http://www.eurekalert.org/pub_releases/2015-06/uop-pca062215.php

Patient-controlled analgesia in the emergency department is effective

Twin studies, the first to analyse the effectiveness of patient controlled analgesia, (PCA, or patient administered pain relief) by following participants from the emergency department to the ward, show that PCA is an option for treating pain in emergency

Patients who arrive at the emergency department (ED) in moderate or severe pain are often given intravenous morphine, administered by a nurse. This is safe and works in the short term but is demanding of nursing time, particularly when repeated doses of painkillers are necessary.

One potential solution is for patients to administer their own pain relief using a patient controlled analgesia (PCA) device. A PCA device is a syringe usually containing morphine that can be connected to a drip in the patient's arm, which allows the patient to deliver their own pain relief by pressing a button. PCA devices are commonly used in other areas of the hospital (typically after an operation), but are not usually used in the ED.

Until now there has been little evidence to support the use of such a method in the emergency setting, and no previous study has assessed its effectiveness in the hours following admission to the ward.

Two randomised controlled trials carried out by NIHR-funded research teams from Plymouth Hospitals NHS Trust and Plymouth University Peninsula Schools of Medicine and Dentistry, and managed by the Peninsula Clinical Trials Unit at Plymouth University, have for the first time addressed this 'evidence gap' by assessing patient controlled analgesia in the ED and following admission in two clinical circumstances - patients with pain from traumatic injury and patients with non-traumatic abdominal pain. The studies were conducted in five NHS hospitals in England, and were supported by funding from the National Institute for Health Research (NIHR) Research for Patient Benefit programme.

The results of the trials, published today, 22nd June 2015, on-line in The BMJ, show that patient controlled analgesia is statistically and clinically superior for patients with non-traumatic abdominal pain when compared with standard methods of pain relief delivery. In patients with pain from traumatic injury, the results were more equivocal and it remains uncertain whether PCA offers any advantages to this group.

Both trials worked with a patient sample of 200, all of whom presented with moderate to severe pain and were expected to be admitted to hospital for at least 12 hours.

The routine care aspect of both trials was based on best current practice using different modes of analgesia according to NHS trust analgesia policy.

The difference was marked in the trial relating to patients presenting with abdominal pain, with PCA users reporting an average total pain score of 35.3 compared with 47.3 for those receiving usual pain relief.

The other trial, involving patients with pain from traumatic injuries, showed that total pain reported by those using PCA and those treated via usual pain relief methods were similar. Those using PCA reported an average total pain score of 44, compared to 47.2 for those who did not.

There were interesting, small yet clinically meaningful, secondary results from the studies. For example, patients in the trauma PCA group were almost twice as likely to be very or perfectly satisfied with their treatment compared with patients receiving routine care.

Professor Jason Smith, Consultant in Emergency Medicine at Plymouth Hospitals NHS Trust and Professor of Emergency Medicine at Plymouth University Peninsula Schools of Medicine and Dentistry, led the studies.

He said: "We were surprised that these two studies produced quite different results, but there are several possible reasons that have subsequently been suggested. Other factors may be important in patients with traumatic injuries, such as the effect of splinting on limb injuries."

He added: "Notwithstanding, my take on this is that in emergency patients who are in pain (either abdominal pain or pain from traumatic injuries), PCA should be considered as a possible treatment option, particularly in patients whose pain is difficult to manage. We have, on the back of the results of these studies, set up a clinical protocol for the use of PCA in emergency patients at Plymouth Hospitals NHS Trust."

http://bit.ly/1HkBHn7

Extreme Exercise Can Poison the Blood

Even four hours of intense activity may be enough to let bacteria escape from the gut into the blood, setting off a chain of inflammation. Christopher Intagliata reports

By Christopher Intagliata | June 22, 2015

If you're serious about fitness, you know the importance of training your muscles and your brain. Without the right prep, you won't have the physical or mental endurance to finish, whether it's a five-k or an Ironman. But it turns out that it may be just as important to train your gut—or suffer inflammatory consequences. So says a study in the International Journal of Sports Medicine. [Gill SK et al, The Impact of a 24-h Ultra-Marathon on Circulatory Endotoxin and Cytokine Profile]

Researchers sampled the blood of 17 runners before and after a 24-hour ultramarathon—where runners covered anywhere from 75 to 130 miles on foot. During the race, their guts got leaky—due to a lack of blood flow to the intestines, and the physical trauma from so many jarring miles. Gut bacteria escaped into the blood, where some released toxins. The runners' bodies then responded by launching an immune response, and inflammation set in.

Some runners actually had blood profiles identical to those of patients admitted to the hospital with blood poisoning, or sepsis. But the most well-trained competitors avoided the problem. Their bodies launched a counterattack, unleashing anti-inflammatory compounds to tamp down their bodies' immune overreaction.

The authors say just four hours of activity is extreme enough to kick off this chain of inflammation. Suggesting it's key to gradually build up to new personal bests, even if they're not ultraworthy. As has long been said: slow and steady wins the race.

http://bit.ly/1dkSGcw

A Better Way to Find Patient Zero

Computer simulations and a little math could help narrow the search for an outbreak's origins.

Nathan Collins

When George Soper, then a little-known sanitation engineer, was finally able to track down Mary Mallon, he was pretty sure he'd found the woman responsible for a series of typhoid outbreaks in early-20th century New York. Discovering patient zero—Typhoid Mary, in Soper's case—takes tireless effort even today, and while the concept has been criticized, identifying an outbreaks' origins can help scientists understand and prevent the next one. Now, health officials might get a helping hand: Researchers have found a new way to whittle down the list of likely candidates for that dubious title of patient zero.

Ordinarily, health officials try to gather the information necessary to finding patient zero through extensive interviews with patients. Often, that information isn't complete or entirely accurate, so Nino Antulov-Fantulin, a computational biologist at the Ruđer Bŏsković Institute in Zagreb, Croatia, and his colleagues tried to see if they could at least narrow the search.

Their method begins with real-world information about a disease outbreak—who's come into contact with whom, who's already gotten sick, and who hasn't. Step two is to pick someone at random, whom they assume is patient zero, and use computer simulations of a standard model called susceptible-immune-recovered (SIR) to see what happens next. In the SIR model, each sick person infects a fraction of the healthy people they come into contact with, and sick people recover at a rate determined by the disease in question.

It's a good start for an epidemiologist searching a population of 15,000 or more for patient zero.

For each potential patient zero, the team simulated 20,000 hypothetical epidemics and computed the fraction of those that matched the real-world list of people who'd contracted the disease—in other words, the likelihood a given person could have started an actual, observed outbreak. Compute those likelihoods for every possible patient zero, and the researchers can infer each person's probability of having been the source of the sickness.

The team tested its approach using data on sexual contacts between 6,642 escorts and 10,106 clients in Brazil between 2002 and 2008. Unfortunately, that data came from clients' online reviews of their escorts, so there wasn't much mention of sexually transmitted infections. The fix: Cook up 500 simulated epidemics and treat those as if they were real-world data.

With those caveats in mind, how well did the technique perform? The method couldn't reliably identify the true patient zero, but it did narrow things down quite a bit: In nearly all of the test runs, the technique identified the originator as either the true patient zero or someone within four degrees of separation on the contact network—friends of friends of friends of friends, so to speak. That's not perfect, but it's a good start for an epidemiologist searching a population of 15,000 or more for patient zero.

Even if the method isn't infallible, it has broad applicability, the team writes in Physical Review Letters; for example, it could help trace certain computer viruses back to their seedy hacker homes.

http://www.medscape.com/viewarticle/846692

Is SCD in Athletes Too Rare to Warrant Serious Precautions?

Sideline Consult: *How Seriously Should We Take the Risk for SCD?*

Bert R. Mandelbaum, MD, DHL (hon)

When midfielder Marc-Vivien Foé collapsed in the center circle of a French soccer field in 2003, sports medicine changed forever.

Foé's death during an international match showed just how poorly the world of professional sports had attended to sudden cardiac death (SCD), the leading medical cause of death among athletes. According to press reports, several minutes passed before anyone attempted to defibrillate the 28-year-old Cameroonian. An autopsy later revealed hypertrophic cardiomyopathy.[1]

Not only could his condition have been diagnosed long before he collapsed, but immediate defibrillation also might have revived him. Now professional sports leagues have begun to institute screening and make automated external defibrillators (AEDs) available. I'd like to see both of these programs expanded throughout competitive sports.

By the 2006 World Cup, the Fédération Internationale de Football Association (FIFA) had instituted screening for professional soccer players and referees with echocardiography and electrocardiogram (ECG) as part of a comprehensive medical examination. And in 2013, the organization began distributing medical emergency bags with AEDs to all 209 member associations.

Sports medicine has been divided on the screening part of this two-pronged approach. The Sports Cardiology Study Group of the European Society of Cardiology recommends universal ECG screening prior to sports participation.[2] But the American Heart Association (AHA) recommends only a cardiovascular-oriented history and physical examination.[3] Opponents of mandatory ECG screening argue that it is not cost-effective and that false positives would unnecessarily bar too many athletes from sports.[4]

Inaccurate Estimates of the Incidence of SCD

In part, these arguments rest on inaccurate estimates of the incidence of SCD. For example, the US Registry of Sudden Death in Athletes (USRSDA) attempted to extrapolate the number of sudden cardiac deaths by using media reports, reports by next of kin, and electronic databases. The researchers arrived at an incidence of 1 death in 164,000 US athletes.[5]

But studies in US college athletes, using more precise numbers of athletes and deaths, suggest that the incidence is closer to 1:50,000.[6] That puts US numbers more in line with a prospective cohort study in the Veneto region of Italy, in which the reported rate was 1:28,000 from 1979 to 1980 per athlete.[7] The incidence sank to 1:250,000 in the Veneto cohort from 2003 to 2004 following the implementation of mandatory screening with ECG throughout Italy.[7]

There was no change in the incidence of SCD in the general population during this time, suggesting that the screening program prevented athletes' deaths by disqualifying those most at risk from sports.[7]

Of course, initial screening will produce some false positives. But by using ECG and echocardiogram together with a detailed history and physical exam, we can flag those athletes who need further testing. Once these more extensive tests are completed, the risk for an unnecessary disqualification is low.

And it's worth noting that the AHA program of physical exams and family history without ECG can also produce false positives. In a study of 1596 US professional, college, and high school athletes, 23.8% had at least one positive response to the AHA personal and family elements questions.[8]

As technology improves, screening will become increasingly accurate. And screening itself will improve our understanding about the way risk factors vary.

Already we have learned about important demographic differences in athletes. Male athletes appear much more likely than female athletes to suffer from SCD. The most common cause of SCD in athletes in the United States appears to be hypertrophic cardiomyopathy, while in Italians it appears to be arrhythmogenic right ventricular cardiomyopathy.[9] Age matters too; in the United States, arteriosclerosis is the most common cause of SCD among athletes over age 40.[10]

FIFA has set up a registry to analyze SCD during soccer matches. As we learn more about this condition, our ability to screen for it will also improve.

Can Widespread Screening Be Cost-Effective?

Advances in technology can also address the other main objection to universal screening with ECG and echocardiogram: its price.

Cost-effectiveness projections have varied wildly. If the physical exam and family history from the AHA guidelines are combined with an ECG for an annual screening, Halkin and colleagues[11] estimate a staggering cost of $10.6 million-$14.4 million per life saved in the United States.

On the other hand, Wheeler and coworkers,[12] using a one-time screen, found a cost-effectiveness of $76,100 per year of life saved for the combination of history and physical and ECG, with an incremental cost-effectiveness of the ECG at $42,900.

As our healthcare system gradually shifts from fee-for-service to population health maintenance, I believe the costs of screening will come down and cost-effectiveness will increase. Step by step, we can move screening out to all of our athletes. In the future, it will become as routine as an influenza vaccination.

In the meantime, we need to take better advantage of another rapidly improving technology: automated defibrillation.

A Defibrillator at Every Athletic Venue?

In contrast to the clash over ECG screening, few experts debate the utility of making AEDs more available. The technology is rapidly improving. On newer models, once the cables are connected, the computer instructs the operator as to whether the patient can benefit from a shock, and if so, when and how many times to shock. It also explains when and even how to perform cardiopulmonary resuscitation.

But it's not only a matter of supplying a machine at every athletic venue. Staff must be prepared to act quickly. Once an athlete goes down, you have 2 minutes to shock the patient. The defibrillator must be charged and ready.

And defibrillation isn't enough. Every venue must prepare a system for swiftly evacuating patients to a medical center for more advanced care.

Last year, 25-year-old Italian soccer player Piermario Morosini suffered a sudden cardiac arrest and received defibrillation on the field.[13] But according to press reports, the ambulance's path was blocked by a city police car, slowing his transport to the hospital. Whether or not this delay actually played a role in his

death, the situation illustrates the importance of preparing for each step of the appropriate treatment of an athlete in cardiac arrest.

An example of how this can work took place in 2013 when 24-year-old Fabrice Muamba of the Bolton Wanderers, a professional soccer team in Bolton, England, also suffered a sudden cardiac arrest.[14] This time, the team was prepared. They first defibrillated him and then swiftly transported him to a hospital. The treatment he received there saved his life.[15]

I believe that every athlete—not just professionals—deserves this standard of care.

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Cell that replenishes heart muscle found by UT Southwestern researchers

Regenerative medicine researchers at UT Southwestern Medical Center have identified a cell that replenishes adult heart muscle by using a new cell lineage-tracing technique they devised

DALLAS - Regenerative medicine researchers at UT Southwestern Medical Center have identified a cell that replenishes adult heart muscle by using a new cell lineage-tracing technique they devised.

Adult heart muscle is comprised of cells called cardiomyocytes. Most cardiomyocytes don't replenish themselves after a heart attack or other significant heart muscle damage. The UT Southwestern researchers were able to devise a new cell-tracing technique, allowing them to detect cells that do replenish themselves after being damaged.

"We identified a cell that generates new heart muscle cells. This cell does not appear to be a stem cell, but rather a specialized cardiomyocyte, or heart muscle cell, that can divide, which the majority of cardiomyocytes cannot do," said Dr. Hesham Sadek, Assistant Professor of Internal Medicine and with the Hamon Center for Regenerative Science and Medicine.

Previous research by UT Southwestern scientists revealed that it is the highly oxygenated environment of the heart that prevents most heart muscle cells from dividing. The researchers reasoned that the cells that do divide must, therefore, be low on oxygen, which is a condition called hypoxic. They then devised a technique to identify and trace the lineage of hypoxic cells. That technique led them to the identification of the proliferating cells within heart muscle.

"For decades, researchers have been trying to find the specialized cells that make new muscle cells in the adult heart, and we think that we have found that cell," said Dr. Sadek, senior author of the study, which appears online in Nature.

"Now we have a target to study. If we can expand this cell population, or make it divide more, then we can make new muscle cells. This is what this cell does naturally, and we can now work toward harnessing this ability to make new heart muscle when the heart has been damaged."

The researchers found hypoxic microenvironments with proliferating cells scattered throughout the heart muscle. They found the rate of formation of new cells to be between 0.3 percent and 1 percent annually.

"This is exciting work from both scientific and methodological standpoints," said Dr. Joseph Hill, Chief of the Division of Cardiology and Professor of Internal Medicine at UT Southwestern, who holds the James T. Willerson, M.D. Distinguished Chair in Cardiovascular Diseases and the Frank M. Ryburn, Jr. Chair in Heart Research. "Dr. Sadek's discovery points to a novel mechanism of cell-cycle control in cardiac myocytes and lends credence to the potential for regenerating - rebuilding - the diseased heart."

The new technique used to find the regenerative cells, a process called fate mapping, is an equally important development that may prove useful for distinguishing similar regenerating cells in other organs, as well as in cancers, the researchers said.

Traditional fate mapping, which is somewhat like developing a family tree for cells, labels cells based on the expression of a certain gene. That didn't work for the hypoxic cells, which are mainly regulated at the protein level rather than the gene-expression level. Instead, the researchers developed a sophisticated protein-tracking technique based on the presence of a hypoxia-responsive protein called Hif-1alpha. Researchers developed a genetically modified mouse in which the Hif-1alpha protein is fused to another protein, called Cre recombinase, which could then be used for cellular labeling.

"This fate-mapping approach, based on protein stabilization rather than gene expression, is an important tool for studying hypoxia in the whole organism. It can identify any hypoxic cell, not just cardiomyocytes, so this has broad implications for cellular turnover in any organ, and even in cancer," said Dr. Sadek, whose lab focuses on cardiac regeneration and stem cell metabolism.

Other UT Southwestern researchers who contributed to the study are Dr. Wataru Kimura, Assistant Instructor in Internal Medicine; Dr. Feng Xiao, postdoctoral researcher; Dr. Diana C. Canseco, Assistant Instructor in Internal Medicine; Shalini Muralidhar, former postdoctoral researcher; Yezan Abdulrahman, postdoctoral fellow; SuWannee Thet, research associate; Helen M. Zhang, research assistant; Dr. Rui Chen, former Assistant Professor of Internal Medicine; Dr. Joseph A. Garcia, Associate Professor of Internal Medicine; John M. Shelton, senior research scientist; Dr. James A. Richardson, Professor of Pathology, Microbiology, and Plastic Surgery; Abdulrahman M. Ashour, research assistant; Dr. Asaithamby Aroumougame, Assistant Professor of Radiation Oncology; Hanquan Liang, computational biologist; Dr. Chao Xing, Associate Professor of Clinical Science; Dr. Zhigang Lu, research associate; and Dr. Cheng Cheng Zhang, Associate Professor of Physiology and Developmental Biology.

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Researchers find molecular mechanisms within fetal lungs that initiate labor

Researchers at UT Southwestern Medical Center have identified two proteins in a fetus' lungs responsible for initiating the labor process, providing potential new targets for preventing preterm birth.

DALLAS - Previous studies have suggested that signals from the fetus initiate the birth process, but the precise molecular mechanisms that lead to labor remained unclear. UT Southwestern biochemists studying mouse models found that the two proteins - steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2) - control genes for pulmonary surfactant components that promote the initiation of labor. Surfactant is a substance released from the fetus' lungs just prior to birth that is essential for normal breathing outside the womb.

"Our study provides compelling evidence that the fetus regulates the timing of its birth, and that this control occurs after these two gene regulatory proteins - SRC-1 and SRC-2 - increase the production of surfactant components, surfactant protein A and platelet activating factor," said senior author Dr. Carole Mendelson, Professor of Biochemistry, and Obstetrics and Gynecology at UT Southwestern.

"By understanding the factors and pathways that initiate normal-term labor at 40 weeks, we can gain more insight into how to prevent preterm labor," said Dr. Mendelson, Director of the North Texas March of Dimes Birth Defects Center at UT Southwestern.

Each year about one in every nine infants in the United States is born preterm (before 37 weeks), according to the Centers for Disease Control and Prevention. Premature birth can cause brain hemorrhage and respiratory distress for babies, as well as long-term conditions such as cerebral palsy, chronic lung disease, and impaired vision.

The study, which appears in the Journal of Clinical Investigation, was supported by the National Institutes of Health and a Prematurity Research Initiative grant from the March of Dimes Foundation.

UT Southwestern researchers found that the proteins SRC-1 and SRC-2 activate genes inside the fetus' lungs near full term, resulting in an increased production of surfactant components, surfactant protein A (SP-A), and platelet-activating factor (PAF). Both SP-A and PAF are then secreted by the fetus' lungs into the amniotic

fluid, leading to an inflammatory response in the mother's uterus that initiates labor.

The current study showed that a deficiency of both SRC-1 and SRC-2 inside the fetus' lungs drastically decreased the production of SP-A and PAF, causing a one- to two-day labor delay in mouse models, comparable to a three- to four-week labor delay in women.

Researchers further found that injecting either SP-A or PAF into the amniotic fluid of the deficient mice allowed the mothers to deliver on time. Together, the findings further define the underlying molecular mechanisms by which fetuses control the timing of birth.

Future research will include defining how fetal signals are transmitted to the mother's uterus, and relating these findings to the causes of preterm labor.

The study was conducted with current and former UT Southwestern researchers, including first author Dr. Lu Gao; Dr. Elizabeth Rabbitt; Dr. Jennifer Condon; Dr. Nora Renthal; Dr. John Johnston; Dr. Matthew Mitsche; and researchers from the Institut de Génétique et de Biologie Moléculaire et Cellulaire, France, and Baylor College of Medicine in Houston.

http://www.eurekalert.org/pub_releases/2015-06/hhmi-sfe061915.php

Studies find early European had recent Neanderthal ancestor

First genetic evidence that humans interbred with Neanderthals in Europe

In 2002, archaeologists discovered the jawbone of a human who lived in Europe about 40,000 years ago. Geneticists have now analyzed ancient DNA from that jawbone and learned that it belonged to a modern human whose recent ancestors included Neanderthals.

Neanderthals lived in Europe until about 35,000 years ago, disappearing at the same time modern humans were spreading across the continent. The new study, co-led by Howard Hughes Medical Institute (HHMI) investigator David Reich at Harvard Medical School and Svante Pääbo at the Max Planck Institute in Germany, provides the first genetic evidence that humans interbred with Neanderthals in Europe. The scientists reported their findings in the June 22, 2015, issue of the journal Nature.

"We know that before 45,000 years ago, the only humans in Europe were Neanderthals. After 35,000 years ago, the only humans in Europe were modern humans. This is a dramatic transition," Reich says. There is archaeological evidence that modern humans interacted with Neanderthals during the time that they both lived in Europe: Changes in tool making technology, burial rituals, and body decoration imply a cultural exchange between the groups. "But we have very few skeletons from this period," Reich points out.

So the jawbone that archaeologists uncovered in Romania in 2002, which radiocarbon dating determined was between 37,000 and 42,000 years old, was an important find. "It's an amazing bone," Reich says. The jawbone was found along with the skull of another individual in a cave called Pe?tera cu Oase. No artifacts were discovered nearby, so anthropologists had no cultural clues about who the individuals were or how they lived. The physical features of the jawbone were predominantly those of modern humans, but some Neanderthal traits were also apparent, and the anthropologists proposed that the bone might have belonged to someone descended from both groups.

Pääbo and Reich teamed up to investigate that possibility by analyzing DNA from the jawbone. Trace amounts of ancient DNA can be recovered from bones as old as the Oase jawbone, but to analyze it, that ancient DNA must be sifted out of an overwhelming amount of DNA from other organisms. When Qiaomei Fu, who was a graduate student in Pääbo's lab, obtained DNA from the bone, most of it was from microbes that lived in the soil where the bone was found. Of the fraction of a percent that was human DNA, most had been introduced by people who handled the bone after its discovery.

Using methods pioneered in Pääbo's lab, Fu enriched the proportion of human DNA in the sample, using genetic probes to retrieve pieces of DNA that spanned any of 3.7 million positions in the human genome that are considered useful in evaluating variation between human populations. Most of the DNA she ended up with was human, but came from people who had handled the jawbone since 2002, rather than the jawbone itself. Fu, who is now a postdoctoral researcher in Reich's group, solved that problem by restricting her analysis to DNA with a kind of damage that deteriorates the molecule over tens of thousands of years.

Once they had discarded the contaminating DNA, Reich's team could compare the fossil's genome to genetic data from other groups. Through a series of statistical analyses, a surprising conclusion emerged. "The sample is more closely related to Neanderthals than any other modern human we've ever looked at before," Reich says. "We estimate that six to nine percent of its genome is from Neanderthals. This is an unprecedented amount. Europeans and East Asians today have more like two percent."

That suggested the Oase individual's ancestry was recent. As DNA is passed on from generation to generation, segments are broken up and recombined, so that the DNA inherited from any one individual becomes interspersed with the DNA of other ancestors. Reich found segments of intact Neanderthal DNA in the fossil that were large enough to indicate that the Oase individual had a Neanderthal ancestor just four to six generations back. That suggests that modern humans interbred with Neanderthals after they had arrived in Europe.

"It's an incredibly unexpected thing," Reich says. "In the last few years, we've documented interbreeding between Neanderthals and modern humans, but we never thought we'd be so lucky to find someone so close to that event."

The Oase individual is not responsible for passing his Neanderthal ancestry on to present day humans, however. Reich found no evidence that he is closely related to later Europeans. "This sample, despite being in Romania, doesn't yet look like Europeans today," he says. "It is evidence of an initial modern human occupation of Europe that didn't give rise to the later population. There may have been a pioneering group of modern humans that got to Europe, but was later replaced by other groups."

http://www.eurekalert.org/pub_releases/2015-06/uoc-etd061915.php

Expanding the DNA alphabet: 'Extra' DNA base found to be stable in mammals

Researchers from the University of Cambridge and the Babraham Institute have found that a naturally occurring modified DNA base appears to be stably incorporated in the DNA of many mammalian tissues, possibly representing an expansion of the functional DNA alphabet.

The new study, published today (22 June) in the journal Nature Chemical Biology, has found that this rare 'extra' base, known as 5-formylcytosine (5fC) is stable in living mouse tissues. While its exact function is yet to be determined, 5fC's physical position in the genome makes it likely that it plays a key role in gene activity.

'This modification to DNA is found in very specific positions in the genome -- the places which regulate genes,' said the paper's lead author Dr. Martin Bachman, who conducted the research while at Cambridge's Department of Chemistry. 'In addition, it's been found in every tissue in the body -- albeit in very low levels.'

'If 5fC is present in the DNA of all tissues, it is probably there for a reason,' said Professor Shankar Balasubramanian of the Department of Chemistry and the Cancer Research UK Cambridge Institute, who led the research.

'It had been thought this modification was solely a short-lived intermediate, but the fact that we've demonstrated it can be stable in living tissue shows that it could regulate gene expression and potentially signal other events in cells.'

Since the structure of DNA was discovered more than 60 years ago, it's been known that there are four DNA bases: G, C, A and T (Guanine, Cytosine, Adenine and Thymine). The way these bases are ordered determines the makeup of the genome.

In addition to G, C, A and T, there are also small chemical modifications, or epigenetic marks, which affect how the DNA sequence is interpreted and control how certain genes are switched on or off. The study of these marks and how they affect gene activity is known as epigenetics.

5fC is one of these marks, and is formed when enzymes called TET enzymes add oxygen to methylated DNA -- a DNA molecule with smaller molecules of methyl attached to the cytosine base.

First discovered in 2011, it had been thought that 5fC was a 'transitional' state of the cytosine base which was then being removed from DNA by dedicated repair enzymes.

However, this new research has found that 5fC can actually be stable in living tissue, making it likely that it plays a key role in the genome.

Using high-resolution mass spectrometry, the researchers examined levels of 5fC in living adult and embryonic mouse tissues, as well as in mouse embryonic stem cells - the body's master cells which can become almost any cell type in the body.

They found that 5fC is present in all tissues, but is very rare, making it difficult to detect. Even in the brain, where it is most common, 5fC is only present at around 10 parts per million or less. In other tissues throughout the body, it is present at between one and five parts per million.

The researchers applied a method consisting of feeding cells and living mice with an amino acid called L-methionine, enriched for naturally occurring stable isotopes of carbon and hydrogen, and measuring the uptake of these isotopes to 5fC in DNA. The lack of uptake in the non-dividing adult brain tissue pointed to the fact that 5fC can be a stable modification: if it was a transient molecule, this uptake of isotopes would be high.

The researchers believe that 5fC might alter the way DNA is recognised by proteins.

'Unmodified DNA interacts with a specific set of proteins, and the presence of 5fC could change these interactions either directly or indirectly by changing the shape of the DNA duplex,' said Bachman.

'A different shape means that a DNA molecule could then attract different proteins and transcription factors, which could in turn change the way that genes are expressed.'

'This will alter the thinking of people in the study of development and the role that these modifications may play in the development of certain diseases,' said Balasubramanian. 'While work is continuing in determining the exact function of this 'extra' base, its position in the genome suggests that it has a key role in the regulation of gene expression.'

The research was supported by Cancer Research UK, the Wellcome Trust and the Biotechnology and Biological Sciences Research Council UK.

http://bit.ly/1LJSIXA

A Pickle A Day May Keep Your Anxiety At Bay

Fermented food appears to calm the nerves of the socially challenged

By Helen Thompson

Pickles, like many other fermented foods, can be an acquired taste. But, evidence suggests that might be a taste worth acquiring if you suffer from anxiety, as Rebecca Rupp reports for National Geographic.

A study in the August issue of Psychiatry Research finds that fermented foods—such as pickles, sauerkraut, and yogurt—eases the eater's social anxiety and in particular their neuroticism. The culprit: Probiotics or healthy bacteria that ferments the food. "It is likely that the probiotics in the fermented foods are favorably changing the environment in the gut, and changes in the gut in turn influence social anxiety," Matthew Hillimire, a psychologist at the College of William and Mary and a co-author of the study, said in a statement.

Hillmire and his colleagues enlisted 710 college students at William & Mary to record how much fermented food they ate and any symptoms of neuroticism, anxiety or social phobia that they felt over the same period. The team found a link between the amount of fermented food subjects consumed and the level of social anxiety they felt. Particularly neurotic subjects saw a decrease in their symptoms of shyness and fear of social situations when they ate more fermented food.

The study may suggest a link between fermented food and anxiety, but it's unclear if or how the sour foods might be relieving the socially challenged, but they think the microbiome may be involced. Previous studies in mice and other animals hinted that probiotics positively influence the human gut, and that healthy gut bacteria might have some implications for the mind as well. Rupp cites studies suggesting that mice without bacteria are more anxious and susceptible to stress. Clinical trials of probiotic substances had also pointed to potential mental health benefits, but those results are less clear-cut.

The good bacteria may increase levels of chemical in the brain called GABA controls anxiety. GABA sends messages to activate the same neural pathways as compounds in anti-anxiety medication. As Rupp puts it, "In other words, if you've got a case of social jimjams, eating a bowl of sauerkraut may be the equivalent of popping a Valium. Or maybe even better."

It's worth noting that the microbial ecosystem that inhabits human bodies varies from one individual to another. Figuring out the exact cause and effect relationship between fermented food and anxiety will require further study.

So, if you're socially challenged, a pickle might not be a cure-all, but there's a chance it could help calm your fears.

http://www.eurekalert.org/pub_releases/2015-06/p-dit061215.php

Discovery in the US of the New Guinea flatworm -- one of the worst known invasive species

has now been found in additional localities including in the Pacific area, as well as in France, the Caribbean, and the first report in mainland U.S., in Florida

The land planarian Platydemus manokwari, or New Guinea flatworm, is a highly invasive species, already reported in many territories in the Pacific area, and as well as in France. This is the only land planarian in the '100 worst invasive alien species' list and it has now been found in additional localities including islands in the Pacific area, Puerto Rico, the first record in the Caribbean, and the first report in mainland U.S., in Florida.

Platydemus manokwari, the New Guinea flatworm, consumes land snails and thus endangers endemic species. Very flat, it measures 50 mm long and 5 mm wide, the back is a black olive colour with a clear central stripe, and it has a pale white belly. The head is elongated, with two prominent black eyes and the mouth is in the middle of the belly. Although it lives on the ground, it is able to climb trees to follow and consume native snails.

An international research effort in to the spread of this invasive species was made up of 14 co-authors from eight countries and was led by Jean-Lou Justine of the Institute of Systematics, Evolution, Biodiversity, Paris, France (Muséum National d'Histoire Naturelle / CNRS / UPMC / EPHE). Their findings are published today in the Open Access Journal, PeerJ.

Specimens of the flatworm from various territories were identified by their characteristic appearance, a histological study and molecular analysis of the gene Cytochrome Oxidase Type I (which is often used to characterize animals). As a result, the species is now reported in additional countries and territories in the Pacific, including New Caledonia (mainland and Loyalty Islands), Tahiti (French Polynesia), Wallis and Futuna, Singapore, and the Solomon Islands, as well as in San Juan (Puerto Rico) and several gardens in Miami, Fla.

Two haplotypes (genetic variants) of the Cytochrome Oxidase Type I sequence were detected: the 'World haplotype' found in France, New Caledonia, French Polynesia, Singapore, Puerto Rico and Florida; and the 'Australian haplotype' found in Australia. The only locality with both haplotypes was in the Solomon Islands. The country of origin of Platydemus manokwari is New Guinea, and Australia and the Solomon Islands are the countries closest to New Guinea from which the researchers had specimens. This suggest that two haplotypes exist in the

area of origin of the species, but that only one of the two haplotypes (the 'World haplotype') has, through human agency, been widely dispersed.

Platydemus manokwari is a known threat for endemic terrestrial molluscs. The record in Florida is of particular concern because it is in mainland America. Until now, infested territories were mostly islands, and the spread of the species from island to island is limited. However, the flatworms now established in Florida will not be subjected to these limitations. In addition to their natural spread, flatworms can easily be passively spread with infested plants, plant parts and soil. Therefore, Platydemus manokwari could potentially spread from Florida throughout the U.S. mainland, and this should be considered a significant threat to the whole of the U.S. and even to the rest of the Americas.

Citation to the article: Justine, JL et. al. (2015) The invasive land planarian Platydemus manokwari (Platyhelminthes, Geoplanidae): records from six new localities, including the first in the U.S.A. PeerJ 3:e1037 https://dx.doi.org/10.7717/peerj.1037

http://www.eurekalert.org/pub_releases/2015-06/bu-coc061715.php

Cocktail of chemicals may trigger cancer -- global taskforce calls for research into how everyday chemicals in our environment may cause cancer

Fifty chemicals the public is exposed to on a daily basis may trigger cancer when combined, according to new research

A global taskforce of 174 scientists from leading research centres across 28 countries studied the link between mixtures of commonly encountered chemicals and the development of cancer. The study selected 85 chemicals not considered carcinogenic to humans and found 50 supported key cancer-related mechanisms at exposures found in the environment today.

Longstanding concerns about the combined and additive effects of everyday chemicals prompted the organisation Getting To Know Cancer led by Leroy Lowe from Halifax Nova Scotia, to put the team together - pitching what is known about mixtures against the full spectrum of cancer biology for the first time.

Cancer Biologist Dr Hemad Yasaei from Brunel University London contributed his knowledge regarding genes and molecular changes during cancer development. He said: "This research backs up the idea that chemicals not considered harmful by themselves may be combining and accumulating in our bodies to trigger cancer and might lie behind the global cancer epidemic we are witnessing. We urgently need to focus more resources to research the effect of low dose exposure to mixtures of chemicals in the food we eat, air we breathe and water we drink."

Professor Andrew Ward from the Department of Biology and Biochemistry at the University of Bath, who contributed in the area of cancer epigenetics and the environment, said: "A review on this scale, looking at environmental chemicals from the perspective of all the major hallmarks of cancer, is unprecedented".

Professor Francis Martin from Lancaster University who contributed to an examination of how such typical environmental exposures influence dysfunctional metabolism in cancer endorsed this view.

He said: "Despite a rising incidence of many cancers, far too little research has been invested into examining the pivotal role of environmental causative agents. This worldwide team of researchers refocuses our attention on this under-researched area."

In light of the compelling evidence the taskforce is calling for an increased emphasis on and support for research into low dose exposures to mixtures of environmental chemicals. Current research estimates chemicals could be responsible for as many as one in five cancers. With the human population routinely exposed to thousands of chemicals, the effects need to be better understood to reduce the incidence of cancer globally.

The research will be published in a special series of Oxford University Publishing's Carcinogenesis journal on Tuesday 23 June. William Goodson III, a senior scientist at the California Pacific Medical Center in San Francisco and lead author of the synthesis said: "Since so many chemicals that are unavoidable in the environment can produce low dose effects that are directly related to carcinogenesis, the way we've been testing chemicals (one at a time) is really quite out of date. Every day we are exposed to an environmental 'chemical soup', so we need testing that evaluates the effects of our ongoing exposure to these chemical mixtures."

The paper 'Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead' will be published on Tuesday, 23 June at 5.05am. A copy of the article is available here http://carcin.oxfordjournals.org/content/36/Suppl_1 please contact Gillian Trevethan above.

http://www.eurekalert.org/pub_releases/2015-06/uow-npc062215.php

Nonphotosynthetic pigments could be biosignatures of life on other worlds

To find life in the universe, it helps to know what it might look like.

If there are organisms on other planets that do not rely wholly on photosynthesis -- as some on Earth do not -- how might those worlds appear from light-years away?

That's among the questions University of Washington doctoral student Edward Schwieterman and astronomer Victoria Meadows of the UW-based, interdisciplinary Virtual Planetary Laboratory sought to answer in research published in May in the journal Astrobiology.

Using computer simulations, the researchers found that if organisms with nonphotosynthetic pigments -- those that process light for tasks other than energy production -- cover enough of a distant planet's surface, their spectral signal could be strong enough to be detected by powerful future telescopes now being designed. The knowledge could add a new perspective to the hunt for life beyond Earth.

Such organisms 'will produce reflectance, or brightness, signatures different than those of land vegetation like trees,' said lead author Schwieterman. 'This could push us to broaden our conception of what surface biosignatures might look like' on an exoplanet, or world beyond our solar system.

He said the research grew from a meeting with co-author Charles Cockell of the UK Centre for Astrobiology in 2012. Schwieterman sought a topic for a research rotation in the UW Astrobiology program in which students do work outside their main field of study.

'I was interested in doing biology in the lab and linking it to remotely detectable biosignatures, which are indications there is life on a planet based on observations that could be made from a space-based telescope or large ground-based telescope,' Schwieterman said.

There had already been literature about looking for something akin to Earth's vegetation 'red edge' as a possible biosignature on exoplanets, he said. The red edge -- caused by oxygen-producing organisms such as trees -- is the increase in brightness when you move from the visible wavelength range to the infrared, or light too red to see. It's why foliage looks bright in infrared photography and is often used to map vegetation cover by Earth-observing satellites.

Schwieterman and Cockell, a University of Edinburgh astrobiologist, decided to look further, and measure the reflectance of earthly organisms with different kinds of pigments. They included those that do not rely on photosynthesis to see what biosignatures they produce and how those might differ from photosynthetic organisms -- or indeed from nonliving surface features like rocks and minerals.

Pigments that absorb light are helpful to earthly organisms in ways other than just producing energy. Some protect against the sun's radiation or have antioxidants to help the organism survive extreme environments such as salt concentrations, high temperatures or acidity. There are even photosynthetic pigments that do not produce oxygen at all.

Schwieterman and Meadows then plugged their results Virtual Planetary Laboratory spectral models -- which include the effects of the atmosphere and clouds -- to simulate hypothetical planets with surfaces covered to varying degrees with such organisms.

'With those models we could determine the potential detectability of those signatures,' he said.

Exoplanets are much too far away to observe in any detail; even near-future telescopes will deliver light from such distant targets condensed to a single pixel. So even a strong signal of nonphotosynthetic pigments would be seen at best only in the 'disk average,' or average planetary brightness in the electromagnetic spectrum, Schwieterman said.

'This broader perspective might allow us to pick up on something we might have missed or offer an additional piece of evidence, in conjunction with a gaseous biosignature like oxygen, for example, that a planet is inhabited,' Schwieterman said.

The UW-based planetary lab has a growing database of spectra and pigments of nonphotosynthetic organisms and more that is available to the public, and to which data from this project have been added.

Schwieterman said much work remains to catalogue the range of spectral features that life on Earth produces and also to quantify how much of a planetary surface could conceivably be covered with pigmented organisms of any type.

'We also need to think about what kinds of adaptations might exist on other worlds that don't exist on Earth -- and what that means for the interaction of those possible extraterrestrial organisms with their light environments.'

http://www.eurekalert.org/pub_releases/2015-06/au-nkp062315.php

New knowledge: Parkinson's disease may begin in the gut

A major epidemiological registry-based study from Aarhus University and Aarhus University Hospital indicates that Parkinson's disease begins in the gastrointestinal tract; the study is the largest in the field so far

The chronic neurodegenerative Parkinson's disease affects an increasing number of people. However, scientists still do not know why some people develop Parkinson's disease. Now researchers from Aarhus University and Aarhus University Hospital have taken an important step towards a better understanding of the disease.

New research indicates that Parkinson's disease may begin in the gastrointestinal tract and spread through the vagus nerve to the brain.

"We have conducted a registry study of almost 15,000 patients who have had the vagus nerve in their stomach severed. Between approximately 1970-1995 this procedure was a very common method of ulcer treatment. If it really is correct that Parkinson's starts in the gut and spreads through the vagus nerve, then these vagotomy patients should naturally be protected against developing Parkinson's disease," explains postdoc at Aarhus University Elisabeth Svensson on the hypothesis behind the study.

A hypothesis that turned out to be correct:

"Our study shows that patients who have had the the entire vagus nerve severed were protected against Parkinson's disease. Their risk was halved after 20 years. However, patients who had only had a small part of the vagus nerve severed where not protected. This also fits the hypothesis that the disease process is strongly dependent on a fully or partially intact vagus nerve to be able to reach and affect the brain," she says.

The research project has just been published in the internationally recognised journal Annals of Neurology.

The first clinical examination

The research has presented strong evidence that Parkinson's disease begins in the gastrointestinal tract and spreads via the vagus nerve to the brain. Many patients have also suffered from gastrointestinal symptoms before the Parkinson's diagnosis is made.

"Patients with Parkinson's disease are often constipated many years before they receive the diagnosis, which may be an early marker of the link between neurologic and gastroenterologic pathology related to the vagus nerve ," says Elisabeth Svensson.

Previous hypotheses about the relationship between Parkinson's and the vagus nerve have led to animal studies and cell studies in the field. However, the current study is the first and largest epidemiological study in humans.

The research project is an important piece of the puzzle in terms of the causes of the disease. In the future the researchers expect to be able to use the new knowledge to identify risk factors for Parkinson's disease and thus prevent the disease.

"Now that we have found an association between the vagus nerve and the development of Parkinson's disease, it is important to carry out research into the factors that may trigger this neurological degeneration, so that we can prevent the development of the disease. To be able to do this will naturally be a major *breakthrough," says Elisabeth Svensson.*

Facts

Parkinson's disease is a chronic and neurodegenerative disease which affects approx. 1 out of every 1,000 people.

The first signs of the disease are most often seen between the ages of 50-60.

The researchers carried out a registry study involving 14,883 patients who had undergone a vagotomy.

The research project was supported by the Danish Parkinson's Disease Association and PROCRIN (Program for Clinical Research Infrastructure).

Read the scientific article here:
http://onlinelibrary.wiley.com/doi/10.1002/ana.24448/abstract

http://www.bbc.com/news/health-33237991

Mushroom used in Chinese medicine 'slows weight gain'

A mushroom used for centuries in Chinese medicine reduces weight gain in animals, say researchers in Taiwan.

By James Gallagher Health editor, BBC News website

Ganoderma lucidum growing on a fallen tree

The study, published in Nature Communications, suggested Ganoderma lucidum slowed weight gain by altering bacteria in the gut. The researchers suggested the mushroom could eventually be used in the treatment of obesity.

Experts said the science was good, but putting mushroom extract in cans of cola would not help people lose weight. G. lucidum has traditionally been sold for "health and longevity" say researchers at Chang Gung University.

They analysed the impact of the fungus on mice being fed a high-fat diet.

Those on just a high-fat diet reached 42g after their first two months whereas mice that were also fed a high dose of mushroom extract reached only 35g.

Mice were still much slimmer if they were fed a normal diet.

In their report, the team said mushroom extract "may be used as pre-biotics to reduce body weight gain, chronic inflammation and insulin resistance [type 2 diabetes] in obese individuals." Although this would, they said, need further testing in people.

Gut bugs

The team in Taiwan showed that adding the mushroom to the mice's meals altered the types of bacteria living in the gut. Gut bugs are heavily involved in digestion and the release of energy, and some species are associated with slim people and others with fat people. The scientists showed that transplanting faeces from the mushroom-fed mice to other mice - known as horizontal faeces transfer - helped the recipient keep off the pounds.

Prof Colin Hill, a microbiologist at University College Cork in Ireland, told the BBC News website: "I like the idea of some of these Chinese medicine stories coming back into science, I love the idea of revisiting traditional medicines.

"The microbiome is certainly a key player in weight gain and weight loss, it's certainly involved in extracting energy from our food. "But no intervention will overcome someone drinking lots of fizzy drinks, there won't be a magic pill, no mushroom extract in a can of coke will help people lose weight."

http://www.eurekalert.org/pub_releases/2015-06/asfm-ieu062415.php

In ERs, UTIs and STIs in women misdiagnosed, even mixed up nearly half the time

Urinary tract and sexually transmitted infections in women are misdiagnosed by emergency departments nearly half the time, according to a paper in the Journal of Clinical Microbiology, a publication of the American Society for Microbiology.

These misdiagnoses result in overuse of antibiotics, and increased antibiotic resistance, according to Michelle Hecker, MD, an assistant professor in the Department of Medicine, Division of Infectious Diseases, MetroHealth Medical Center, Case Western Reserve University, Cleveland, and her collaborators.

"Less than half the women diagnosed with a urinary tract infection actually had one," said Hecker. "Sexually transmitted infections were missed in 37 percent of the women, many of whom were wrongly diagnosed with urinary tract infections." The results, she said, indicate that emergency department diagnostic testing strategies for both types of infection need to be re-evaluated.

"Overdiagnosis of UTI [urinary tract infection] was not only a common cause of unnecessary antibiotic use but also contributed to the underdiagnosis of STI [sexually transmitted infection] since 64 percent of the patients with a missed STI were diagnosed as having a UTI instead," the investigators write. "An abnormal UA [urinalysis] result, seen in 92 percent of our subjects, was a common finding, poorly predicted the presence of a positive urine culture, and may also have contributed to the overdiagnosis of UTI."

Part of the problem arises from the fact that lower urinary tract infections share symptoms with some sexually transmitted infections, including dysuria (painful or difficult urination), frequency, and urgency. Additionally, urinary tract and sexually transmitted infections can result in similar findings from urinalysis.

Furthermore, the investigators found that women were often treated for urinary tract infections in the absence of related symptoms, and without having had a urine culture. "Twenty-four percent of the subjects diagnosed with UTIs had no possible UTI-related symptoms documented," the investigators write.

Additionally, of 21 subjects who received antibiotic therapy within a week after urine culture--eight percent of the total--10 had had negative urine cultures, and 12 received antibiotics which had no activity, or limited activity against the usual uropathogens, according to the report.

The study examined records from 264 women, ages 18-65, who were seen at the MetroHealth Medical Center emergency department. The investigators were able to retrieve urine samples the women had provided, and to test these for the sexually transmitted infections gonorrhea, chlamydia, and trichomonas in cases where these tests had not been ordered as part of routine care.

More than 1 million cases of urinary tract infections are diagnosed by emergency departments annually. The Centers for Disease Control and Prevention estimates that nearly 20 million new sexually transmitted infections occur annually, but many go unreported, and many more are undiagnosed.

The article can be found online at http://jcm.asm.org/cgi/reprint/JCM.00670-15v1?ijkey=mwWMjdx5ap9N6&keytype=ref&siteid=asmjournals.

http://bit.ly/1BHgrqS

Selection for a 'speed gene' behind increase in racehorse speed

Racehorses have been getting ever faster in races over all distances, a study of finishing times over the past 162 years has found.

15:30 24 June 2015 by Andy Coghlan

The findings challenge previous research that thoroughbreds had reached the limits of their speed. If anything, the improvement among sprinters is now accelerating.

"Over the past 15 years, sprinters have improved faster than over the previous 150 years," says Patrick Sharman of the University of Exeter.

Sharman and Alastair Wilson, also at Exeter, analysed 616,084 race times in the UK by 70,388 horses between 1850 and 2012. They then took a closer look at races between 1997 and 2012, for which more extensive and accurate data was available, including the speeds of non-winners inferred from finishing times.

The results show that since 1850, the speeds of winning horses in elite races have improved by 9-13 per cent, depending on the distance run. Winning horses now run between 1.5 and 2 metres per second faster than their counterparts did in 1850.

In the period between 1997 and 2012, sprinters improved most, adding 0.1 per cent to their speeds per year. Non-winners improved, too, adding between 0.03 and 0.09 per cent to their speeds per year.

So a 2012 horse would beat a 1997 horse in a sprint race by around 17 metres. The average winning margin in elite races is just 3 metres.

Speed gene

"The big question is why the improvement?" says Sharman. "Is it that we're breeding more successfully or the environment – factors such as better nutrition, changes in veterinary practice or training methods?" he asks.

Patrick Cunningham, from Trinity College Dublin, says that teasing apart genetic and environmental influences will be tricky.

"It's notoriously difficult to disentangle genetic from management factors in horse racing," he says. "Inevitably, they are confounded, as better bred horses go to better trainers, for example."

He thinks much of the improvement is down to selection.

"These analyses support the notion that selection is shifting speed, and more so at shorter distances," says Cunningham. "Selection is becoming more effective, with extended use of top stallions and increasing use of selection for a 'speed gene' – a variant of the gene that makes myostatin, a muscle protein."

Sharman believes that sprinters have improved fastest because breeders in the UK have focused more on winning short-distance races. "They do tend to select for speed rather than long-distance stamina," he says.

So can the horses carry on getting faster?

"There's got to be a limit at some point, but we don't know where that limit is," says Sharman. "At some point, there will be physiological and mechanical constraints that will prevent further improvements. Maybe they've already been reached for middle- and long-distance runners."

Not everyone was impressed with the gains in speed, however.

"The annual rates of improvement are very small, despite the attentions not only of breeders and genetic improvement but also of vets, nutritionists and other animal scientists," says William Hill of the University of Edinburgh. "It contrasts with rates of improvement in farm livestock, with annual genetic change in growth of broilers and milk yields of cattle exceeding 1 per cent a year."

"I think that at best, very slow improvement in the primary trait of racehorses needs explanation by contrast with changes in other species," he says.

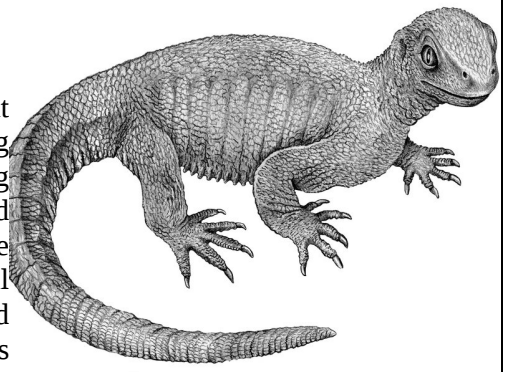
Journal reference: Biology Letters, DOI: 10.1098/rsbl.2015.0310

http://bit.ly/1TUdI3x

This Ancient Creature Shows How the Turtle Got Its Shell

The 240-million-year-old "grandfather turtle" may be part of the evolutionary bridge between lizards and shelled reptiles

By Rachel Nuwer



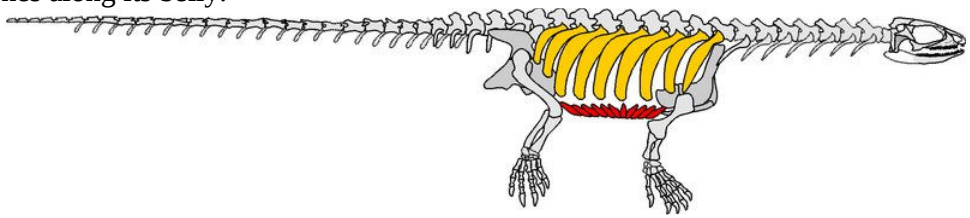
A reconstruction of "grandfather turtle." **Rainer Schoch**

Turtles are pretty mellow creatures, but they excel at causing strife among paleontologists. Researchers have long been left guessing as to how soft-backed animals somehow transitioned into the shell-carrying creatures we know so well today. Now, they have finally found fossils that help fill in the details of this critical evolutionary period.

The fossils, discovered in an ancient lakebed in Germany, belong to a newly named species called *Pappochelys*, Greek for "grandfather turtle." Estimated to be about 240 million years old—putting it smack dab in the middle of the Triassic period—*Pappochelys* seems to hit the evolutionary sweet spot between older suspected turtle ancestors and more recent and established family members.

Rainer R. Schoch from the Natural History Museum in Stuttgart, Germany, and Hans-Dieter Sues at the Smithsonian's National Museum of Natural History in Washington, D.C., gleaned knowledge about *Pappochelys* by studying an assortment of 18 fossil specimens, plus one skull. As they report today in *Nature*, the living animal would have been about 8 inches long from nose to tail, roughly the same size as a modern-day box turtle.

Pappochelys looked quite different than the turtles and tortoises of today, however. The animal had no shell, but it did have what appear to be the makings of one. Its ribs are broad and sturdy, and they fan out from the spine, a physiological set-up that the researchers suspect evolved not only for protection but also as a "bone ballast"—a way for the animal, which was likely aquatic or semiaquatic, to better control its buoyancy. That wasn't the only hint of what would eventually become turtles' trademark feature: *Pappochelys* also has a line of hard, almost shell-like bones along its belly.



Pappochelys' skeleton, viewed from the side, with turtle-elucidating rib and belly bones highlighted. **Rainer Schoch**

Pappochelys is critical for understanding "a new stage in the evolution of the turtle body plan," the researchers write. Prior to this discovery, a 220-million-year-old specimen from China, which displayed a partly formed shell and other turtle-like features, was the closest thing experts had to a seemingly sure-fire turtle relative. Other specimens, including a 260-million-year-old fossil from South Africa, were hypothesized to represent an even earlier turtle ancestor, but with such a large temporal gap separating them from the China specimen, researchers could not say for sure. Morphologically and chronologically, *Pappochelys* fits neatly between the two specimens, tying them together.

"At the time during which turtles evolved, all continents formed a single giant landmass known as Pangaea," Sues says in an email. "Thus, there were few—if

any—major obstacles to the dispersal of animals, so [fossils of] very closely related species can be found in South Africa and China, among other places."

In addition to illustrating how the turtle's shell evolution likely took place, *Pappochelys* helps answer another hotly debated question: whether turtles are more closely related to lizards and snakes or to dinosaurs and birds. Based on an examination of *Pappochelys'* skull, the researchers now possess evidence that turtles and tortoises fall firmly within the lizard and snake camp.

http://bit.ly/1eOuvF4

Blood test for pancreatic cancer could catch disease in time

It's the sneakiest of cancers – and as many as 80 per cent of cases are identified too late.

18:00 24 June 2015 by Andy Coghlan

But we now have a way to test for pancreatic cancer before it spreads.

The disease has one of the worst cancer survival rates, with less than 4 per cent of people living for five years or more after diagnosis. A major cause of this is that by the time symptoms start appearing, pancreatic cancer is often too advanced to treat successfully.

The disease is only identified in time for curative surgery in about 15 per cent of people, so early diagnosis is crucial for improving survival rates. Now, researchers have identified a protein that is present in the blood at much higher levels when a person has the disease, giving us a way to test for it.

The protein, glypican-1, sticks out from the surface of exosomes – little globules that are thought to bud off from pancreatic cancer cells. Other cells in the body also produce these exosomes, but they seem to carry much less of this protein.

Raghu Kalluri of the University of Texas MD Anderson Cancer Center in Houston found that there is so much more glypican-1 in people with pancreatic cancer that a blood test can be used to accurately distinguish them from both healthy controls and people with the disease pancreatitis. "The margin is always large enough to detect cancer exosomes," says Kalluri.

When to test?

"If exosomes from cancer cells can be reliably spotted, this technique could be a valuable way to spot and analyse genetic mistakes found in tumours," says Nell Barrie of the charity Cancer Research UK. "This could, in turn, one day offer a way to spot diseases like pancreatic cancer at a much earlier stage, although there is much more work to be done to develop this into an actual test," she says.

But Kalluri hopes a test for pancreatic cancer based on his team's findings can be made available soon. One use for it could be to screen those at particular risk, such as obese over-60s who smoke and have a family history of the disease.

The test could also be used for tracking the progress of therapies and recovery, says Kalluri. His team found that the concentration of glypican-1 increases with the disease's severity, potentially providing doctors with a measure for how advanced the cancer is and a way to monitor the effectiveness of treatments.

Former Apple CEO Steve Jobs and actor Patrick Swayze both had pancreatic cancer, which is so deadly partly because of its limited treatment options, with few new and effective drugs and therapies available.

Journal reference: Nature, DOI: 10.1038/nature14581

http://bit.ly/1CAonW2

What is artificial blood and why is the UK going to trial it?

Artificial blood will soon be tested in the UK for the first time. New Scientist takes a look at how – and why – this blood is made.

00:01 25 June 2015 by Colin Barras

What is artificial blood?

Blood substitutes aim to replicate one particular job of real blood: supplying oxygen to tissues. In other words, the goal is to find an alternative to oxygen-carrying red blood cells that could be used for transfusions. Today, the UK National Health Service announced it plans to start transfusing people with artificial blood by 2017 – the first clinical trials of this kind anywhere in the world.

Are there many different types?

More than you might think. Some researchers are working on blood substitutes based on the haemoglobin molecule that binds oxygen in red blood cells. One such product – Hemopure – is based on bovine haemoglobin, and was approved for human use in South Africa back in 2001. It is currently undergoing clinical trials in the US to help treat life-threatening anaemia.

Others are investigating whether it's possible to make entirely synthetic substitutes based on oxygen-carrying molecules like perfluorocarbons. But the version the NHS will trial is based around real red blood cells that were generated in the lab.

How are these cells made?

From stem cells. Researchers have previously managed to take hematopoietic stem cells from volunteers' bone marrow and encourage them to grow into red blood cells using chemical growth factors. The NHS will probably use a similar approach, although it also plans to explore using blood from umbilical cords – another rich source of hematopoietic stem cells.

Will it work?

It should do. Robert Lanza, chief scientific officer at Ocata Therapeutics – formerly Advanced Cell Technology - in Marlborough, Massachusetts, and his colleagues first grew red blood cells on a large scale in the lab in 2008. In 2011, Luc Douay at Pierre and Marie Curie University in Paris, France, and his

colleagues performed the first small transfusion of such lab-grown red blood cells into human volunteers. These cells behaved just like normal red blood cells, with about 50 per cent still circulating in the blood 26 days after the transfusion.

So there are no more hurdles to overcome?

Perhaps there is still one – volume. Douay said in 2011 that it will be a big challenge to scale up the technology to generate enough artificial cells for regular transfusion. In his team's experiment, they injected 10 billion artificial cells into volunteers, but that's equivalent to only 2 millilitres of blood.

Although Lanza's team was able to generate 100 billion cells, their technique used controversial embryonic stem cells. Even then, they produced about a twentieth of the number of cells that would be needed for a single transfusion.

Why even bother then?

The number of new volunteers giving blood fell in England and North Wales by 40 per cent last year. Because of this decline, the NHS says alternative supplies could become increasingly vital for its day-to-day operations. Artificial blood might also be an effective way of helping people with rarer blood types, for whom compatible donors are particularly thin on the ground.

http://bit.ly/1GAa5Xk

Our eye sockets give us a wider field of view than other apes

We have a lateral view that is unimpeded by the skull

14:00 25 June 2015 by Colin Barras

Among primates, humans are the kings of lateral thinking – and also of lateral vision. It seems that the shape of our eye sockets means we can view more of our world without moving our head than other great apes.

This may have given our ancestors an edge when they descended from forests into savannahs – but whether it drove our evolution or was the consequence of it is unclear.

Primates have forward-facing eyes, and humans are no exception. But look closely, says Eric Denion at the French Institute of Health and Medical Research in Caen, and you'll see that human eyes are different.

To work out just how different, Denion's team examined 100 modern human skulls and 120 ape skulls – 30 each belonging to gibbons, orangutans, gorillas and chimpanzees.

They found that the human eye sockets, or orbits, were much wider relative to their height than the other ape eye sockets. What's more, the outer margin – the side of the orbit furthest from the nose – is recessed much further back in the human skull than in other ape skulls.

This means that when we swivel our eyeballs sideways, we have a lateral view of the world that is unimpeded by the bones of the skull, unlike other apes.

Rolling eyes

Last year Denion and his colleagues showed that we can increase our visual field by almost 50 per cent by simply moving our eyes while our head is held still.

This suggests that the trait may have been beneficial to early humans. It would be more energy efficient and quicker to move the eyes rather than the whole head when they wanted to scan the savannah, says Denion.

That makes sense, says Robin Dunbar at the University of Oxford. "Better all-round vision would certainly be more advantageous for predator detection," he says.

Or perhaps they simply emerged as a consequence of other changes in the shape of our head. For example, our chewing muscles are smaller than those of our distant ancestors, who had to chew on harder, uncooked food, he says, which has affected the shape of our skull. Our eyes might protrude as an indirect consequence. But Dunbar says our protruding eyes are unlikely to have evolved purely by chance. "Given the significance of the difference, it must have fitness consequences," he says.

Another alternative is that our eyes began to protrude because there was a relaxation of the pressures forcing other apes to have relatively recessed eyes, says Denion. In forests, there is a constant danger of a stray branch damaging the eyes, and so other ape species may have evolved deep-set eyes to reduce the risk of injury. As humans moved out of forests, this evolutionary pressure might have diminished.

Journal reference: Scientific Reports, DOI: 10.1038/srep11528

http://www.eurekalert.org/pub_releases/2015-06/uoc--mpp062515.php

Multiple pathways progressing to Alzheimer's disease

Disorder develops differently in individuals, complicating efforts to diagnose early

The amyloid cascade hypothesis of Alzheimer's disease (AD) posits that sticky aggregations or plaques of amyloid-beta peptides accumulate over time in the brain, triggering a series of events that ultimately result in the full-blown neurodegenerative disorder. The hypothesis has been a major driver of AD research for more than 20 years.

However, in a new study published this week online in the Journal of Alzheimer's Disease, researchers at University of California, San Diego School of Medicine and Veterans Affairs San Diego Healthcare System suggest the picture is not so clear-cut, reporting that early indicators or biomarkers of AD development are not fixed in a specific sequence.

"Our current ability to identify early stages of AD is limited by the focus on amyloid accumulation and the expectation that biomarkers follow the same

timeline for all individuals," said Emily C. Edmonds, PhD, a senior postdoctoral fellow in the Department of Psychiatry and first author of the study.

But, Edmonds said, "AD is complex in the sense that there may be different neurobiological pathways leading to expression of the disease. Our findings suggest that the number of abnormal biomarkers and cognitive markers an individual possesses, without regard to the temporal sequence, is most predictive of future decline."

"Preclinical AD" is a very early stage of AD prior to the appearance of diagnosable symptoms. Current National Institute of Aging-Alzheimer's Association (NIA-AA) criteria for preclinical AD describe a disease progression that begins with accumulation of amyloid-beta, leading to neurodegeneration, cognitive decline and, eventually, diagnosable AD.

In their study, researchers classified 570 cognitively normal participants in the Alzheimer's Disease Neuroimaging Initiative according to NIA-AA criteria, and then separately examined the participants based upon the presence and number of abnormal biological and cognitive markers associated with preclinical AD. They found that neurodegeneration alone was 2.5 times more common than amyloid accumulation alone at baseline measurements.

They then examined only those participants who progressed to a diagnosis of mild cognitive impairment, which is an at-risk cognitive state of AD. They found that it was most common to show neurodegeneration as the first sign of early AD, and equally common to show amyloid accumulation or subtle cognitive decline as the first sign.

Edmonds said that the findings underscore the need to improve identification of persons at risk for AD through the use of multiple, diverse assessment tools. This includes sensitive learning and memory tests capable of reliably identifying cognitive changes at the earliest stages.

"At present, it is much more common for assessment of cognition to be based on insensitive screening measures or reports of cognitive problems by patients or their family members," said Edmonds. "These blunt screening tools can be very unreliable, which might explain why cognitive decline has traditionally been viewed as occurring later in the disease process. The integration of sensitive neuropsychological measures with assessment of biomarkers of AD can enhance our ability to more accurately identify individuals who are at risk for future progression to AD."

Co-authors include Lisa Delano-Wood, Douglas R. Galasko, and Mark W. Bondi, UCSD and Veterans Affairs San Diego Healthcare System; and David P. Salmon, UCSD.

Funding for this research came, in part, National Institutes of Health grants R01 AG012674, K24 AG026431 and P50 AG05131.

http://bit.ly/1IBtwzn

Most of America's poor have jobs, study finds

New study could shape poverty debate in presidential election

The majority of the United States' poor aren't sitting on street corners. They're employed at low-paying jobs, struggling to support themselves and a family.

In the past, differing definitions of employment and poverty prevented researchers from agreeing on who and how many constitute the "working poor."

But a new study by sociologists at BYU, Cornell and LSU provides a rigorous new estimate. Their work suggests about 10 percent of working households are poor. Additionally, households led by women, minorities or individuals with low education are more likely to be poor, but employed.

Science magazine says the data from this study is relevant to the upcoming presidential election, as candidates discuss ways to help the working poor move out of poverty. Understanding the size and characteristics of the group makes this goal more realistic.

BYU professor Scott Sanders says the findings dispel the notion that most impoverished Americans don't work so they can rely on government handouts.

"The toxic idea is if we clump all those people together and treat them as the same people, then we don't solve the real problem that the majority of people in poverty are working, trying to improve their lives, and we treat them all as deadbeats," Sanders.

Working poor is the term used to describe individuals or families who hold jobs, but can't break out of poverty. No standards currently exist for determining exactly who qualifies as working poor, so previous estimates vary widely in their results. This study compared 126 different measures of working poverty using 2013 population data. The authors found the most useful representation is determined when a head of household works at least half time and the household income is below 125 percent of the official poverty line.

"Having a unifying line saying we're all measuring working poverty the same way is important before we can see how any changes or improvements are made," Sanders said. "You can't fix a problem until you know what is the problem."

The study estimates that between 6.4 million and 8 million heads of families classify as working poor, which is actually less than the U.S. Bureau of Labor Statistics' 2011 estimate of 10.6 million.

Accurate data on the working poor is timely for current political dialogue. Recent months have seen low-wage workers staging "Fight for $15" rallies to raise the minimum wage nationwide. Whether or not a minimum wage hike would fix the problem, Sanders says the status quo is not the answer.

"It's been the push, that if we can get people working, then they'll get out of poverty," Sanders said. "But we have millions of Americans working, playing by the rules, and they're still trapped in poverty."

Brian Thiede of LSU is the lead study author. Sanders co-authored the study along with Daniel Lichter of Cornell University.

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Compound in magnolia may combat head and neck cancers

Honokiol, from magnolia bark, shuts down cancer cells in lab

Magnolias are prized for their large, colorful, fragrant flowers. Does the attractive, showy tree also harbor a potent cancer fighter?

Yes, according to a growing number of studies, including one from VA and the University of Alabama at Birmingham that is now online in the journal Oncotarget.

The study focused on squamous cell head and neck cancers, a scourge among those who use tobacco and alcohol. According to the National Cancer Institute, at least 3 in 4 head and neck cancers are caused by the use of tobacco and alcohol. The cancers have only a 50 percent survival rate, killing some 20,000 Americans each year.

Enter honokiol--chemical formula C18H18O2. As one of the major active compounds in magnolia extract, the phytochemical has been used for centuries in traditional Chinese and Japanese medicine to treat anxiety and other conditions. More recently, scientists have been discovering that the compound, found in magnolia bark, is a wily and versatile adversary of cancer. It seems to exploit many biochemical pathways to shrink tumors of various types, or to keep them from growing in the first place.

The Alabama scientists have now shown how it works against head and neck cancers: It blocks a protein called epidermal growth factor receptor, or EGFR. Prior research has found that almost all head and neck cancer cells display an over-abundance of the protein, and it had been suggested in the literature as a potential target.

The VA-UAB team says, based on its lab studies, that honokiol binds more strongly with EGFR than does the drug gefitinib (sold as Iressa), which is commonly used to treat head and neck cancers.

The researchers tested honokiol on cell lines derived from human cancers of the oral cavity, larynx, tongue, and pharynx. In all cases, the botanical shut down the aberrant cells. The team also tested it against tumors implanted into mice, with similar results.

Senior author Dr. Santosh K. Katiyar and his colleagues wrote, "Conclusively, honokiol appears to be an attractive bioactive small molecule phytochemical for the management of head and neck cancer which can be used either alone or in combination with other available therapeutic drugs."

Katiyar has published extensively in the past on other natural substances that work against tumors, especially skin cancer. Some of his recent work has focused on compounds in green tea, for example, and grape seed proanthocyanidins.

http://www.eurekalert.org/pub_releases/2015-06/cp-asm061815.php

A single mutation helped last year's flu virus gain an advantage over the vaccine

Most H3N2 influenza viruses circulating during the 2014-2015 influenza season were antigenically mismatched to the H3N2 component of the 2014-2015 influenza vaccine.

The 2014-2015 flu vaccine didn't work as well compared to previous years because the H3N2 virus recently acquired a mutation that concealed the infection from the immune system. A study published on June 25 in Cell Reports reveals the major viral mutation responsible for the mismatch between the vaccine strain and circulating strains. The research will help guide the selection of viral strains for future seasonal flu vaccines.

"Flu vaccines work best when they are similar to most circulating flu strains," says senior study author Scott Hensley of the Wistar Institute. "The World Health Organization recently recommended that a new H3N2 component should be incorporated into future formulations of seasonal flu vaccines. Our studies support this decision, since most circulating H3N2 strains are mismatched to the 2014-2015 vaccine strain."

Seasonal flu vaccines are designed to activate the immune system, but they are ineffective when viruses acquire mutations that help them evade the host's defenses. Flu vaccines must be updated regularly because influenza viruses continuously acquire mutations in a surface protein called hemagglutinin, which is targeted by antibodies in the infected host.

According to the Centers for Disease Control and Prevention, last season's flu vaccine was less than 20% effective at preventing medical visits associated with seasonal influenza illness, compared with up to 60% effectiveness of other seasonal flu vaccines during the past 10 years. Although previous studies revealed a mismatch between the H3N2 vaccine strain and most H3N2 strains circulating in the Northern Hemisphere during the 2014-2015 season, until now, it was not clear exactly which viral mutations were responsible for this mismatch.

To answer this question, Hensley and his team applied a reverse-engineering approach to convert the 2014-2015 H3N2 vaccine strain into a panel of H3N2 strains with hemagglutinin mutations that are present in currently circulating

H3N2 strains. They then examined whether these viruses would be recognized by antibodies present in blood samples taken from ferrets and sheep that had been exposed to the H3N2 vaccine strain. They found that a single mutation in the F159S amino acid residue of hemagglutinin decreased antibody recognition by as much as 75% compared with antibody recognition of the unaltered H3N2 vaccine strain.

The researchers then performed tests with blood samples taken from humans before and after immunization with the 2014-2015 vaccine. They found that vaccination was significantly less effective at increasing antibody recognition of the F159S-mutant strain compared with the unaltered vaccine strain. Taken together, the findings show that a single viral mutation could largely explain the ability of flu strains to get past the 2014-2015 flu vaccine.

"We find that some human immune responses are heavily focused on single regions of the flu virus and that single viral mutations can evade these immune responses," Hensley says. "Influenza viruses might have evolved in a way that promotes the generation of narrow immune responses that are easy to circumvent via single viral mutations."

Hensley and his team are now examining whether the new 2015-2016 H3N2 vaccine strain elicits robust immune responses to the different types of H3N2 strains that are currently circulating. To guide the design of subsequent vaccines, they are also attempting to predict how flu viruses might mutate in the future.

In the meantime, Hensley urges the public to continue to get annual flu vaccines. "Most years, vaccine strains are well matched to most circulating strains, and seasonal flu vaccines are usually more effective," he says. "The best way to prevent flu infection is by getting a flu vaccine."

The research was supported by the National Institute of Allergy and Infectious Diseases of the NIH under award numbers 1R01AI113047 and 1R01AI108686.

Cell Reports, Chambers et al.: "Identification of Hemagglutinin Residues Responsible for H3N2 Antigenic Drift during the 2014-2015 Influenza Season" http://dx.doi.org/10.1016/j.celrep.2015.06.005

http://www.eurekalert.org/pub_releases/2015-06/si-nds062415.php

New drug squashes cancer's last-ditch efforts to survive

Salk Institute and Sanford Burnham Prebys Medical Discovery Institute created a compound that stops a cellular recycling process to target cancer

LA JOLLA - As a tumor grows, its cancerous cells ramp up an energy-harvesting process to support its hasty development. This process, called autophagy, is normally used by a cell to recycle damaged organelles and proteins, but is also co-opted by cancer cells to meet their increased energy and metabolic demands.

Salk Institute and Sanford Burnham Prebys Medical Discovery Institute (SBP) scientists have developed a drug that prevents this process from starting in cancer cells. Published June 25, 2015 in Molecular Cell, the new study identifies a small molecule drug that specifically blocked the first step of autophagy, effectively cutting off the recycled nutrients that cancer cells need to live.

"The finding opens the door to a new way to attack cancer," says Reuben Shaw, a senior author of the paper, professor in the Molecular and Cell Biology Laboratory at the Salk Institute and a Howard Hughes Medical Institute Early Career Scientist. "The inhibitor will probably find the greatest utility in combination with targeted therapies."

Besides cancer, defects in autophagy have been linked with infectious diseases, neurodegeneration and heart problems. In a 2011 study in the journal Science, Shaw and his team discovered how cells starved of nutrients activate the key molecule that kicks off autophagy, an enzyme called ULK1.

Reasoning that inhibiting ULK1 might snuff out some types of cancer by stifling a main energy supply that comes from the recycling process, Shaw's group and others wanted to find a drug that would inhibit the enzyme. Only a fraction of such inhibitors that show promise in a test tube end up working well in living cells. Shaw's group spent more than a year studying how ULK1 works and developing new strategies for screening its function in cells.

A key breakthrough came when Shaw met the paper's other senior author, Nicholas Cosford, a professor in the NCI-Designated Cancer Center at SBP. Cosford had been investigating ULK1 using medicinal chemistry and chemical biology, and had identified some promising lead compounds using rational design. The two labs combined efforts to screen hundreds of potential molecules for ULK1 inhibition, narrowing the list down to a few dozen, and eventually one.

"The key to success for this project came when we combined Reuben's deep understanding of the fundamental biology of autophagy with our chemical expertise," says Cosford.

"This allowed us to find a drug that targeted ULK1 not just in a test tube but also in tumor cells. Another challenge was finding molecules that selectively targeted the ULK1 enzyme without affecting healthy cells. Our work provides the basis for a novel drug that will treat resistant cancer by cutting off a main tumor cell survival process."

The result was a highly selective drug they named SBI-0206965, which successfully killed a number of cancer cell types, including human and mouse lung cancer cells and human brain cancer cells, some of which were previously shown to be particularly reliant on cellular recycling.

Interestingly, some cancer drugs (such as mTOR inhibitors) further activate cell recycling by shutting off the ability of those cells to take up nutrients, making them more reliant on recycling to provide all the building blocks cells need to stay alive.

Rapamycin, for example, works by shutting down cell growth and division. In response, the cells launch into recycling mode by turning on ULK1, which may be one reason why, rather than dying, some cancer cells seem to go into a dormant state and return--often more drug resistant--after treatment stops.

"Inhibiting ULK1 would eliminate this last-ditch survival mechanism in the cancer cells and could make existing anti-cancer treatments much more effective," says Matthew Chun, one of the study's lead authors and a postdoctoral fellow in the Shaw lab at Salk.

Indeed, combining SBI-0206965 with mTOR inhibitors made it more effective, killing two to three times as many lung cancer cells as SBI-0206965 alone or the mTOR inhibitors alone.

Drugging the autophagy pathway to combat cancer has been tried before, but the only drugs that currently block cell recycling work by targeting the cell organelle known as the lysosome, which functions at the final stage of autophagy. Although these lysosomal therapies are being tested in early-stage clinical trials, they inhibit other lysosomal functions beyond autophagy, and therefore may have additional side effects.

Comparing equivalent concentrations of the lysosomal drug chloroquine with SBI-0206965, in combination mTOR inhibitors, the scientists found that SBI-0206965 was better than chloroquine at killing cancer cells.

The group is now testing the drug in mouse models of cancer. "An important next step will be testing this drug in other types of cancer and with other therapeutic combinations," says Shaw, who is deputy director of Salk's NCI-Designated Cancer Center.

"In the meantime, this discovery gives researchers an exciting new toolbox for the inhibition and measurement of cell recycling."

Other authors on the study include co-lead author Daniel Egan of Salk's Molecular and Cell Biology Laboratory; Mitchell Vamos, Haixia Zou, Juan Rong, Dhanya Raveendra-Panickar, Douglas Sheffler, and Peter Teriete of the Cell Death and Survival Networks Research Program in the NCI-Designated Cancer Center at SBP; Chad Miller, Hua Jane Lou, and Benjamin Turk of the Department of Pharmacology in Yale University School of Medicine; John Asara of the Division of Signal Transduction in Beth Israel Deaconess Medical Center and the Department of Medicine in Harvard Medical School; and Chih-Cheng Yang of SBP's Functional Genomics Core.

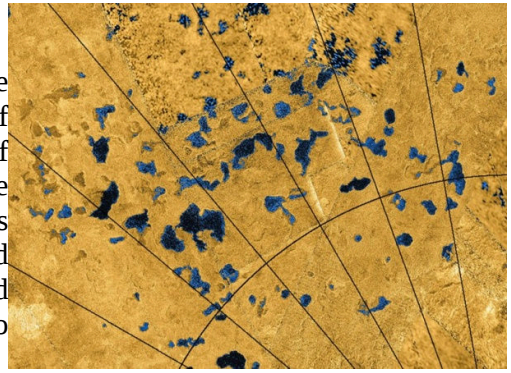
The research was supported by National Institutes of Health, the Department of Defense, and the Leona M. and Harry B. Helmsley Charitable Trust.

http://bit.ly/1BJzLUl

Sinkholes Filled With Liquid Methane and Ethane

Strange and changeable lakes might form just as certain water-filled lakes do on Earth

By Marissa Fessenden



For a long time, nobody knew what the surface of Titan looked like. One of Saturn's moons, a thick atmosphere of methane and other gases kept the surface obscured. It wasn't until the Huygens probe landed on the Titan's surface, and the Cassini orbiter used its infrared and radar sensors, that scientists were able to peer beyond the haze.

***Colorized radar images from the Cassini spacecraft show some of the many lakes on Titan* (NASA/JPL-Caltech/ASI/USGS)**

With their newfound imagery of Titan, researchers learned that the moon is spotted and marked with liquid — not water, but hydrocarbons like ethane and methane. Now, a team of scientists has figure out how Titan's lakes form, reports Jessica Mendoza for The Christian Science Monitor.

Titan is home to three large seas called mares, the largest of which (the Kraken Mare) stretches about 680 miles long. Rivers of hydrocarbons flow from them. The many shallower lakes however, are generally in flat areas and didn't have rivers feeding them. Those depressions were a mystery for researchers who wondered how they formed, especially since they can change depth and shape. Geology on Earth gave them clues. Mendoza writes:

Though the moon's icy surface temperatures – roughly minus 292 degrees Fahrenheit — means that liquid methane and ethane, not water, dominate its surface, Cornet and his team found that Titan's lakes resemble Earth's caves, sinkholes, and sinking streams.

These Earthly features, known as karstic landforms, result from erosion of dissolvable rocks, such as limestone and gypsum, in groundwater and rainfall. How fast the rocks erode depends on factors such as humidity, rainfall, and surface temperature. The scientists, assuming that Titan's surface is covered in solid organic material and that the main dissolving agent is liquid hydrocarbons, calculated how long it would take for parts of Titan's surface to create these features.

The team reports in the Journal of Geophysical Research, Planets that in the rainy polar regions, a 300-foot depression could form in about 50 million years. That rate is about 30 times slower than such lakes form on Earth's surface. Closer to the equator, a drier region, the same depression might take 375 million years.

"Of course, there are a few uncertainties: The composition of Titan's surface is not that well constrained, and neither are the long-term precipitation patterns, but our calculations are still consistent with the features we see today on Titan's relatively youthful billion-year-old surface," says Thomas Cornet of the European Space Agency in a press statement by Emily Baldwin from NASA's Jet Propulsion Laboratory.

For his blog "Life Unbounded" at Scientific American, Caleb Scharf adds:

Once again, Titan - for all of its utterly un-earthly characteristics - is seemingly sculpted by a set of universal planetary processes. It's an excellent example of how our quest to discover and explore new worlds is ultimately deeply connected to understanding the Earth itself.

http://bit.ly/1GArWNI

Could This Head Gear Help Treat Parkinson's Disease?

Students at Johns Hopkins University have created an at-home brain-stimulating device to ease Parkinson's symptoms

By Emily Matchar

One million Americans suffer from the tremors, stiffness and slurred speech of Parkinson's disease. Major depression affects some 16 million US adults a year, and nearly 30 million Americans deal with the pain of migraine headaches, while about 1 in 1,000 endure the agony of even more painful cluster headaches. Medications are usually the first-line treatment for these and other neurological conditions, with deep brain stimulation surgery—where a surgeon cracks a patient's skull and places tiny electrodes in the brain tissue as a sort of "brain pacemaker"—sometimes used as a last resort.

What if, instead of side effect-ridden drug regimens or invasive surgeries, these conditions could be treated by painlessly stimulating the brain from outside the skull?

"What if there's a way to do this noninvasively?" Ian Graham, a biomedical engineering graduate student at Johns Hopkins University, wondered after witnessing a multi-hour deep brain stimulation surgery for depression.

Transcranial stimulation, or stimulating the brain from outside the skull, has become one of the hottest areas in biomedical engineering. The method is usually done in one of two ways. One technique, called transcranial direct current stimulation, uses electrodes placed on the scalp to send electrical signals to the brain. The other, called transcranial magnetic stimulation, uses a magnetic coil on the scalp to produce electrical activity in the brain. Different locations of the brain are stimulated at different intensities and frequencies based on the condition being treated. While no one is sure precisely how brain stimulation improves Parkinson's and other conditions, it's understood that the stimulation can affect how neurons fire and can regulate neurotransmitters like serotonin and dopamine.

Graham and other biomedical engineers at Johns Hopkins invented a headpiece that uses electrodes to stimulate the brains of Parkinson's patients. The STIMband device, which will begin clinical trials later this year or early next year, is meant to be used at home, which sets it apart from other transcranial stimulation devices. The students hope it will help deal with some of the more debilitating symptoms of Parkinson's, including tremor and balance issues. Earlier this month, the STIMband won a $5,000 second-place prize in VentureWell's BMEidea national design contest for biomedical and bioengineering students.

With STIMband, the students place the electrodes in locations known from computer modeling to stimulate parts of the brain affected by Parkinson's. They observed patients participating in Johns Hopkins studies on transcranial direct current stimulation and were impressed by the results.

"I've seen a patient come in, and after treatment he had to sign his name," says Graham. "He said he hadn't been able to write like that in years."

The students met with patients in the hospital's Parkinson's clinic over many months to gather data about what people really needed in an at-home device. Eventually, they came up with a battery-powered design roughly based on a baseball cap, which can be easily slipped on and controlled with a large button.

STIMband treatment would start in the neurologist's office, where the device would be fitted to the patient. The patient would then take the STIMband home and use it for 20 minutes a day, every day. Treatment might eventually be modified based on individual results, but Graham says the patients would likely use the STIMband indefinitely, as long as they're seeing positive results.

"Since PD [Parkinson's Disease] is degenerative, and the STIMband acts differently than the medication, it should also prove beneficial for a longer period of time," says Graham. "Unfortunately that period of time is still unknown."

If STIMband trials prove successful, the group hopes to achieve FDA approval. The device would likely cost between $600 and $1,000, depending on material choices.

Transcranial stimulation is currently being studied by researchers as a treatment for neurological and neuropsychiatric conditions, including epilepsy, stroke, Tourette's syndrome, depression and mania, migraine, schizophrenia, eating disorders, dystonia (painful involuntary muscle contractions) and chronic pain. But the FDA has only approved transcranial magnetic stimulation for medication-resistant depression.

"This is not like placing refrigerator magnets on people's heads," says neurologist David Brock, the medical director of Neuronetics, the company that produces

NeuroStar, a transcranial magnetic stimulation device for depression. NeuroStar treatment is given in a doctor's office. For a period of four to six weeks, patients come in five days a week for 45-minute sessions. They sit in a chair reading or listening to music while the device, placed over the left side of their forehead, stimulates their left prefrontal cortex.

People often mistakenly consider transcranial stimulation to be an alternative treatment, Brock says, but it's actually backed up by clinical data. Studies show about 30 to 40 percent of treatment-resistant depression patients go into remission after using NeuroStar, while more have some improvement of symptoms.

Nor is transcranial stimulation like electroconvulsive therapy (ECT), or "shock treatment," the stigmatized but often highly effective depression treatment that uses electricity to induce a seizure. Unlike ECT, transcranial stimulation doesn't induce a seizure and doesn't necessitate general anesthesia or a hospital stay. It's also free from ECT's more notorious side effects, including memory loss and confusion.

Brock says transcranial stimulation will almost certainly become an approved treatment for other conditions in coming years, once researchers pin down the right location and intensity to treat the issue at hand. "[Transcranial stimulation] is a lot like a Swiss Army knife," he says. "We've figured out how to use the blade, but we haven't figured out how to use all the other tools yet."

http://www.eurekalert.org/pub_releases/2015-06/uoc--as062315.php

A 'hydrothermal siphon' drives water circulation through the seafloor

New study explains previous observations of ocean water flowing through the seafloor from one seamount to another

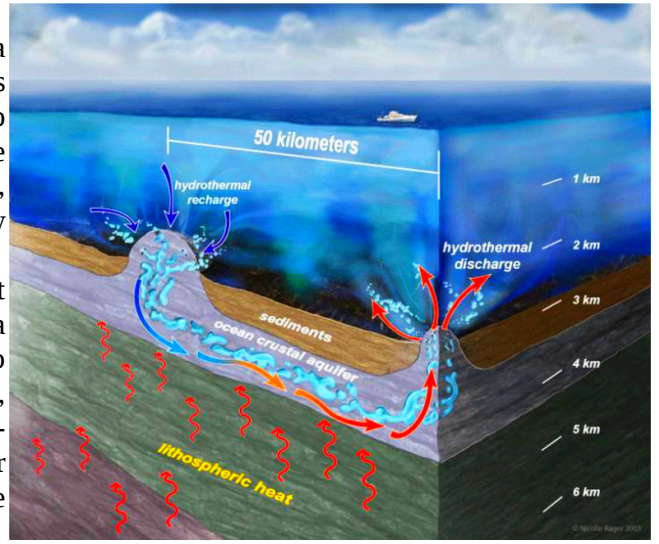
Vast quantities of ocean water circulate through the seafloor, flowing through the volcanic rock of the upper oceanic crust. A new study by scientists at UC Santa Cruz, published June 26 in Nature Communications, explains what drives this global process and how the flow is sustained.

About 25 percent of the heat that flows out of the Earth's interior is transferred to the oceans through this process, according to Andrew Fisher, professor of Earth and planetary sciences at UC Santa Cruz and coauthor of the study. Much of the fluid flow and heat transfer occurs through thousands of extinct underwater volcanoes (called seamounts) and other locations where porous volcanic rock is exposed at the seafloor.

Fisher led an international team of scientists that in the early 2000s discovered the first field site where this process could be tracked from fluid inflow to outflow, in the northeastern Pacific Ocean. In a 2003 paper published in Nature, Fisher and others reported that bottom seawater entered into one seamount, traveled horizontally through the crust, gaining heat and reacting with crustal rocks, then discharged into the ocean through another seamount more than 50 kilometers away.

'Ever since we discovered a place where these processes occur, we have been trying to understand what drives the fluid flow, what it looks like, and what determines the flow direction,' Fisher said.

For the new study, first author Dustin Winslow, a UCSC Ph.D. candidate who graduated this month, developed the first three-dimensional computer models showing how the process works.



Studies by Andrew Fisher and colleagues have shown that seamounts provide conduits through which enormous quantities of water flow between the ocean and the rocks beneath the seafloor. **Courtesy of Nicolle Rager**

The models reveal a 'hydrothermal siphon' driven by heat loss from deep in the Earth and the flow of cold seawater down into the crust and of warmed water up out of the crust.

'Dustin's models provide the best, most realistic view of these systems to date, opening a window into a hidden realm of water, rock, and life,' Fisher said.

The models show that water tends to enter the crust ('recharge') through seamounts where fluid flow is easiest due to favorable rock properties and larger seamount size. Water tends to discharge where fluid flow is more difficult due to less favorable rock properties or smaller seamount size. This finding is consistent with field observations suggesting that smaller seamounts are favored as sites of hydrothermal discharge.

'This modeling result was surprising initially, and we had to run many simulations to convince ourselves that it made sense,' Winslow said. 'We also found that models set up to flow in the opposite direction would spontaneously flip so that discharge occurred through less transmissive seamounts. This seems to be fundamental to explaining how these systems are sustained.'

Winslow's project was funded by the U.S. National Science Foundation through a graduate fellowship and as part of the Center for Dark Energy Biosphere Investigations (C-DEBI). UCSC is a partner in C-DEBI, which is headquartered at the University of Southern California.

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Schizophrenia May Be the Price We Pay for a Big Brain

The disease is linked to genetic changes on the evolutionary road from ape to human

By Bret Stetka | Jun 11, 2015

Plenty of us have known a dog on Prozac. We have also witnessed the eye rolls that come with the mention of canine psychiatry. Doting pet owners—myself included—ascribe all kinds of questionable psychological ills to our pawed companions. But in fact, the science suggests that numerous nonhuman species do suffer from psychiatric symptoms. Birds obsess; horses on occasion get pathologically compulsive; dolphins and whales, especially those in captivity, self-mutilate. And that thing when your dog woefully watches you pull out of the driveway from the window—that might be DSM-certified separation anxiety. "Every animal with a mind has the capacity to lose hold of it from time to time," wrote science historian and author Laurel Braitman in her 2014 book Animal Madness.

But at least one mental malady, while common in humans, seems to have spared other animals: schizophrenia, which affects an estimated 0.4 to 1 percent of adults. Although animal models of psychosis exist in laboratories, and odd behavior has been observed in creatures confined to cages, most experts agree that psychosis has not typically been seen in other species, whereas depression, obsessive-compulsive disorder and anxiety traits have been reported in many nonhuman species.

This raises the question of why such a potentially devastating, often lethal disease is still hanging around plaguing humanity. We know from an abundance of recent research that schizophrenia is heavily genetic in origin. One would think that natural selection would have eliminated the genes that predispose to psychosis. A study published earlier this year in Molecular Biology and Evolution provides clues as to how the potential for schizophrenia may have arisen in the human brain and, in doing so, suggests possible treatment targets. It turns out that psychosis may be an unfortunate cost of having a big brain that is capable of complex cognition.

Hotspots in the Human Genome

The study, led by Joel Dudley, a genomics professor at the Icahn School of Medicine at Mount Sinai, proposes that because schizophrenia is relatively prevalent in humans, it perhaps has a complex evolutionary backstory that would explain its persistence and apparent exclusivity to humans. Specifically, Dudley and his colleagues were curious about segments of our genome called human accelerated regions, or HARs, first identified in 2006. HARs are short stretches of DNA that were conserved in other species but underwent rapid evolution in humans following our split with chimpanzees, presumably because they provided some benefit specific to our species. Rather than encoding for proteins themselves, HARs often help to regulate neighboring genes. Because both schizophrenia and HARs appear to be, for the most part, human-specific, the researchers wondered if there might be a connection between the two.

To find out, Dudley and his colleagues used data culled from the Psychiatric Genomics Consortium, a massive study identifying genetic variants associated with schizophrenia. They first assessed whether schizophrenia-related genes sit close to HARs along the human genome—closer than would be expected by chance. It turns out they do, suggesting that HARs play a role in regulating genes contributing to schizophrenia. Furthermore, by comparing the patterns of change in humans and chimpanzees, it was revealed that HAR-associated schizophrenia genes were under stronger evolutionary selective pressure than other schizophrenia genes. This observation implies that the human variants of these genes are essential to us in some way, despite the risk they harbor.

To help understand what these benefits might be, Dudley's group then turned to gene expression profiles. Gene sequencing provides an organism's genome sequence, but gene expression profiling reveals where and when in the body certain genes are active. Dudley's team found that HAR-associated schizophrenia genes are found in regions of the genome that influence other genes expressed in the prefrontal cortex, a brain region just behind the forehead that is involved in higher-order thinking. Impaired function in the prefrontal cortex is thought to contribute to psychosis.

They also found that these culprit genes are involved in various key human neurological functions within the prefrontal cortex, including the transmission of the neurotransmitter GABA across a synapse from one neuron to another. GABA serves as an inhibitor or regulator of neuronal activity, in part by suppressing dopamine in certain parts of the brain. In schizophrenia, GABA appears to malfunction, and dopamine runs wild, contributing to the hallucinations, delusions and disorganized thinking that are common to psychosis. In other words, the schizophrenic brain lacks restraint.

"The ultimate goal of the study was to see if evolution may help provide additional insights into the genetic architecture of schizophrenia so that we can better understand and diagnose the disease," Dudley explains. Identifying which

genes are most implicated in schizophrenia and how they are expressed could lead to more effective therapies such as those influencing the function of GABA.

When Bigger Isn't Better

Dudley's findings offer a possible explanation for why schizophrenia arose in humans in the first place and why it does not seem to occur in other animals. “It's been suggested,” Dudley explains, “that the emergence of human speech and language bears a relationship with schizophrenia genetics and, incidentally, autism.” Indeed, language dysfunction—typified by disorganized speech or jumping from one topic to another—is a feature of schizophrenia, and GABA is critical to speech, language and many other aspects of higher-order cognition. “The fact that our evolutionary analysis converged on GABA function in the prefrontal cortex seems to tell an evolutionary story connecting schizophrenia risk with intelligence.”

Put another way, with complicated, highly social human thought—and the complicated genetics at the root of higher cognition—perhaps there is just more that can go wrong: complex function begets complex malfunction.

Dudley is careful not to exaggerate the evolutionary implications of his work. “It is important to note that our study was not specifically designed to evaluate an evolutionary trade-off,” he observes, “but our findings support the hypothesis that evolution of our advanced cognitive abilities may have come at a cost—a predisposition to schizophrenia.” He also acknowledges that the new work did not identify any “smoking gun genes” and that schizophrenia genetics is profoundly complex. Still, Dudley feels that evolutionary genetic analysis can help identify the most relevant genes and pathological mechanisms at play in schizophrenia and possibly other mental illnesses that preferentially affect humans—that is, neurodevelopmental disorders related to higher cognition and GABA activity, including autism and attention-deficit/hyperactivity disorder.

In fact, a study published online this past March in Molecular Psychiatry reported a link between gene variants associated with autism spectrum disorder and better cognitive function in the general population—specifically, enhanced general cognitive ability, memory and verbal intelligence. “It would suggest that some of these variants can have beneficial effects on cognition,” says lead author Toni-Kim Clarke of the University of Edinburgh. The findings might also help explain why individuals with autism sometimes exhibit unusual cognitive gifts.

Clarke's findings support Dudley's speculation that higher cognition might have come at a price. As we broke away from our primate cousins, our genomes—HARs especially—hastily evolved, granting us an increasing cache of abilities that other species lack. In doing so, they may have left our brains prone to occasional complex dysfunction—but also capable of biomedical research aimed at one day curing the ailing brain.

Common Polygenic Risk for Autism Spectrum Disorder (ASD) Is Associated with Cognitive Ability in the General Population. T.-K. Clarke et al. in Molecular Psychiatry. Published online March 10, 2015.

http://www.eurekalert.org/pub_releases/2015-06/uoct-irp062615.php

Inactivity reduces people's muscle strength

New research reveals that it only takes two weeks of not using their legs for young people to lose a third of their muscular strength, leaving them on par with a person who is 40-50 years their senior.

The Center for Healthy Aging and the Department of Biomedical Sciences at the University of Copenhagen conducted the research.

Time and again, we are told that we need to stay physically active and exercise daily. But how quickly do we actually lose our muscular strength and muscle mass if we go from being averagely active to being highly inactive? For example when we are injured, fall ill or simply take a very relaxing holiday. Researchers from the University of Copenhagen have examined what happens to the muscles in younger and older men after a period of high inactivity, by way of so-called immobilization with a leg pad.

Both older and younger people lose muscular strength

"Our experiments reveal that inactivity affects the muscular strength in young and older men equally. Having had one leg immobilized for two weeks, young people lose up to a third of their muscular strength, while older people lose approximately one fourth. A young man who is immobilized for two weeks loses muscular strength in his leg equivalent to ageing by 40 or 50 years," says Andreas Vigelsoe, PhD at the Center for Healthy Aging and the Department of Biomedical Sciences at the University of Copenhagen.

Young people lose twice as much muscle mass

With age, our total muscle mass diminishes, which is why young men have approximately one kilogram more muscle mass in each leg than older men. Both groups lose muscle mass when immobilized for two weeks - young men lose 485 grams on average, while older men lose approximately 250 grams. The participants' physical fitness was also reduced while their one leg was immobilized in a pad.

"The more muscle mass you have, the more you'll lose. Which means that if you're fit and become injured, you'll most likely lose more muscle mass than someone who is unfit, over the same period of time. But even though older people lose less muscle mass and their level of fitness is reduced slightly less than in young people, the loss of muscle mass is presumably more critical for older

people, because it is likely to have a greater impact on their general health and quality of life," says Martin Gram, researcher at the Center for Healthy Aging and the Department of Biomedical Sciences, explains.

Cycling is not enough

After two weeks of immobilization, the participants bicycle-trained 3-4 times a week for six weeks.

"Unfortunately, bicycle-training is not enough for the participants to regain their original muscular strength. Cycling is, however, sufficient to help people regain lost muscle mass and reach their former fitness level. If you want to regain your muscular strength following a period of inactivity; you need to include weight training," Andreas Vigelsoe states.

"It's interesting that inactivity causes such rapid loss of muscle mass, in fact it'll take you three times the amount of time you were inactive to regain the muscle mass that you've lost. This may be caused by the fact that when we're inactive, it's 24 hours a day," Martin Gram concludes.

These results have just been published in the scientific Journal of Rehabilitation Medicine. The Nordea-fonden supports the research carried out by the Center for Healthy Aging.

http://www.eurekalert.org/pub_releases/2015-06/byu-hbp062515.php

High blood pressure linked to reduced Alzheimer's risk, meds may be reason

Study authors say its likely protective effect comes from antihypertensive drugs

A new study suggests that people with a genetic predisposition to high blood pressure have a lower risk for Alzheimer's disease.

However, authors conclude the connection may have more to do with anti-hypertension medication than high blood pressure itself.

"It's likely that this protective effect is coming from antihypertensive drugs," said co-author John Kauwe, associate professor of biology at Brigham Young University. "These drugs are already FDA approved. We need to take a serious look at them for Alzheimer's prevention."

The study, published this month in PLOS Medicine, analyzed genetic data from 17,008 individuals with Alzheimer's and 37,154 people without the disease. Data came from the Alzheimer's Disease Genetics Consortium and the International Genomics of Alzheimer's Project.

BYU researchers worked with scholars from the University of Cambridge, Aarhus University in Denmark and the University of Washington on the massive study. BYU's role was to flex its muscles in supercomputing and bioinformatics. With the help of BYU's supercomputer, Kauwe and undergraduate student Kevin Boehme pieced together 32 data sets for the analysis.

The research team looked for links between Alzheimer's disease and a number of health conditions -- including diabetes, obesity, and high cholesterol -- but only found a significant association between higher systolic blood pressure and reduced Alzheimer's risk. (A weak connection between smoking and Alzheimer's also surfaced.)

"Our results are the opposite of what people might think," said fellow co-author Paul Crane, a University of Washington associate professor of internal medicine. "It may be that high blood pressure is protective, or it may be that something that people with high blood pressure are exposed to more often, such as antihypertensive medication, is protecting them from Alzheimer's disease."

University of Cambridge senior investigator scientist Robert Scott led the study, which used "Mendelian randomization" to find if the risk factors (BMI, insulin resistance, blood pressure, cholesterol, diabetes) for Alzheimer's had a causal impact. Mendelian randomization uses subjects' genetics as a proxy for a randomized clinical trial.

"This is to date the most authoritative paper looking at causal relationships between Alzheimer's disease and these potentially modifiable factors," Kauwe said. "In terms of the number of samples, it can't get bigger at this point."

http://bit.ly/1HmjpSl

No, soup of everyday chemicals isn't a cancer-causing combo

Could chemicals deemed safe at common doses be carcinogenic when mixed?

It's a fair question, but there is no evidence of harm, says Cancer Research UK's health information officer

14:00 26 June 2015 by Fiona Osgun

Once again, headlines this week screamed about everyday chemicals that are supposedly "cancer causing". People could be forgiven for being alarmed. But while stories like this seem to appear almost daily, the claims aren't often supported by the science.

The publication that sparked the latest media storm was a large review of pre-existing studies published in the journal *Carcinogenesis*.

It assessed the state of the evidence around cancer and a group of common chemicals that many people are likely to be exposed to, ranging from Bisphenol A (used to make plastics more mouldable) to the antibacterial agent triclosan (found in some soaps) to iron.

All are widely present in the environment but aren't considered carcinogenic. What these chemicals have in common is that, while they don't cause cancer, they can affect cells in other ways, including causing them to exhibit some of the hallmarks of cancer.

These are characteristics that together set cancer cells apart from normal cells. They include things like resisting natural cell death, being able to induce a blood supply and evading destruction by the immune system.

But while as a group these hallmarks have helped our understanding of what is happening inside cancerous cells, and how they function differently from their normal counterparts, each one on its own doesn't mean a cell is cancerous.

Cancer hallmarks

The researchers argue that, although the chosen chemicals "were not selected to somehow imply (based on current information) that they are endangering us", there is a gap in the evidence when it comes to the impact of exposure to a combination of them, all at low doses. Classically, chemicals are tested in isolation to determine an often very conservative safe level.

The key question raised by this review was if individual chemicals can lead to one hallmark change in cells in the lab, is it possible that many chemicals together could cause a number of these changes in cells? And could that lead to cancer?

Unfortunately, the evidence so far can't answer this question. It also can't tell us whether the result of any studies of cells in the lab exposed to chemical mixtures will hold true for the general public.

When it comes to cancer risk, research has shown that there are other factors which play a clear and important role. We can say with certainty that lifestyle has a big impact. More than 4 in 10 cases of cancer could be prevented, largely through lifestyle changes like giving up smoking, maintaining a healthy weight, eating a balanced diet and cutting down on alcohol.

When it comes to everyday chemicals and cancer there are still some very big ifs and buts that research needs to iron out. Until we have solid evidence I wouldn't read too much into the hype on "cancer-causing chemicals".

http://www.eurekalert.org/pub_releases/2015-06/uomh-has062615.php

Having a stroke? Where you are makes a huge difference in your treatment

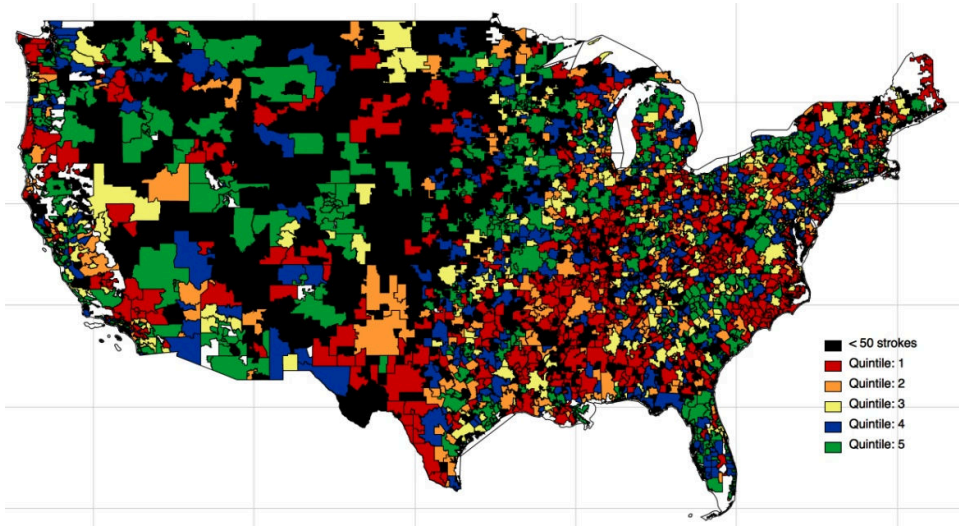
Major regional variation in use of clotbuster drug tPA reveals opportunities to improve care & prevent disability

ANN ARBOR, Mich. - It looks like a crazy quilt spread over the continent. But a new map of emergency stroke care in America shows just how much of a patchwork system we still have for delivering the most effective stroke treatment.

And thousands of people a year may end up unnecessarily disabled as a result.

In the July issue of the journal Stroke, University of Michigan Medical School researchers report the results of a study that for the first time shows wide geographic variation in use of "clotbuster" treatment for stroke.

Only 4.2 percent of more than 844,000 stroke victims received the drug called tPA, or another urgent stroke treatment, the study finds.



This map of the 3,426 hospital service areas in the continental US shows rates of tPA use for emergency care, from highest (green and blue) to lowest (yellow, orange and red). Areas in black had fewer than 50 strokes a year. **University of Michigan**

If given in the first hours after a stroke, tPA and other treatments can restore blood flow in the brain and prevent the damage that causes stroke-related disability and drives up the long-term cost of caring for stroke survivors.

But when the researchers looked at how tPA was used - or not - in Medicare participants who had strokes in each of the nation's 3,436 different hospital markets between 2007 and 2010, deep divides emerged. In one-fifth of these regions, no patients receive tPA.

Meanwhile, in places like Stanford, CA and Asheville, NC, as many as 14 percent of stroke patients received tPA through an intravenous line, or a direct-to-brain (intrarterial) treatment that involved tPA or another strategy.

"These results scream that a major opportunity exists to improve emergency stroke care, if only we can understand how these differences arise and how to eliminate them," says James Burke, M.D., M.S., the study's senior author and an assistant professor in neurology at U-M and the VA Ann Arbor Healthcare System. "If we had a perfect system in place nationwide, which delivered treatment at the highest rates seen in this study, thousands of patients could be spared disability."

When the researchers grouped the regions from best-performing to poorest-performing, and looked at them more closely, they found more surprises.

In the top fifth, an average of 9 percent of patients got clot-busting treatment, while the bottom fifth, no patients received it.

Even after they adjusted for the number of strokes that each region reported during the four years, there was a wide gap in use of emergency stroke treatment. In addition, older patients, women, and members of racial and ethnic minority groups were less likely to receive tPA no matter where they lived.

And while patients were somewhat more likely to get tPA if they had their strokes in regions where hospitals were certified as primary stroke centers, which can deliver tPA around the clock, or where ambulance companies had a policy of driving stroke patients further to get to a stroke center, those factors didn't make a major difference.

"We can clearly do much better, but existing policy solutions are only going to get us so far," says Burke. "In our findings, we do see positive results from primary stroke center designation and ambulance bypass, but we are talking about a complex mix of hospital, EMS, and individual response to stroke. We need to understand better what the areas with the highest rates of use are doing differently." At the time of the study's data, comprehensive stroke center designation, which indicates the most advanced level of stroke care including intrarterial tPA, was not yet in use.

The researchers calculated that if all regions achieved the same rates of tPA use as the Stanford region, more than 92,800 people would get treated, and 8,078 people would survive their stroke disability-free. Even if all regions doubled their current tPA use, 7,206 people would be spared disability.

Variation in tPA use did track to lower average levels of education and income, and higher unemployment, in hospital service areas, and use was slightly higher across all densely populated areas compared with more sparsely populated areas.

But the top 20 areas for tPA use are scattered across the country, in urban and rural areas, rich and poor ones.

"By studying communities that treated a lot of stroke patients, we may learn how best to help low-performing communities treat more acute stroke patients in their community," says first author Lesli Skolarus, M.D., a stroke neurologist and assistant professor at U-M.

The study was funded by the National Institute for Neurological Disorders and Stroke, and by the National Institute of Minority Health and Health Disparities. NS073685, MD008879, NS082597.

In addition to Burke and Skolarus, the authors are William J. Meurer, MD, MS; Krithika Shanmugasundaram, BS; Eric E. Adelman, MD; and Phillip A. Scott, MD. All are members of the U-M Comprehensive Stroke Program, and all except Shanmugasundaram are members of the U-M Institute for Healthcare Policy and Innovation.

Reference: Stroke, July 2015, doi: 10.1161/STROKEAHA.115.009163

CME for physicians is available via the journal at cme.ahajournals.org/a/19582PxVuSK

http://www.eurekalert.org/pub_releases/2015-06/slu-ssd062615.php

SLU scientists develop potential new class of cancer drugs in lab

Drug takes aim at cancer metabolism, stops most kinds of cancer

ST. LOUIS -- In research published in Cancer Cell, Thomas Burris, Ph.D., chair of pharmacology and physiology at Saint Louis University, has, for the first time, found a way to stop cancer cell growth by targeting the Warburg Effect, a trait of cancer cell metabolism that scientists have been eager to exploit.

Unlike recent advances in personalized medicine that focus on specific genetic mutations associated with different types of cancer, this research targets a broad principle that applies to almost every kind of cancer: its energy source.

The Saint Louis University study, which was conducted in animal models and in human tumor cells in the lab, showed that a drug developed by Burris and colleagues at Scripps Research Institute can stop cancer cells without causing damage to healthy cells or leading to other severe side effects.

The Warburg Effect

Metabolism -- the ability to use energy -- is a feature of all living things. Cancer cells aggressively ramp up this process, allowing mutated cells to grow unchecked at the expense of surrounding tissue. "Targeting cancer metabolism has become a hot area over the past few years, though the idea is not new," Burris said.

Since the early 1900s, scientists have known that cancer cells prefer to use glucose as fuel even if they have plenty of other resources available. In fact, this is how doctors use PET (positron emission tomography) scan images to spot tumors. PET scans highlight the glucose that cancer cells have accumulated. This preference for using glucose as fuel is called the Warburg effect, or glycolysis.

In his paper, Burris reports that the Warburg effect is the metabolic foundation of oncogenic (cancer gene) growth, tumor progression and metastasis as well as tumor resistance to treatment.

Cancer's goal: to grow and divide

Cancer cells have one goal: to grow and divide as quickly as possible. And, while there are a number of possible molecular pathways a cell could use to find food, cancer cells have a set of preferred pathways. "In fact, they are addicted to certain pathways," Burris said. "They need tools to grow fast and that means they need to have all of the parts for new cells and they need new energy."

"Cancer cells look for metabolic pathways to find the parts to grow and divide. If they don't have the parts, they just die," said Burris. "The Warburg effect ramps

up energy use in the form of glucose to make chemicals required for rapid growth and cancer cells also ramp up another process, lipogenesis, that lets them make their own fats that they need to rapidly grow."

If the Warburg effect and lipogenesis are key metabolic pathways that drive cancer progression, growth, survival, immune evasion, resistance to treatment and disease recurrence, then, Burris hypothesizes, targeting glycolysis and lipogenesis could offer a way to stop a broad range of cancers.

Cutting off the energy supply

Burris and his colleagues created a class of compounds that affect a receptor that regulates fat synthesis. The new compound, SR9243, which started as an anti-cholesterol drug candidate, turns down fat synthesis so that cells can't produce their own fat. This also impacts the Warburg pathway, turning cancer cells into more normal cells. SR9243 suppresses abnormal glucose consumption and cuts off cancer cells' energy supply. When cancer cells don't get the parts they need to reproduce through glucose or fat, they simply die.

Because the Warburg effect is not a feature of normal cells and because most normal cells can acquire fat from outside, SR9243 only kills cancer cells and remains non-toxic to healthy cells. The drug also has a good safety profile; it is effective without causing weight loss, liver toxicity, or inflammation.

Promising Results So far, SR9243 has been tested in cultured cancer cells and in human tumor cells grown in animal models. Because the Warburg pathway is a feature of almost every kind of cancer, researchers are testing it on a number of different cancer models.

"It works in a wide range of cancers both in culture and in human tumors developing in animal models," Burris said. "Some are more sensitive to it than others. In several of these pathways, cells had been reprogramed by cancer to support cancer cell growth. This returns the metabolism to that of more normal cells."

In human tumors grown in animal models, Burris said, "It worked very well on lung, prostate, and colorectal cancers, and it worked to a lesser degree in ovarian and pancreatic cancers."

It also seems to work on glioblastoma, an extremely difficult to treat form of brain cancer, though it isn't able to cross the brain/blood barrier very effectively. The challenge for researchers in this scenario will be to find a way to allow the drug to cross this barrier, the body's natural protection for the brain, which can make it difficult for drug treatments to reach their target.

And, in even more promising news, it appears that when SR9243 is used in combination with existing chemotherapy drugs, it increases their effectiveness, in a mechanism apart from SR9243's own cancer fighting ability.

Other researchers on the study include Colin A. Flaveny, Kristine Griffett, Bahaa El-Dien M. El-Gendy, Melissa Kazantzis, Monideepa Sengupta, Antonio L. Amelio, Arindam Chatterjee, John Walker, Laura A. Solt and Theodore M. Kamenecka.