a project in 2012.

Scientists and companies can now change the DNA in cells, for example, by adding foreign genes or changing the letters in the existing genes.

This technique is routinely used to make drugs, such as insulin for diabetes, inside genetically modified cells, as well as to make genetically modified crops.

And scientists are now debating the ethics of new technology that might allow genetic changes to be made in embryos.

But synthesizing a gene, or an entire genome, would provide the opportunity to make even more extensive changes in DNA.

For instance, companies are now using organisms like yeast to make complex chemicals, like flavorings and fragrances.

That requires adding not just one gene to the yeast, like to make insulin, but numerous genes in order to create an entire chemical production process within the cell. With that much tinkering needed, it can be easier to synthesize the DNA from scratch.

Right now, synthesizing DNA is difficult and error-prone. Existing techniques can reliably make strands that are only about 200 base pairs long, with the base pairs being the chemical units in DNA.

A single gene can be hundreds or thousands of base pairs long. To synthesize one of those, multiple 200-unit segments have to be spliced together.

But the cost and capabilities are rapidly improving. Dr. Endy of Stanford, who is a co-founder of a DNA synthesis company called Gen9, said the cost of synthesizing genes has plummeted from $4 per base pair in 2003 to 3 cents now. But even at that rate, the cost for three billion letters would be $90 million. He said if costs continued to decline at the same pace, that figure could reach $100,000 in 20 years.

J. Craig Venter, the genetic scientist, synthesized a bacterial genome consisting of about a million base pairs. The synthetic genome was inserted into a cell and took control of that cell.

While his first synthetic genome was mainly a copy of an existing genome, Dr. Venter and colleagues this year synthesized a more original bacterial genome, about 500,000 base pairs long.

Dr. Boeke is leading an international consortium that is synthesizing the genome of yeast, which consists of about 12 million base pairs. The scientists are making changes, such as deleting stretches of DNA that do not have any function, in an attempt to make a more streamlined and stable genome.

But the human genome is more than 200 times as large as that of yeast and it is not clear if such a synthesis would be feasible.

Jeremy Minshull, chief executive of DNA2.0, a DNA synthesis company, questioned if the effort would be worth it.

“Our ability to understand what to build is so far behind what we can build,” said Dr. Minshull, who was invited to the meeting at Harvard but did not attend.

“I just don’t think that being able to make more and more and more and cheaper and cheaper and cheaper is going to get us the understanding we need.”

http://bit.ly/24Tbyp8

Would we want to regenerate brains of patients who are clinically dead?

A trial to see if it is possible to regenerate the brains of patients who have been declared clinically dead has been approved.

Reanima Advanced Biosciences aims to use stem cells, injections of peptides, and nerve stimulation to reverse "brain death as noted in clinical examination or EEG", a project which at least scores highly on ambition.

There is a small problem with the study, however, and a major one. The first issue is our definition of brain death, which involves the irreversible end of function – if it is curable, then patients were never brain dead in the first place.

We can get around this if we recognise that being "irreversibly dead" is technology dependent. For a long time, a lack of breathing and pulse were regarded as hallmarks of death, until resuscitation methods improved.

Today, drowning victims that suffer extreme hypothermia, lack of oxygen, and lack pulse and breathing for several hours can be revived (with luck and some heavy medical interventions). Even not having a heart isn't death if you are on the transplant surgeon's table.

Given historical precedent, then, we should not discount the possibility that some people currently regarded as irreversibly dead may be revivable by future medical technology. And if the Reanima project succeeds, we will have to revise our concept of brain death and possibly the status of some patients. Presumably, this also will make further research on patients in this state harder, since they are potentially savable and can be harmed by some interventions.

Whose brain is it anyway?

The tougher, ethical question is whether this actually would help the deceased person, or (assuming it works) even bring about a new person.

Personal identity is generally assumed to involve some form of continuity. For someone to survive, we are generally discontent with mere bodily survival, there has to be a person with some psychological continuity, too. Exactly what kind of continuity is often glossed over in standard philosophical considerations about personal identity since these are more often concerned with the metaphysics of what is going on than the messy issues of radical personality change or brain damage.

In the best possible case, the proposed Reanima treatment would miraculously restore the previously-declared dead person. They would regain full psychological continuity, the death certificate would be nullified, and they would continue their old life. They would clearly benefit because they would get a second chance at life.

But it is not hard to imagine that the treatment would not restore the brain completely: memories, personality and functions might be scrambled, lost, or replaced with newly-grown tissue.

A new person may have a life worth living and enjoy existing. They could be said to have benefited in the same way a child benefits from being brought into the world.

But if there is limited or no psychological continuity, then the original person won't benefit: they are now truly dead, since their body and brain have become a new person.

Would it make sense to want this kind of treatment if it only makes new people? It is not a health-restoring treatment for anybody, merely an unusual way of reproduction. And though we may want some part of the original person to remain, we could equally well transplant the organs to benefit other people.

The real problem of course is the possibility of creating persons who have lives that are not worth living, or beings that are not people but who we still have a moral duty to care for.

A new hope?

So, is this research worth doing? At the very least it may help us to learn more about neuro-regeneration, which is scientifically and medically useful. But this is still theoretical and unlikely to be successful

It might also be subtly self-defeating. If it shows promise, the ethical oversight will tighten, and if it looks really promising then the state of the body will start to shift from an anatomical donation to a very sick patient.

Navigating these practical ethics issues will require careful judgement.

The real problem may simply be that Reanima cannot deliver. Looking at their website leaves me wondering what the company actually is, beside a website offering an app.

It wouldn't surprise me if it turns out to be a viral campaign for some upcoming horror movie that fooled various news outlets. Still, it has registered a clinical trial and the CEO seems to be a real person with real ambitions.

Going after the high impact jugular rather than trying to tinker with small effects might be just what the doctor ordered for the medical industry, which has been criticised for not trying to solve the big problems.

Disrupting death is unlikely to be easy, but as author Seth Godin said: "Waiting for perfect is never as smart as making progress."

http://bit.ly/1ThV1G9

April was the warmest month ever recorded on Earth: NASA

Another month, another new record — for rising temperatures.

Alex Garofalo

The latest NASA data reveals that April was the warmest month ever recorded on Earth. The new record marks the 12th consecutive month of record-high global temperatures, as the scientific consensus remains that human activity is contributing to detrimental climate change across the globe.

NASA data uses the average global temperatures between 1951 and 1980 as a control. April 2016 was 1.11 degrees Celsius above that 1951-1980 average, the sixth straight month that the average global temperature has exceeded that average.

According to Slate, Gavin Schmidt, director of NASA's Goddard Institute for Space Studies, concluded that scientists can already predict with near certainty that 2016 will be the hottest year on record - a claim that's hardly astonishing because 15 of the 16 hottest years on record have occurred since 2001, according to AccuWeather.

The somber data comes in the wake of the landmark Paris Agreement, a global accord to reduce greenhouse gas emissions and transition from high-carbon fuels to cleaner energy sources.

Leaders from more than 170 nations signed the historic climate change pact April 22 during an Earth Day ceremony in New York City. The signing was the second of four steps required to cement the Paris Agreement into international policy. Individual countries now must ratify the deal domestically before the agreement has the force of law.

Some developing countries - including Belize, Fiji, the Marshall Islands, Somalia, Samoa and Tuvalu - have already taken this step, while other major powers, including the U.S. and China, the world's biggest polluters, are moving more slowly. U.S. Secretary of State John Kerry signed the agreement in April on behalf of the U.S. government. The U.S. "looks forward to formally joining this agreement this year, and we call on all of our international partners to do so," he said from the U.N. headquarters.