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Overgrowth of baby in the womb may begin weeks before women are tested for maternal diabetes

Screening women earlier on in pregnancy is likely to improve their health outcomes

The excessive growth of a baby in the womb, a common complication of gestational diabetes, begins weeks before women are tested for the disease, according to new research being presented at this year's European Association for the Study of Diabetes (EASD) Annual Meeting in Barcelona, Spain (16-20 September).

The analysis of almost 8,000 singleton pregnancies in South Korea revealed that in women subsequently diagnosed with gestational diabetes, abdominal fetal growth was already abnormally large between 20 and 24 weeks--more than 4 weeks before the recommended screening time.

Given the high risk of complications for both mother and baby from maternal diabetes, screening women earlier on in pregnancy is likely to improve their health outcomes, researchers say.

"Abdominal overgrowth of the baby in the womb is believed to indicate fetal obesity, not just a big baby", explains Dr Yoo Lee Kim from CHA University, Republic of Korea who led the research. "Our findings suggest that diagnosing gestational diabetes and implementing interventions to reduce the risk of excessive fetal growth such as diet and exercise earlier in pregnancy may be necessary to prevent harm to mothers and their babies."

Gestational diabetes, a temporary form of diabetes in which hormonal changes disrupt insulin function, affects 3-20% of pregnant women, with those who are obese and/or older at greater risk. Women who develop gestational diabetes are seven times as likely to develop type 2 diabetes in the years following pregnancy. If left undiagnosed and untreated, the condition can also cause the unborn child to have increased birthweight, higher body fat, and lower insulin sensitivity, and increases the likelihood of obesity and diabetes in later life.

Current guidelines in South Korea, the UK, and USA recommend that all pregnant women are screened for gestational diabetes using an oral glucose test at 24-28 weeks of pregnancy. However, previous research suggests that excessive fetal growth can already be detected at the time of screening (24-28 weeks), especially in older women and those with obesity. Whether the onset of this fetal growth disorder predates the recommended screening time is unclear.

To determine whether fetal overgrowth is already present at 20-24 weeks' gestation, researchers analysed medical records of 7,820 pregnant women attending the outpatient clinic of Cha Gangnam Medical Center in Seoul, Korea. Ultrasound scans were used to measure the fetuses' abdominal circumference, head size, and femur length at least 4 weeks before screening for gestational diabetes (at 22 weeks' gestation; 7297 scans), at the same time as the screening test (26 weeks; 5388 scans), and at near term (35 weeks; 5404 scans).

At the 22nd week of pregnancy, ultrasound scans revealed that the fetuses of mothers subsequently diagnosed with gestational diabetes were already significantly larger in abdominal circumference than the babies of women with normal glucose tolerance, and they remained abnormally large through the 35th week of pregnancy. However, head size and femur length were not significantly different between the two groups.

Even among women without diabetes, the babies of mothers who were older or obese were at far greater risk of being abnormally large in abdominal circumference at the 22 week scan, but not in younger and non-obese women.

Dr Kim concludes: "Early screening and careful monitoring may be particularly beneficial for obese and older mothers, as fetal abdominal growth is already abnormal at 5 months in these high-risk women, meaning that their babies are already large at the time of diagnosis."

This is an observational study, so no firm conclusions can be drawn about cause and effect, and the authors point to several limitations including that the study was done in a single centre in South Korea which could affect the generalisability of the results. Additionally, they could not determine exactly why the foetuses of women with gestational diabetes were larger than foetuses in the non-diabetic group.

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Hiding in plain sight

Early rice farmers unwittingly selected for weedy imposters

Early rice growers unwittingly gave barnyard grass a big hand, helping to give root to a rice imitator that is now considered one of the world's worst agricultural weeds.

New research from Zhejiang University, the Chinese Academy of Sciences and Washington University in St. Louis provides genomic evidence that barnyard grass (*Echinochloa crus-galli*) ***(稗)*** benefited from human cultivation practices, including continuous hand weeding, as it spread from the Yangtze River region about 1,000 years ago.

The common form of barnyard grass (top) has red stems, while the mimic has green stems -- more like rice. **Jordan R. Brock/Washington University**

Barnyard grass is a globally common invasive weed of cultivated row crops and cereals. The new study was published Sept. 16 in the journal Nature Ecology & Evolution.

"In Asia, rice farmers have traditionally planted and weeded their paddies by hand. Any weeds that stick out are easily detected and removed," said Kenneth Olsen, professor of biology in Arts & Sciences. "Over hundreds of generations, this has selected for some strains of barnyard grass that specialize on rice fields and very closely mimic rice plants. This allows them to escape detection."

Olsen collaborated on data analyses and interpretation for the new study. He is working with the study's corresponding author, Longjiang Fan of Zhejiang University, on other research related to rice evolutionary genomics and agricultural weed evolution.

This study sequenced the genomes of rice-mimic and non-mimic forms of the weed as a step towards understanding how this process has occurred.

This form of mimicry, called Vavilovian mimicry, is an adaptation of weeds to mimic domesticated plants. In the case of barnyard grass, the rice mimics grow upright like a rice plant instead of sprawling along the ground like most barnyard grass. They also have green stems like rice plants instead of the red stems more commonly found in the weed.

"With the advent of agriculture about 10,000 years ago, humans all over the planet began creating a wonderful habitat for naturally weedy plant species to exploit," Olsen said. "The most successful and aggressive agricultural weeds were those that evolved traits allowing them to escape detection and proliferate in this fertile new environment."

The researchers estimate that the mimic version of *E. crus-galli* emerged at about the same time that Chinese historical records indicate that the regional economic center was shifting from the Yellow River basin to the Yangtze River basin. During this period of the Song Dynasty, human populations were growing rapidly, demand for rice as the staple grain was paramount. This is also the time when a quick-maturing, drought-resistant variety of rice called

Champa rice was introduced to the Yangtze basin from Southeast Asia -- to allow two harvests in a year. Weed management in paddies might have been intensified in the context of these conditions.

Traditional farming preserves diversity of Thai purple rice

However, while common barnyard grass is a major agricultural weed in the U.S., the rice mimic form has never become widespread in the main rice growing region -- the southern Mississippi valley.

Olsen speculates that this is because U.S. rice farmers rely on mechanized farming instead of hand labor.

"Without farmers out in the fields planting and weeding by hand, there's not such strong selection for weeds to visually blend in with the rice crop," he said.

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Meatballs might wreck the anti-cancer perks of tomato sauce

Study finds twofold decrease in lycopene uptake with iron supplement

COLUMBUS, Ohio - Eating your tomato sauce with meatballs piled on top could have a surprising downside, new research suggests.

Some of the anti-cancer benefits of tomatoes, specifically those from a compound called lycopene, could disappear when they're eaten with iron-rich foods, according to a new study from The Ohio State University.

Researchers analyzed the blood and digestive fluid of a small group of medical students after they consumed either a tomato extract-based shake with iron or one without iron. Lycopene levels in digestive fluid and in the blood were significantly lower when the study subjects drank the liquid meal mixed with an iron supplement, meaning there was less for the body to use in potentially beneficial ways.

"When people had iron with their meal, we saw almost a twofold drop in lycopene uptake over time," said the study's lead author, Rachel Kopec, an assistant professor of human nutrition at Ohio State.

"This could have potential implications every time a person is consuming something rich in lycopene and iron - say a Bolognese sauce, or an iron-fortified cereal with a side of tomato juice. You're probably only getting half as much lycopene from this as you would without the iron."

Iron is essential in the diet, performing such critical functions as allowing our bodies to produce energy and get rid of waste. But it's also a nutrient that is known to monkey with other cellular-level processes.

"We know that if you mix iron with certain compounds it will destroy them, but we didn't know if it would impair potentially beneficial carotenoids, like lycopene, found in fruits and vegetables," Kopec said.

Carotenoids are plant pigments with antioxidant properties responsible for many bright red, yellow and orange pigments found in the produce aisle. These include lycopene, which is found in abundance in tomatoes and also colors watermelon and pink grapefruit. Scientists have identified several potential anti-cancer benefits of lycopene, including in prostate, lung and skin cancers.

The small study, which included seven French medical students who had repeated blood draws and digestive samples taken from tubes placed in their stomachs and small intestines, took this research out of the test tube and into the human body, allowing for a better examination of human metabolism in action, Kopec said.

It's unclear precisely what is happening that is changing the uptake of lycopene, but it could be that the meal with iron oxidizes the lycopene, creating different products of metabolism than those followed in the study.

"It's also possible that iron interrupts the nice emulsified mix of tomato and fats that is critical for cells to absorb the lycopene. It could turn it into a substance like separated salad dressing - oil on top and vinegar on the bottom - that won't ever mix properly," Kopec said.

Researchers continue to work to better understand lycopene's role in fighting cancer, and the importance of its interplay with other compounds and nutrients.

"Nutrition can play an important role in disease prevention, but it's important for us to gather the details about precisely how what we eat is contributing to our health so that we can give people reliable, science-based recommendations," Kopec said.

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Drinking Tea Improves Brain Efficiency, New Study Shows

Habitual tea drinking has positive effects on brain organization and gives rise to greater efficiency in functional and structural connectivity, according to a new study led by the National University of Singapore (NSU).

Tea has been a popular beverage since antiquity times, with records referring to consumption dating back to the dynasty of Shen Nong (2700 BCE) in China.

Tea is consumed in diverse ways, with brewed tea and products with a tea ingredient extremely prevalent in Asia, especially in China and Japan. It also is more fashionable than ever in Western countries.

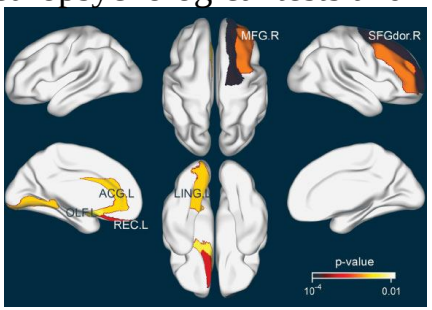
A growing literature has demonstrated that tea consumption is beneficial to human health, including mood improvement, risk reduction of cognitive decline, cardiovascular disease prevention, lower cancer incidence, and reduced mortality.

“Our results offer the first evidence of positive contribution of tea drinking to brain structure, and suggest that drinking tea regularly has a protective effect against age-related decline in brain organization,” said lead author Dr. Feng Lei, a researcher in the Department of Psychological Medicine, the NSU Yong Loo Lin School of Medicine.

For the study, Dr. Lei and colleagues recruited 36 adults aged 60 and above, and gathered data about their health, lifestyle, and psychological well-being.

The participants also had to undergo neuropsychological tests and magnetic resonance imaging (MRI).

The scientists found that individuals who consumed green tea, oolong tea, or black tea at least four times a week for about 25 years had brain regions that were interconnected in a more efficient way.



***Brain regions exhibiting significant differences in structural nodal efficiency between the tea drinking group and the non-tea drinking group. Abbreviations: SFGdor.R – right superior frontal gyrus (dorsal), MFG.R – right middle frontal gyrus, OLF.L – left olfactory, REC.L – left gyrus rectus, ACG.L – left anterior cingulate and paracingulate gyri, LING.L – left lingual gyrus, which primarily reside in the frontal cortex.* Li *et al,* doi: 10.18632/aging.102023.**

“Our study comprehensively investigated the effects of tea drinking on brain connectivity at both global and regional scales using multi-modal imaging data (i.e., functional and structural imaging) and provided the first compelling evidence that tea drinking positively contributes to brain structure making network organization more efficient,” they said.

“The study suggests that tea drinking is effective in preventing (slowing) or ameliorating cognitive decline and that tea drinking might be a simple lifestyle choice that benefits brain health.”

The study was published in the journal Aging.

J. Li et al. *2019. Habitual tea drinking modulates brain efficiency: evidence from brain connectivity evaluation.* Aging *11: 3876-3890; doi: 10.18632/aging.102023*

http://bit.ly/2lUhy5q

In human cells and mice, a cure for the common cold, Stanford-UCSF study reports

Temporarily disabling a single protein inside our cells might be able to protect us from the common cold

Temporarily disabling a single protein inside our cells might be able to protect us from the common cold and other viral diseases, according to a study led by researchers at Stanford University and University of California-San Francisco.

The findings were made in human cell cultures and in mice.

"Our grandmas have always been asking us, 'If you're so smart, why haven't you come up with a cure for the common cold?'" said Jan Carette, PhD, associate professor of microbiology and immunology. "Now we have a new way to do that."

The approach of targeting proteins in our own cells also worked to stop viruses associated with asthma, encephalitis and polio.

Colds, or noninfluenza-related upper respiratory infections, are for the most part a weeklong nuisance. They're also the world's most common infectious illness, costing the United States economy an estimated $40 billion a year. At least half of all colds are the result of rhinovirus infections. There are roughly 160 known types of rhinovirus, which helps to explain why getting a cold doesn't stop you from getting another one a month later. Making matters worse, rhinoviruses are highly mutation-prone and, as a result, quick to develop drug resistance, as well as to evade the immune surveillance brought about by previous exposure or a vaccine.

In a study to be published online Sept. 16 in *Nature Microbiology*, Carette and his associates found a way to stop a broad range of enteroviruses, including rhinoviruses, from replicating inside human cells in culture, as well as in mice. They accomplished this feat by disabling a protein, in mammalian cells and that all enteroviruses appear to need in order to replicate.

Carette shares senior authorship with Or Gozani, MD, PhD, professor of biology at Stanford and the Dr. Morris Herzstein Professor of Biology; Raul Andino, PhD, professor of microbiology and immunology at UCSF; and Nevan Krogan, PhD, professor of cellular and molecular pharmacology at UCSF. The lead authors are former Stanford graduate student Jonathan Diep, PhD, and Stanford postdoctoral scholars Yaw Shin Ooi, PhD, and Alex Wilkinson, PhD.

Well-known and feared

One of the most well-known and feared enteroviruses is poliovirus. Until the advent of an effective vaccine in the 1950s, the virus spelled paralysis and death for many thousands of children each year in the United States alone. Since 2014, another type of enterovirus, EV-D68, has been implicated in puzzling biennial bursts of a poliolike disease, acute flaccid myelitis, in the United States and Europe. Other enteroviruses can cause encephalitis and myocarditis -- inflammation of the brain and the heart, respectively.

Like all viruses, enteroviruses travel lightly. To replicate, they take advantage of proteins in the cells they infect.

To see what proteins in human cells are crucial to enteroviral fecundity, the investigators used a genomewide screen developed in Carette's lab. They generated a cultured line of human cells that enteroviruses could infect. The researchers then used gene editing to randomly disable a single gene in each of the cells. The resulting culture contained, in the aggregate, cells lacking one or another of every gene in our genome.

The scientists infected the culture with RV-C15, a rhinovirus known to exacerbate asthma in children, and then with EV-C68, implicated in acute flaccid myelitis. In each case, some cells managed to survive infection and spawn colonies. The scientists were able to determine which gene in each surviving colony had been knocked out of commission. While both RV-C15 and EV-D68

are both enteroviruses, they're taxonomically distinct and require different host-cell proteins to execute their replication strategies. So, most of the human genes encoding the proteins each viral type needed to thrive were different, too. But there were only a handful of individual genes whose absence stifled both types' ability to get inside cells, replicate, bust out of their cellular hotel rooms and invade new cells. One of these genes in particular stood out. This gene encodes an enzyme called SETD3. "It was clearly essential to viral success, but not much was known about it," Carette said.

The scientists generated a culture of human cells lacking SETD3 and tried infecting them with several different kinds of enterovirus -- EV-D68, poliovirus, three different types of rhinovirus and two varieties of coxsackievirus, which can cause myocarditis. None of these viruses could replicate in the SETD3-deficient cells, although all proved capable of pillaging cells whose SETD3-producing capability was restored.

The researchers observed a 1,000-fold reduction in a measure of viral replication inside human cells lacking SETD3, compared with controls. Knocking out SETD3 function in human bronchial epithelial cells infected with various rhinoviruses or with EV-D68 cut replication about 100-fold.

Impervious mice

Mice bioengineered to completely lack SETD3 grew to apparently healthy adulthood and were fertile, yet they were impervious to infection by two distinct enteroviruses that can cause paralytic and fatal encephalitis, even when these viruses were injected directly into the mice's brains soon after they were newly born.

"In contrast to normal mice, the SETD3-deficient mice were completely unaffected by the virus," Carette said. "It was the virus that was dead in the water, not the mouse."

Enteroviruses, the scientists learned, have no use for the section of SETD3 that cells employ for routine enzymatic activity. Instead, enteroviruses cart around a protein whose interaction with a different part of the SETD3 molecule, in some as yet unknown way, is necessary for their replication.

"This gives us hope that we can develop a drug with broad antiviral activity against not only the common cold but maybe all enteroviruses, without even disturbing SETD3's regular function in our cells," Carette said.

Carette and Gozani are members of Stanford Bio-X and the Stanford Maternal & Child Health Research Institute, as well as faculty fellows of Stanford ChEM-H. Gozani is a member of the Stanford Cancer Institute.

Other Stanford co-authors are graduate student Christine Peters; postdoctoral scholar James Zengel, PhD; Siyuan Ding, PhD, instructor in medicine gastroenterology & hepatology; basic life research scientist Kuo-Feng Weng, PhD; former visiting research student Kristi Kobluk, DVM; Joshua Elias, PhD, assistant professor of chemical and systems biology; Peter Sarnow, PhD, professor of microbiology and immunology; Harry Greenberg, MD, professor of gastroenterology and hepatology and of microbiology and immunology; and Claude Nagamine, PhD, DVM, associate professor of comparative medicine.

Researchers at the Chan Zuckerberg Biohub and the VA Palo Alto Health Care System also contributed to the work.

Stanford's departments of Microbiology and Immunology and of Biology also supported the work.

http://bit.ly/2mmkuYH

Electronic nose can sniff out which lung cancer patients will respond to immunotherapy

eNose device measures the mix of volatile organic compounds to assess whether or not the patient will respond to anti-PD-1 immunotherapy

An electronic nose that detects chemicals in the breath of lung cancer patients can identify with 85% accuracy those who will or will not respond to immunotherapy, according to new research published in the leading cancer journal Annals of Oncology [1] today (Wednesday).

The results of the first study to investigate this show that the eNose is more accurate than the current gold standard of

immunohistochemistry (IHC) for selecting patients who will respond to anti-PD-1 immunotherapies such as nivolumab or pembrolizumab. IHC involves testing tissue samples for the presence of the protein called programmed death ligand 1 (PD-L1), which is the target for anti-PD 1 therapies, but it is invasive and takes time to obtain results.

Professor Michel van den Heuvel, professor of thoracic oncology at the Radboud University Medical Centre (Nijmegen, The Netherlands), who led the research, said: "The introduction of immunotherapy has dramatically improved the treatment of advanced stage non-small cell lung cancer but unfortunately it is only effective in a subset of patients, which was about 20% when we started the study. Currently, there is no test available that can accurately predict who will benefit from this treatment, apart from PD-L1 testing by immunohistochemistry. This is today's biomarker of choice, despite its analytic and predictive limitations, when making clinical decisions about whether or not to treat a patient with immunotherapy."

Ms Rianne de Vries, a PhD student in the department of respiratory medicine at Amsterdam University Medical Centres (The Netherlands), who is joint first author of the study, said: "We hypothesised that exhaled breath analysis using eNose technology might be a non-invasive and rapid alternative to the current standard and would enable doctors to avoid treating patients with an immunotherapy to which they would not respond."

The eNose is a small device [2] that contains sensors to detect chemicals called volatile organic compounds (VOCs), which are present in about one per cent of our exhaled breath. The rest of our breath mainly consists of nitrogen, oxygen, carbon dioxide and water. The researchers thought that the mix of VOCs in the breath of patients with advanced non-small cell lung cancer (NSCLC) might indicate whether or not the patient would respond to anti-PD1 therapy; VOCs can vary depending on metabolic processes that occur in the whole body or in parts of it, such as the lungs.

Ms de Vries, who is also chief operating officer of Breathomix, which is currently producing the eNose, continued: "When using the eNose, the patient takes a deep breath, holds it for five seconds and then slowly exhales into the device. The eNose sensors respond to the complete mixture of VOCs in the exhaled breath; each sensor has its highest sensitivity to a different group of molecules. The sensor readings are sent directly to and stored at an online server for real-time processing of the data and for ambient air correction because the air that you exhale is influenced by the air that you inhale. The measurement takes less than a minute, and the results are compared to an online database where machine-learning algorithms immediately identify whether or not the patient is likely to respond to anti-PD1 therapy."

Between March 2016 and February 2018, the researchers at The Netherlands Cancer Institute, Amsterdam, recruited 143 patients with advanced NSCLC. They used the eNose to take the breath profiles of the patients two weeks before they started treatment with nivolumab or pembrolizumab, and after three months they used standard criteria (Response Evaluation Criteria of Solid Tumours, RECIST) to assess whether the patients were responding to the treatment nor not. Results from the first 92 patients (who started treatment between March 2016 and February 2017) were validated by the results from the remaining 51 patients (who started treatment after April 2017).

The other first author of the study, Dr Mirte Muller, a PhD student in the department of thoracic oncology at The Netherlands Cancer Institute, said: "We found that before the start of treatment with immunotherapy, the eNose analysis of exhaled breath from the patients with non-small cell lung cancer could distinguish between responders and non-responders with an accuracy of 85%.

"Our findings show that breath analysis by eNose can potentially avoid application of ineffective treatment to patients that are identified by eNose as being non-responders to immunotherapy, which in our study was 24% of the patients. This means that in 24% of NSCLC patients this treatment could be avoided, without denying anyone effective treatment.

"ENose technology is cheap compared to other available medical technologies and diagnostic tests and biomarkers. The eNose qualifies as a non-invasive and rapid point-of-care test that provides feedback within seconds in the doctor's office. Our results form a solid base for taking the next step to validate these findings in a large prospective multi-centre study."

Although immunotherapy tends to have fewer side effects than chemotherapy, with fatigue being the most common, it can trigger more serious side effects in about 10% of patients. Organs such as the lungs, liver and bowel can become inflamed when the body's immune system starts to attack its own cells. By correctly identifying patients who will not respond to immunotherapy, side effects related to the treatment can be avoided.

Prof van den Heuvel concluded: "We are convinced that this study merely scratches the surface. It represents the first introduction of modern precision medicine, namely that molecular fingerprints can be easily obtained and quickly analysed on the spot. This truly offers new possibilities for the individual patient and the doctor. The power of this eNose system is that it has been properly validated, both technically and clinically, which is essential. We believe that analysis of exhaled breath is going to become an important diagnostic tool and will guide future treatment in oncology as well as in many other diseases."

Notes:

[1] "Prediction of response to anti-PD-1 therapy in patients with non-small cell lung cancer by electronic nose analysis of exhaled breath", by Rianne de Vries et al. Annals of Oncology. doi:10.1093/annonc/mdz279

http://bit.ly/2lZDGLO

Rare 10 million-year-old fossil unearths new view of human evolution

New study of an ape-like pelvis suggests human ancestors might not have been built like modern African apes

Rudapithecus was pretty ape-like and probably moved among branches like apes do now -- holding its body upright and climbing with its arms. However, it would have differed from modern great apes by having a more flexible lower back, which would mean when Rudapithecus came down to the ground, it might have had the ability to stand upright more like humans do.

Illustration courtesy of John Siddick

COLUMBIA, Mo. - Near an old mining town in Central Europe, known for its picturesque turquoise-blue quarry water, lay Rudapithecus. For 10 million years, the fossilized ape waited in Rudabánya, Hungary, to add its story to the origins of how humans evolved.

What Rudabánya yielded was a pelvis -- among the most informative bones of a skeleton, but one that is rarely preserved. An international research team led by Carol Ward at the University of Missouri analyzed this new pelvis and discovered that human bipedalism -- or the ability for people to move on two legs -- might possibly have deeper ancestral origins than previously thought.

The Rudapithecus pelvis was discovered by David Begun, a professor of anthropology at the University of Toronto who invited Ward to collaborate with him to study this fossil. Begun's work on limb bones, jaws and teeth has shown that Rudapithecus was a relative of modern African apes and humans, a surprise given its location in Europe. But information on its posture and locomotion has been limited, so the discovery of a pelvis is important.

"Rudapithecus was pretty ape-like and probably moved among branches like apes do now -- holding its body upright and climbing with its arms," said Ward, a Curators Distinguished Professor of Pathology and Anatomical Sciences in the MU School of Medicine and lead author on the study. "However, it would have differed from modern great apes by having a more flexible lower back, which would mean when Rudapithecus came down to the ground, it might have had the ability to stand upright more like humans do. This evidence supports the idea that rather than asking why human ancestors stood up from all fours, perhaps we should be asking why our ancestors never dropped down on all fours in the first place."

Modern African apes have a long pelvis and short lower back because they are such large animals, which is one reason why they typically walk on all fours when on the ground. Humans have longer, more flexible lower backs, which allow them to stand upright and walk efficiently on two legs, a hallmark characteristic of human evolution. Ward said if humans evolved from an African ape-like body build, substantial changes to lengthen the lower back and shorten the pelvis would have been required. If humans evolved from an ancestor more like Rudapithecus, this transition would have been much more straightforward.

"We were able to determine that Rudapithecus would have had a more flexible torso than today's African apes because it was much smaller -- only about the size of a medium dog," Ward said. "This is significant because our finding supports the idea suggested by other evidence that human ancestors might not have been built quite like modern African apes."

Ward teamed up with Begun to study the pelvis along with MU alumna Ashley Hammond, Assistant Curator of Biological Anthropology at the American Museum of Natural History, and J. Michael Plavcan, a professor of anthropology at University of Arkansas. Since the fossil was not 100% complete, the team used new 3D modeling techniques to digitally complete its shape, then compared their models with modern animals. Ward said their next step will be to conduct a 3D analysis of other fossilized body parts of Rudapithecus to gather a more complete picture of how it moved, giving more insight into the ancestors of African apes and humans.

The study, "A late Miocene hominid partial pelvis from Hungary," was published in the Journal of Human Evolution. Funding was provided by the National Science Foundation, Natural Sciences and Engineering Research Council, National Geographic Society, Leakey Foundation, Wenner-Gren Foundation for Anthropological Research and University of Missouri Research Council. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

https://wb.md/2mmpGMb

BRAF/MEK Combo Yields 'Impressive' 5-Year Survival in Melanoma

Discussing an abstract reporting the 5-year follow-up of the phase 3 trials called COMBI-d and COMBI-v

Jeffrey S. Weber, MD, PhD

This transcript has been edited for clarity.

I'm Dr Jeffrey Weber, a medical oncologist at the Laura and Isaac Perlmutter Cancer Center at NYU Langone Health here in New York City.

I want to discuss an abstract Paul Nathan presented at the recent 2019 meeting of the American Society of Clinical Oncology.[1] This abstract reported the 5-year follow-up of the phase 3 trials called COMBI-d and COMBI-v, which compared dabrafenib plus trametinib, the BRAF and MEK drugs, with dabrafenib alone (COMBI-d); and dabrafenib plus trametinib with vemurafenib (COMBI-v), which was then a standard-of-care therapy.

Dr Nathan discussed the outcomes of the 563 patients with unresectable or metastatic melanoma who had received dabrafenib plus trametinib in both trials.

The median progression-free survival (PFS) in those patients was 11.1 months, which is quite similar to what we've seen with most of

our BRAF-MEK drugs. The 5-year PFS was 19%. If you break it down by lactate dehydrogenase (LDH) levels, the PFS goes up to 25% for those with normal baseline LDH levels, but only 8% for those with baseline LDH levels elevated above normal.

And if you go to the very select group of those with normal baseline LDH levels and fewer than three organ sites with metastases, the PFS is 31%.

The important data, of course, is the fact that 62% of patients have died. And a significant proportion of patients actually went on to get other immunotherapies.

But the 5-year overall survival is 34%, or about one third of patients, which is significant. You see what appears to be a plateau suggesting that about one third of patients who start out with the BRAF-MEK drugs, dabrafenib and trametinib, will do well in the long term.

Breaking it down by the LDH level, 43% of patients with a normal LDH survived to 5 years, compared with only 16% of those with an LDH above the upper limit of normal.

For those patients in that select population with normal LDH levels and fewer than three metastatic sites, the overall survival at 5 years was 55%, which is a respectable number.

At 5 years, 19% were complete responders, and the total, best overall response rate at the end of the day was 68%.

The PFS for the complete responders was about 49% at 5 years, and overall survival for the complete responders at 5 years was an impressive 71%. Again, as in many histologies with many therapies, it's always the complete responders who do well.

So, what do we conclude? You can have 5-year disease control in about one quarter of patients when you use dabrafenib and trametinib.

Patients will be alive, doing well, with many in remission—one third of those at 5 years—and a good proportion of these may well be cured, although a number of patients will eventually receive immunotherapies.

The urban legend that all patients who receive dabrafenib and trametinib will progress and all will die by 5 years is not true.

That 34% 5-year survival is an impressive proportion.

References

1. Nathan PD, Robert C, Grob JJ, et al. Five-year analysis on the long-term effects of dabrafenib plus trametinib (D + T) in patients with BRAF V600–mutant unresectable or metastatic melanoma. J Clin Oncol. 2019;37 (suppl; abstr 9507).

http://bit.ly/2mmqC39

New piece of Alzheimer's puzzle found

Researchers discover that two short strings of amino acids could pave the way to new treatments for Alzheimer's disease

Two years after discovering a way to neutralize a rogue protein linked to Alzheimer's disease, University of Alberta Distinguished University Professor and neurologist Jack Jhamandas has found a new piece of the Alzheimer's puzzle, bringing him closer to a treatment for the disease.

In a study published in Scientific Reports, Jhamandas and his team found two short peptides, or strings of amino acids, that when injected into mice with Alzheimer's disease daily for five weeks, significantly improved the mice's memory.

The treatment also reduced some of the harmful physical changes in the brain that are associated with the disease.

"In the mice that received the drugs, we found less amyloid plaque buildup and a reduction in brain inflammation," said Jhamandas, who is also a member of the Neuroscience and Mental Health Institute.

"So this was very interesting and exciting because it showed us that not only was memory being improved in the mice, but signs of brain pathology in Alzheimer's disease were also greatly improved. That was a bit of a surprise for us."

This discovery builds on previous findings of a compound called AC253 that can block the toxic effects of a protein called amyloid beta, which is believed to be a major contributor to Alzheimer's because it is often found in large quantities in the brains of patients with the disease.

AC253 blocks amyloid beta from attaching to certain receptors in brain cells--a process Jhamandas likens to plugging a keyhole.

However, while AC253 was shown to prevent a buildup of amyloid beta, it isn't very effective at reaching the brain and is quickly metabolized in the bloodstream.

As a result, treatment using AC253 requires large amounts of the compound to be effective, which is impractical and increases the chances of the body developing an immune reaction to treatment.

Transforming AC253 from an injectable drug into a pill would address the metabolism issues and increase efficacy, but AC253 was too complex to be able to make an effective oral drug.

Jhamandas' solution was to chop AC253 into pieces to see whether he could create smaller peptide strings that blocked amyloid beta in the same way AC253 did.

Through a series of tests using mice genetically modified to carry Alzheimer's disease, Jhamandas' team found two shorter pieces of AC253 that replicated the preventative and restorative abilities of the larger peptide.

With the short peptides identified, Jhamandas and his team, which includes renowned virologists Lorne Tyrell and Michael Houghton, used a process of computer modelling and artificial intelligence to discover a small-molecule drug--similar to medications used to treat high blood pressure or cholesterol--it's now developing.

The team is focused on manufacturing an optimized and oral version of the drug so human clinical trials can begin, said Jhamandas, who added small-molecule drugs are preferable for treatments, particularly for drug companies, because they are cheaper to make, can be taken orally and can more easily reach the brain through the blood, said Jhamandas.

While Jhamandas is optimistic about the potential of his new drug to change the way Alzheimer's is managed, he is quick to point out the years of research he and other researchers have done to get to this point.

"This has been 15, 20 years of painstaking and incremental work," he said. "And it's like building a house: you put one brick down, then you put another brick on top of that, and pretty soon you have a foundation and then you have a house.

"Occasionally you come across a discovery that has the potential to change the game in a very fundamental way, like hitting a home run, and I'm very excited that we are really on to something here."

Jhamandas' research was supported by grants from the Canadian Institutes of Health Research, Alberta Innovates (Alberta Prion Research Institute), Alzheimer's Society of Alberta and Northwest Territories, and University Hospital Foundation. The research was also supported by the Centre for Prion & Protein Folding Diseases, the Li Ka Shing Institute of Virology and the Applied Virology Institute.

http://bit.ly/2mj5ACo

12 Children with Autism Were Conceived from One Donor's Sperm. Is There an 'Autism Gene'?

The extraordinary case prompted one woman to sue her sperm bank.

By Rachael Rettner - Senior Writer 2 days ago Health

A single sperm donor is the biological father of at least 12 children who all developed autism — an extraordinary case that prompted one woman to sue her sperm bank, according to news reports.

The case came to light when the woman, Danielle Rizzo of Illinois, was researching treatments for her two sons, who both have autism, according to The Washington Post.

Both sons were conceived with sperm from the same donor, and Rizzo was shocked to discover that other mothers who used the same donor also had sons with autism, the Post reported.

Rizzo was told that the likelihood of all these related children having autism by chance was like all the mothers "opening up a dictionary and pointing to the same letter of the same word on the same page at the same time," she told the Post.

That means a mutation in the donor's sperm was likely responsible. But is there a single "autism gene?"

In short, no: There are hundreds of genetic variations tied to autism spectrum disorder, according to the National Institutes of Health (NIH). In most cases, these mutations increase a person's risk of autism, but they don't destine someone to develop the condition.

In other words, genes typically play only a partial role in the risk of developing autism, with environmental factors, such as the parents' ages and birth complications, contributing as well.

But in rare cases, genetic mutations are thought to be the main cause of autism. Only about 2% to 4% of people with autism have these mutations, according to the NIH.

"We call autism one thing, but it's different in every person. In some, it's all about the genes. Some it's a combination of genes and the environment. Some people, it's unknown," Dr. Wendy Chung, a professor of pediatric medicine at Columbia University, told the Post.

Studies of Rizzo's children found that they had two mutations tied to autism in genes called MBD1 and SHANK1.

Most reproductive clinics test for several hundred genetic conditions, but there is no test for autism, The Post reported.

In Rizzo's lawsuit, she alleged that the donor's profile had false information.

For example, she said that the donor did not have a college degree, as the profile listed, and that he had been diagnosed with ADHD, which was omitted from the profile, the Post reported. She settled the lawsuit in March for $250,000.

Read more about the case at The Washington Post.

http://bit.ly/2mqqFxh

Alzheimer's memory loss reversed by new head device using electromagnetic waves

Just released new results in the Journal of Alzheimer's Disease indicate that in-home treatment with a bioengineered head device emitting electromagnetic waves reversed memory impairment of Alzheimer's patients (AD)

This is a patient wearing MemorEM. **NeuroEM Therapeutics, Inc.**

Phoenix, AZ - There is finally some encouraging news for the millions of Americans suffering from Alzheimer's Disease. NeuroEM Therapeutics today announced findings from an open label clinical trial showing reversal of cognitive impairment in Alzheimer's Disease patients after just two months of treatment using the company's wearable head device for in-home treatment.

Results demonstrate that TEMT was safe in all eight participating patients with mild to moderate AD and enhanced cognitive performance in seven of them, as measured by their ADAS-cog score, which is the benchmark for testing AD therapeutics. The study is being published in the new issue of the *Journal of Alzheimer's Disease*.

The investigators had previously demonstrated that treating AD mice with electromagnetic waves in the radiofrequency range resulted in protection against memory impairment in young AD mice and reversal of memory impairment in aged AD mice.

For the present clinical study in humans, the investigators used the same treatment (twice daily for 1-hour) through creation of NeuroEM's first-in-class MemorEMTM head device. The device has multiple, highly-specialized emitters positioned within a head cap that are activated sequentially, with treatments easily administered in-home by the patient's caregiver. As well, the device

allows for near complete mobility to perform nearly all household activities during treatments.

"Perhaps the best indication that the two months of treatment was having a clinically-important effect on the AD patients in this study is that none of the patients wanted to return their head device to the University of South Florida/Byrd Alzheimer's Institute after the study was completed", said Dr.Gary Arendash, CEO of NeuroEM Therapeutics. One patient even exclaimed "I've come back."

The investigators indicated they have strong evidence that TEMT is directly affecting the Alzheimer's disease process by easily penetrating the brain and brain cells to break up aggregates of two toxic proteins inside brain cells called A-beta and tau.

TEMT's ability to disaggregate both toxic proteins inside brain cells (neurons) appears to be key to stopping and reversing the cognitive loss of AD. Present AD drugs in clinical trials have great difficulty getting into the brain and then into brain cells. Even if they succeeded in doing so, they do not yet have the capacity to target the small aggregates of A-beta and tau proteins that appear to be causative to AD.

NeuroEM Therapeutics is planning for a pivotal clinical trial to begin recruitment of approximately 150 mild/moderate AD subjects later this year for treatment with the company's MemorEMTM device. If that trial shows continued safety and cognitive benefits, NeuroEM Therapeutics plans to ask the FDA for approval of the MemorEM device for treatment of AD. The clinical locations for this multi-site trial have not yet been determined.

"Despite significant efforts for nearly 20 years, stopping or reversing memory impairment in people with Alzheimer's disease has eluded researchers," said co-author Amanda Smith, M.D., Director of Clinical Research, University of South Florida Health, Byrd Alzheimer's Institute, the clinical center for the study. "These results provide preliminary evidence that TEMT administration we assessed in this small AD study may have the capacity to enhance cognitive performance in patients with mild to moderate disease."

After two months of treatment administered at home by their caregivers, none of the eight patients in the study exhibited any deleterious side effects on behavior or physiologic measures, as recorded by caregivers in daily diaries. Moreover, post-treatment brain scans revealed no visible induction of tumors or brain bleedings called microhemorrhages.

Using the benchmark ADAS-cog task to assess a variety of cognitive measures, seven of the eight AD patients collectively responded to treatment with a 4+ point increase in cognitive performance by the end of the 2-month treatment period -- the results indicate a very large and clinically-important effect.

Since AD patients typically show a 4+ point decline in ADAS-cog performance over a given one year period, the 4+ point improvement provided by TEMT was as if the treated patients had gone back in time to their better cognitive performance of one year earlier.

"We were particularly surprised that this highly significant improvement in the ADAS-cog was maintained even two weeks after treatment was completed", stated Dr. Arendash. "The most likely explanation for continued benefit after cessation of treatment is that the Alzheimer's Disease process itself was being affected.

Cognitive abilities were improved in other tasks as well, such as the Rey AVLT task, wherein clinically important increases in word recall were present after treatment for 2 months and at two weeks thereafter. Even a 50% reduction in forgetting was observed in this important task.

In addition to cognitive assessment, the study also involved analysis of AD markers in both the blood and the cerebrospinal fluid (CSF) before and at the end of the 2-month treatment period. These AD markers were changed in directions expected for TEMT

disaggregating the two toxic proteins (A-beta and tau) that appear to be the disease's root causes.

Also, MRI brain scans in individual AD patients revealed evidence of increased communication between neurons in a brain area critical for cognitive integration called the cingulate cortex/cingulum.

The investigators believe that TEMT may be an entirely new therapeutic intervention against Alzheimer's disease and that NeuroEM's bioengineering technology may be succeeding where drug therapy against this devastating disease has thus far failed.

Based on the findings and the enthusiasm for continued treatment that all patients expressed, patients were offered and accepted continued TEMT in a now on-going extension study averaging 17 months between initial study start and extension study finish. More information about both the completed and on-going clinical trials is available at NeuroEM's website.

http://bit.ly/2lSIxOF

Biogen, Eisai End Two Late-Stage Trials for Alzheimer's Treatment

The widely expected move comes months after the companies scrapped trials of another Alzheimer's drug.

Emily Makowski

On Friday (September 13), biotechnology firm Biogen and its partner Eisai announced plans to abandon two clinical trials for an Alzheimer's treatment using the drug elenbecestat.

The decision to end the studies came after a data safety monitoring board found that the benefits of administering elenbecestat did not outweigh the risks, reports *Reuters*. In March, the companies ended two late-stage trials of another Alzheimer's drug, aducanumab. Elenbecestat and aducanumab were both *β*-site *amyloid* precursor protein-*cleaving enzyme* (BACE) inhibitors, drugs that curtail the production of the main component of the amyloid plaques found in Alzheimer's patients.

The two Phase III studies, known as MISSION AD1 and AD2, were designed to test the safety and effectiveness of elenbecestat in 2,100 patients with mild cognitive impairment or early Alzheimer's disease. "We are very disappointed with the news, and intend to learn from these data and continue engaging with patients and investigators to pursue the discovery of new medicines for Alzheimer's disease," Lynn Kramer, chief clinical officer of Eisai's neurology business group, says in a news release, according to *FierceBiotech*.

Other pharmaceutical companies such as Amgen and AstraZeneca have stopped trials of BACE inhibitors in the past, according to *Reuters*. Biogen and Eisai's Phase III trial of the anti–amyloid-*β* antibody BAN2401 will continue.

http://bit.ly/2mmP3xs

Cancer cells turn to cannibalism to survive chemotherapy, study suggests

Some cancer cells survive chemotherapy by eating their neighboring tumor cells

Researchers from the Tulane University School of Medicine have discovered that some cancer cells survive chemotherapy by eating their neighboring tumor cells. The study, which will be published September 17 in the *Journal of Cell Biology*, suggests that this act of cannibalism provides these cancer cells with the energy they need to stay alive and initiate tumor relapse after the course of treatment is completed.

Chemotherapy drugs such as doxorubicin kill cancer cells by damaging their DNA, but cells that survive initial treatment can soon give rise to relapsed tumors. This is a particular problem in breast cancers that retain a normal copy of a gene called *TP53*. Instead of dying in response to chemotherapy-induced DNA damage, these cancer cells generally just stop proliferating and enter a dormant but metabolically active state known as senescence.

In addition to surviving chemotherapy, these senescent cancer cells produce large amounts of inflammatory molecules and other factors that can promote the tumor's regrowth. Chemotherapy-treated breast cancer patients with normal *TP53* genes are therefore prone to relapse and have poor survival rates.

"Understanding the properties of these senescent cancer cells that allow their survival after chemotherapy treatment is extremely important," says Crystal A. Tonnessen-Murray, a postdoctoral research fellow in James G. Jackson's laboratory at the Tulane University School of Medicine.

In the new study, Tonnessen-Murray and colleagues discovered that, after exposure to doxorubicin or other chemotherapy drugs, breast cancer cells that become senescent frequently engulf neighboring cancer cells. The researchers observed this surprising behavior not only in cancer cells grown in the lab, but also in tumors growing in mice. Lung and bone cancer cells are also capable of engulfing their neighbors after becoming senescent, the researchers discovered.

Tonnessen-Murray and colleagues found that senescent cancer cells activate a group of genes that are normally active in white blood cells that engulf invading microbes or cellular debris. After "eating" their neighbors, senescent cancer cells digested them by delivering them to lysosomes, acidic cellular structures that are also highly active in senescent cells.

Importantly, the researchers determined that this process helps senescent cancer cells stay alive. Senescent cancer cells that engulfed a neighboring cell survived in culture for longer than senescent cancer cells that didn't. The researchers suspect that consuming their neighbors may provide senescent cancer cells with the energy and materials they need to survive and produce the factors that drive tumor relapse. "Inhibiting this process may provide new therapeutic opportunities, because we know that it is the breast cancer patients with tumors that undergo *TP53*-mediated senescence in response to chemotherapy that have poor response and poor survival rates," Jackson says.

Tonnessen-Murray et al., 2019. J. Cell Biol.
http://jcb.rupress.org/cgi/doi/10.1083/jcb.201904051?PR

http://bit.ly/2mmCQJ5

The First Evidence That Drugs Could Turn Back the Clock on Our Biological Age

The first promising evidence in humans, albeit imperfect and early, that a cocktail of three drugs is enough to reverse the epigenetic clock

By Shelly Fan

After decades of research, here it is: the first promising evidence in humans, albeit imperfect and early, that a cocktail of three drugs is enough to reverse the epigenetic clock—a measure of someone's biological age and health.

The results came as a surprise to even the research team, who originally designed the trial for something a little less dazzling: to look at human growth hormone's effects on the thymus, the cradle of the body's immune system that deteriorates with age.

"Maintained immune function is seen in centenarians," and thymus function is linked to all-cause mortality, explained study author Dr. Gregory Fahy at Intervene Immune, based in Los Angeles, California. "So we were hoping to use a year of growth hormone to maintain thymus function in middle-aged men, right before the tissue's functions take a nosedive," he said.

Yet something gnawed at the back of his mind. To combat the side effects of growth hormone, which includes dangerously increasing blood sugar levels, the team added in two diabetes drugs as a countermeasure. One is DHEA, a hormone secreted by the adrenal gland. The other, metformin, might spark immediate recognition: based on pre-clinical research it's one of the most promising anti-

aging drugs in the longevity pipeline. All three drugs have been linked to slowing the aging process in the lab.

What if the three-drug combination didn't just work on the immune system? What if they can actually induce measurable anti-aging effects in humans?

Before terminating the study, Fahy decided to call up Dr. Steve Horvath at the University of California, Los Angeles. The "watcher" of epigenetic clocks, Horvath has spent his career finding measures to assess a person's biological age, which differs from the number of candles you put on your birthday cake every year but better reflects your "true" age. Taking the drug cocktail for one year shed the participant's chronological age by 2.5 years on average, while showing signs of immune rejuvenation.

While not a massive change, the results caught the team off guard. "I'd expected to see slowing down of the clock, but not a reversal," said Horvath. "That felt kind of futuristic."

It's not to say we've "cured" aging—far from it. But after decades of research in flies, worms, and rodents, this trial in humans, however small and imperfect in control measures, offers hope.

The Hallmarks of Aging

Measuring a person's "true" age is surprisingly difficult. Due to genetics and lifestyle interventions, a population of 60-year-olds, for example, exhibit a spread in their health and mental status. Compared to chronological age, biological age better correlates with general health status, mental abilities, risk of getting age-related diseases, and death. Yet because aging gradually deteriorates the entire body, scientists have struggled to find the best markers.

In 2013, several research groups pooled their ideas to piece together the hallmarks of aging. Here's a taste of some ideas: Genomic instability. The shrinking of telomeres, the "protective" endcaps that protect chromosomes, which house our genes. Protein metabolism gone wild. Mitochondria, the energy producers in cells, break down. Depleted stem cells. Zombie cells run rampant.

A combination of markers may form the best "clock" that measures true age. But when it comes to any single measure, one stood out: epigenetic alterations.

Stay with me. The epigenome controls how genes get turned into proteins, and subsequently, tissues, organs, and the whole body. They're comprised of chemical marks that tag onto the genetic sequence itself, like light switches on every gene lamp. Different marks control whether a gene is turned on or off—methyl groups, for example, shut it off—and the pattern of these tags drastically changes as you age.

For the past few years, Horvath and others screened hundreds of positions on DNA from sample cells to see how often those places have a methyl group. By feeding these epigenetic data into algorithms, the teams have uncovered several mathematical clocks that can remarkably estimate a cell's—and a person's—true biological age. "The greatest hope is that this clock measures the output of a process that really does relate to aging—even causes aging," said Horvath.

An Immune Restoration

The new study's initial focus wasn't epigenetic clocks; rather, it was the immune system. The thymus, a tiny gland nestled between the lungs and the breastbone, helps nurture immune white cells to their full function to combat infections and cancers. The thymus is critical for maintaining the immune system, but it's fragile. It begins to shrink after puberty and fills with fatty deposits, which correlates to all sorts of immune troubles.

Nearly 16 years ago, when Fahy was 46 years old, he reviewed promising studies using growth hormones to restore thymus functions in animals and grew convinced that he found the solution to restoring the organ's function. With striking commitment, he

jabbed himself with growth hormones and the diabetes drug DHEA for a month, and found signs of regeneration in his own thymus.

The new TRIM (Thymus Regeneration, Immunorestoration and Insulin Mitigation) trial built on Fahy's self-experimentation. The study recruited nine white men aged between 51 and 65 years old, and dosed them with the three-drug combo for a year: growth hormone for restoration, and DHEA and metformin to combat high blood sugar. The latter two were also partly chosen for their promising anti-aging effects in animals.

During the trial, the team regularly took blood samples to analyze immune cell counts, and used medical imaging to check the composition of their thymus. With age, the number of different immune cell type changes, with potentially detrimental effects. At the end of the trial, not only were the cell changes reversed, the participants' thymus also showed less signs of fat—they'd been replaced by healthy, regenerated tissue.

A Surprising Rewind

Studying epigenetic clocks came as an afterthought. After the trial was completed, Fahy reached out to Horvath to take a second look at the data.

The results came as a surprise to both. Using four different epigenetic clocks, Horvath measured the biological age of each participant. Every single time he found that the clock rewound: the participants' epigenetic age was, on average, 1.5 years slower than when they first entered the trial. Rather than aging, they had a Benjamin Button moment. What's more, at nine months of treatment, the de-aging effect seemed to accelerate—that is, the longer they took the drug, the faster their epigenetic clocks seemed to rewind. The effects lasted for at least six months after they stopped taking the drugs.

Because the results were so consistent and lasting, Horvath is optimistic it's not a fluke, even with a small sample size. De-aging effects aside, other measures also proved promising: one of the most dangerous side effects of rejuvenation is cancer, characterized by "immortal" cells. Although the study only looked at prostate cancer, a high-risk potential, they didn't find any biomarkers hinting at a dangerous turn.

The study is hardly the final word on rejuvenation in humans. Because the study is so small and "not very well controlled," said Dr. Wolfgang Wagner at the University of Aachen in Germany, who was not involved in the study, "the results are not rock solid."

More importantly, the authors don't know *how* the drugs are working. Their main idea is that they're acting on the same molecular pathways as restricting calories, which is also a strong de-aging intervention in animals. In addition, epigenetic age isn't synonymous with biological age, though it's a tight approximation in terms of age-related health risks.

Regardless, the results are promising. Intervene Immune is now planning a larger trial with a more diverse population, including different age and ethnic groups and women, to further gauge efficacy.

As the authors concluded: "This is to our knowledge the first report of an increase, based on an epigenetic age estimator, in predicted human lifespan by means of a currently accessible aging intervention." It won't be the last.

http://bit.ly/2kn4DbB

Research reveals vital clues about recycling in the evolution of life in our universe

New research by Kent astrophysicists reveals vital clues about the role recycling plays in the formation of life in our universe.

by Michelle Ulyatt, University of Kent

By investigating the different stages in the life journey of stars and gaining new knowledge about their evolutionary cycle, scientists at the Centre for Astrophysics and Planetary Science have discovered

more about a crucial stage in the emergence of life in our universe. Their research reveals for the first time how matter discarded as stars die is recycled to form new stars and planets.

Scientists have long known that the materials that make up human life were not present during the beginnings of the universe. Elements such as carbon and oxygen form deep inside stars and are released when the stars explode. What has not been clear is what happens to these materials in the vast majority of stars which do not explode and how they are then extracted to contribute to the development of new planets and biospheres.

In their paper "Numerical simulations of wind-driven protoplanetary nebulae—I. near-infrared emission," which was published the *Monthly Notices of the Royal Astronomical Society* on 12 September, Professor Michael Smith and Ph.D. student Igor Novikov have discovered this vital missing link. By carrying out 2-D modeling on their Forge supercomputer, which mapped the pattern of light emitted from stars under different environmental conditions, the research team were able to understand how the material ejected is transferred and mixed with interstellar gas to form new astronomical objects.

For the first time, the physicists simulated the detailed formation of Protoplanetary nebula. These are astronomical objects that develop during a star's late evolution. They modeled the formation of the shell of materials that is released as the star ages. These shells form planetary nebulae, or ring-shaped clouds of gas and dust, which are visible in the night sky.

The study revealed how the gas and energy expelled by stars are returned to the universe, and in what forms. It found that the elements produced by dying stars are transferred through a process of fragmentation and recycled into new stars and planets.

Professor Smith said: "Initially, we were perplexed by the results of our simulations. We needed to understand what happens to the expelled shells from dying red giants. We proposed that the shells must be temporary, as if they stayed intact life could not exist in our universe and our planets would be unoccupied.

"The shells are not uniform. Most are likely to be cold and molecular. They disintegrate into protruding fingers and so lose their integrity. In contrast, warm atomic shells remain intact. This provides vital clues about how carbon and other materials are transferred and reused within our universe. Our civilization happens to exist when the generation of recycled material is at its highest. That is probably no coincidence."

More information: *Igor Novikov et al. Numerical simulations of wind-driven protoplanetary nebulae. II. signatures of atomic emission, Monthly Notices of the Royal Astronomical Society (2019). DOI: 10.1093/mnras/stz2377*

https://wb.md/2knBf54

Chronic Myeloid Leukemia: 5 Things to Know

The prognosis for chronic myeloid leukemia (CML) has improved dramatically in recent years.

Victoria Stern, MA

A patient's life expectancy—which once hovered around 5 years post-diagnosis—now approaches that of the general population, thanks in large part to a handful of tyrosine kinase inhibitors (TKIs).[1] Still, these agents do not work for everyone. Approximately half of patients do not respond or become intolerant to their first-line TKI and require an alternative approach. Here are five things to know about treating CML.

1. TKIs do not cure CML.

Despite the success of TKIs, a cure for CML remains elusive. The ultimate goal is for patients to go off TKIs and stay in remission. But most patients need to continue drug therapy indefinitely to maintain a durable molecular response.

The *BCR-ABL* fusion oncogene, which encodes the BCR-ABL oncoprotein, is the molecular signature of CML. Although available TKIs effectively inhibit the kinase activity of BCR-ABL, the drugs

do not eliminate leukemic stem cells.[2,3] In fact, research shows that the survival of these cells, which express *BCR-ABL* transcripts, is independent of BCR-ABL kinase activity.[4] In turn, the persistence of leukemic stem cells may fuel TKI resistance, promote relapse, or drive disease proliferation—all of which represent major roadblocks to a cure. Currently, researchers are exploring strategies to selectively target and wipe out these stem cells.[2]

2. Sustaining treatment-free remission poses a challenge.

A recent treatment goal for patients with CML is to stop TKIs for good. About 50% of patients who receive TKIs achieve a deep molecular response (BCR-ABL transcript level ≤ 0.01%, International Scale) and may be eligible to discontinue TKI therapy.[1] But a growing body of research shows that, of those patients, less than half—approximately 20%-25% overall—maintain treatment-free remission.[5-7]

Predicting which patients will remain in remission without TKIs is tricky. One key factor may be the duration of a patient's molecular response prior to stopping therapy. A 2019 analysis found that patients who had a durable molecular response for 6 years or longer before discontinuing their TKI had the lowest risk for relapse—7% versus 67% in patients with molecular responses for less than 6 years.[5] Patients with a low or intermediate Sokal risk score at diagnosis may also be more likely to maintain treatment-free remission.

Other potential relapse risks, however, are less clear-cut. The 2019 study[5] found, for instance, that the chance of relapse did not depend on whether patients had taken one TKI or had switched due to resistance or intolerance. However, a 2017 analysis reported that patients who had a poor response or resistance to a TKI faced an increased risk for relapse compared with those with intolerance to the TKI imatinib (Gleevec).[8]

Further research is needed to identify which patients are more likely to sustain treatment-free remission.[9] The upside is that almost all patients who relapse will regain their molecular response once they restart TKIs.[5]

Another bright spot for patients who relapse is that they could get a second shot at going off TKIs. Researchers are currently exploring whether a combination of a TKI and the JAK inhibitor ruxolitinib may allow patients to discontinue therapy even after an unsuccessful first attempt. In the phase 2 trial, patients with chronic-phase CML will receive the dual therapy for 12 treatment cycles (approximately 1 year). Those who meet the criteria for treatment-free remission will discontinue the drug regimen and be monitored closely over 36 months.

3. TKI adherence is a problem for younger patients.

Compliance with TKIs is critical for achieving a complete molecular response. Younger patients (≤ 50 years) with CML are less likely than their older peers to adhere to their drug regimen.[10-12]

The financial drain of TKI therapy affects compliance but probably has more to do with a patient's insurance coverage and out-of-pocket expenses than with age.[13,14] The main drivers of poor adherence in younger patients appear to center around quality-of-life issues, including concerns about drug-related side effects, ability to work, and fertility, as well as inadequate information about treatment and medication.[10,15]

4. Novel approaches may better predict treatment-free remission.

Patients who exhibit a robust and rapid response to TKIs may be more likely to achieve a deep molecular response and ultimately treatment-free remission. Hitting certain milestones within the first year on TKIs—such as *BCR-ABL1* transcript levels ≤ 10% by 3 months and < 0.1% by 12 months—is particularly important for

predicting treatment success.[9] Currently, clinicians use real-time quantitative polymerase chain reaction (PCR) to track the path of a patient's response to TKIs. But this conventional PCR method comes with a major limitation: It cannot detect *BCR-ABL1* levels below a certain threshold (≤ 0.0032%).

Being able to measure *BCR-ABL1* levels with greater granularity may allow clinicians to better predict a patient's chance of sustaining treatment-free remission. A growing body of research reveals that a PCR technique called digital PCR can detect *BCR-ABL* levels with more sensitivity and accuracy than real-time PCR. A 2019 analysis found that digital PCR improved clinicians' ability to identify patients in durable deep molecular remission, as well as potential candidates for TKI discontinuation.[16] Another method—long-range nested real-time PCR combined with ultra-deep sequencing of *BCR-ABL*—can identify TKI-resistant *BCR-ABL* mutations.[17] Pinpointing these mutations could help clinicians assess a patient's response to TKI therapy with greater accuracy, as well as whether (and when) a patient should switch drugs.

5. Emerging CML inhibitors could move the needle closer to a cure.

Several new CML inhibitors in preclinical and clinical trials show promise to enhance outcomes, especially for patients who are resistant or intolerant to available TKIs.

One novel inhibitor, asciminib (ABL001), binds to a different pocket on the BCR-ABL oncoprotein than the current collection of TKIs. Combining asciminib with a TKI—thus inhibiting two targets on BCR-ABL—may enhance major molecular response rates and help curb resistance.[18] So far in phase 1 studies, asciminib has demonstrated clinical activity and a solid safety profile in patients resistant or intolerant to two or more TKIs and in patients with the *T315I* mutation.[19]

Janus kinase (JAK) inhibitors, when combined with a TKI, may also improve the likelihood that patients will reach a complete or major molecular response. Preclinical data show that dual therapy—a JAK2 inhibitor plus imatinib, nilotinib (Tasigna), or dasatinib (Sprycel)—can eradicate CML cells and restore TKI sensitivity in resistant CML cell lines.[20] The JAK inhibitor ruxolitinib (Jakafi) has already received FDA approval to treat myelofibrosis, polycythemia vera, and acute graft-versus-host disease. A clinical trial now underway is exploring whether ruxolitinib plus nilotinib can eliminate the CML stem cell population in patients with chronic-phase disease.

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http://bit.ly/2kuqPaL

Psoriasis drug target offers potential for osteosarcoma

A treatment for psoriasis could be repurposed to treat a rare but aggressive form of youth cancer, new findings from the Garvan Institute of Medical Research suggest.

In an animal model, researchers demonstrated that the immune molecule IL23 is central to the development of osteosarcoma, a cancer of the bone. By targeting IL23, study authors successfully shrank osteosarcoma tumours in mice.

The findings, published this week in Cancer Discovery, uncover an opportunity to repurpose an existing medication and bring new hope to those suffering from osteosarcoma.

"There has been no real advance in treatments for this form of cancer in four decades - we have uncovered a new target that we know can be modulated with existing therapy," says senior author Professor David Thomas, Garvan Cancer Research Theme Leader and Director of the Kinghorn Cancer Centre. "We hope our findings will lead to clinical trials that will provide better outcomes for patients with this rare form of cancer."

Urgent need for new treatments

Osteosarcoma is a rare cancer, but among the ten most common cancers affecting males between ages 15 to 29, in Australia. Arising in bone, osteosarcoma is often dismissed as growing pain or injury, and in many cases only detected after it has spread to other parts of the body.

The five-year survival rate of osteosarcoma remains as low as 65%.

"Our search for new potential treatments for osteosarcoma began in 2013 when we investigated genetic risk factors for this form of cancer," says first author Dr Maya Kansara, who leads the Immunobiology of Cancer Group at Garvan.

"From genome-wide association studies conducted with the U.S. National Institutes of Health we saw that variants in a gene that encodes the protein GRM4 were frequently associated with osteosarcoma."

The immune system's link to osteosarcoma

"In a mouse model of osteosarcoma, we investigated the role of GRM4, as well as a number of immune molecules, the production of which is regulated by GRM4," says Dr Kansaras. "In our model, we discovered that the inflammatory molecule IL23 was critical to osteosarcoma formation and progression."

When the researchers removed IL23 in mice, they were protected from developing osteosarcomas. Further, when the researchers blocked IL23 in mice with existing osteosarcoma, tumour growth was slowed, and in synergism with doxorubicin, a current standard of care treatment for this form of cancer, tumour growth was even further suppressed.

The team analysed human osteosarcoma biopsies and found that more than 70% of samples had significantly higher levels of IL23 than non-tumour tissue. As the expression of IL23 is higher in multiple cancer types, the researchers say these findings may have broader implications for cancer outcomes.

Opportunity for repurposed therapy

Therapies targeting IL23 have been investigated extensively for a number of autoimmune diseases, including arthritis, intestinal inflammation and the skin condition psoriasis.

"Drugs that block IL23 are approved and well tolerated, and on the market now for the treatment of psoriasis," says Professor Thomas. "We are now designing clinical trials to see whether they can provide much-needed improved health outcomes for osteosarcoma patients."

Interestingly, data from a Danish cohort study published in 2017 suggested that patients with psoriasis were almost five times more likely to develop sarcomas than individuals without the skin condition. "This data reaffirms the central role IL23 plays in osteosarcoma, and that we're on the right track," says Dr Kansara.

This research was supported by the National Health and Medical Research Council, Cancer Council NSW, Tour de Cure and a Shriver Immunosarc International Collaborative Grant.

http://bit.ly/2moMpXT

How we discovered that an asteroid collision in space 466m years ago boosted life on Earth

Something mysterious happened nearly half a billion years ago that triggered one of the most important changes in the history of life on Earth.

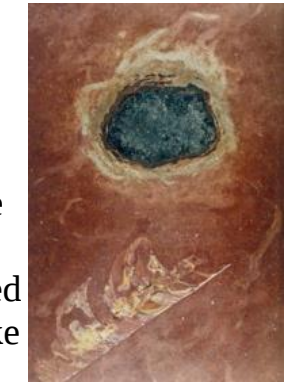
Birger Schmitz*

Suddenly, there was an explosion of species, with the biodiversity of invertebrate animals increasing from a very low level to something similar to what we see today. The most popular explanation for this "Great Ordovician Biodiversification Event" is that it was a result of an uncomfortably hot Earth cooling and eventually heading into an ice age.

But what actually triggered the change in temperature? In our new paper, published in Science Advances, we show that its onset coincided exactly with the largest documented asteroid breakup in the asteroid belt during the past two billion years, caused by a collision with another asteroid or a comet. Even today, almost a third of all meteorites falling on Earth originate from the breakup of this 150 kilometre-wide asteroid between Jupiter and Mars.

Following this event, enormous amounts of dust would have spread through the solar system. The blocking effect of this dust could have partly stopped sunlight from reaching the Earth – leading to cooler temperatures. We know that this involved the climate changing from being more or less homogeneous to becoming divided into climate zones – from Arctic conditions at the poles to tropical conditions at the equator. The high diversity among invertebrates, including green algae, primitive fish, cephalopods and corals, came as an adaptation to the new climate.

Swedish sea floor



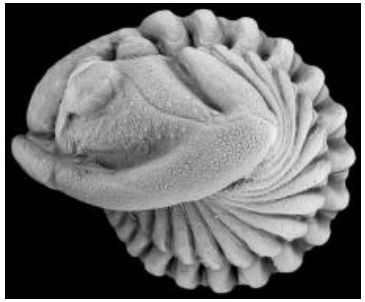
Fossil meteorite. **Birger Schmitz**

Our evidence comes from detailed studies of sea floor sediments of Ordovician age (485m-443m years ago) exposed at Kinnekulle in southern Sweden and Lynna River near St. Petersburg in Russia. In a quarry at Kinnekulle, we found more than 130 "fossil meteorites" – rocks that fell on Earth in the ancient past, which became embedded in sea floor sediments and were preserved just like animal fossils.

All but one of these fossil meteorites, which are up to 20cm in diameter, have the same composition – they are all debris from the same collision. Indeed, they were made up of the same type of material as the large asteroid that broke up in the asteroid belt at the time. The other meteorite probably originates from the smaller body that hit the large asteroid.

We know that the asteroid collision took place 466m years ago. This can be dated by looking at isotopes (variants of chemical elements with a different number of neutrons in the nucleus) in recently fallen meteorites from the Ordovician asteroid breakup. The fossil meteorites in the quarry must therefore represent the material that was transported to Earth immediately after the breakup. And given the large number of meteorites that we found on the sea floor, we can estimate that the flux of meteorites to Earth must have been orders of magnitude higher back then than it is today.

But how do we know that this bombardment created a huge amount of dust that lowered the temperature? We also studied the distribution of very fine-grained, micrometre-sized dust in the sedimentary strata. We could determine that it had an extraterrestrial origin by detecting helium and other substances incorporated in the sediments that could only be explained by the solar wind having bombarded the dust, enriching it with those elements on its way to Earth.



Fossil of tribolite. **Fredrik Terfelt**

Our results clearly show that enormous amounts of fine-grained dust reached Earth shortly after the breakup. And the geological record shows that shortly after the dust arrived, the sea level fell dramatically worldwide – the beginning of the ice age. That was because the sea water was transferred to the high latitudes, where large ice sheets formed.

The result was completely unexpected – we have during the last 25 years leaned against very different hypotheses in terms of understanding what happened during this period. For example, while we suspected that the diversification event was somehow linked to the asteroid breakup, we believed that the many small asteroids that also reached Earth from the breakup, rather than the dust, had something to do with the changes. It wasn't until we got the last helium measurements that everything fell into place.

Lessons for climate research

Global warming continues as a consequence of carbon dioxide emissions, and the temperature rise is greatest at high latitudes. According to the Intergovernmental Panel on Climate Change, we are approaching a situation that is reminiscent of the conditions that prevailed prior to the asteroid collision 466m years ago. Clearly, continuing on that route is not going to be good for biodiversity.

In the last decade or so, researchers have discussed different artificial methods to cool the Earth in case of a major climate catastrophe. One solution would be to place asteroids, much like satellites, in orbits around Earth in such a way that they continuously liberate fine dust and hence partly block the warming sunlight.

Our results show for the first time that such dust at times has cooled Earth dramatically, giving hopes that it could be a viable artificial solution. Our studies can give a more detailed, empirical-based understanding of how this works that can be used to create and evaluate computer models of such events.

But for the foreseeable future, there is no other way to tackle climate change than to reduce our carbon emissions. Ultimately, that is the only way to preserve the spectacular boost in the diversity of life that happened all those 466m years ago.

*Professor of Nuclear Physics, Lund University

Birger Schmitz received funding for this study from the European Research Council (Advanced Grant)

http://bit.ly/2kTZuYV

Brain tumors form synapses with healthy neurons, Stanford-led study finds

Scientists at the Stanford University School of Medicine have shown for the first time that severe brain cancers integrate into the brain's wiring.

The tumors, called high-grade gliomas, form synapses that hijack electrical signals from healthy nerve cells to drive their own growth. Experiments demonstrated that interrupting these signals with an existing anti-epilepsy drug greatly reduced the cancers' growth in human tumors in mice, providing the first evidence for a possible new way to treat gliomas.

A paper describing the findings will be published online Sept. 18 in Nature.

"One of the most lethal aspects of high-grade gliomas is that the cancer cells diffusely invade normal brain tissue so that the tumor and the healthy brain tissue are knitted together," said senior author Michelle Monje, MD, PhD, associate professor of neurology and neurological sciences. The discovery helps explain why gliomas are so intractable, she added. "This is such an insidious group of tumors. They're actually integrating into the brain."

The study's lead author is postdoctoral scholar Humsa Venkatesh, PhD.

Discovering that tumors wire themselves into the brain was "unsettling," Monje said. Still, she said she is optimistic about what the knowledge means for glioma patients. Several drugs already exist for treating electrical-signaling disorders such as epilepsy, and these may prove useful for gliomas, she said. "There is real hopefulness to this discovery," she said. "We've been missing this entire aspect of the disease. Now we have a whole new avenue to explore, one that could complement existing therapeutic approaches."

How the tumors grow

High-grade gliomas form synapses with healthy neurons that transmit electrical signals to the cancerous tissue, the study found. The tumors also contain cell-to-cell electrical connections known as gap junctions. Together, the two types of connections allow electrical signals from healthy nerve cells to be conducted into and amplified within the tumors.

High-grade gliomas include glioblastoma, a brain tumor seen in adults that has a five-year survival rate of 5%; diffuse intrinsic pontine glioma, a pediatric brain tumor with a five-year survival rate below 1%; and other diagnoses such as pediatric glioblastoma and diffuse midline gliomas occurring in the spinal cord and thalamus. Studies published by Monje's team in 2015 and 2017 indicated that high-grade gliomas use normal brain activity to drive their growth.

To learn how this worked, the scientists first analyzed the gene expression of thousands of individual cancer cells biopsied from newly diagnosed glioma patients. The cancer cells strongly increased the expression of genes involved in forming synapses.

The researchers then used electron microscopy, a technique that can reveal tiny details of cell anatomy, to show that structures that look like synapses exist between neurons and glioma cells. To confirm that these synapses indeed connect healthy neurons and malignant glioma cells, the scientists studied mice with cells from human gliomas implanted in their brains. After the glioma tumors had become established, the researchers used antibodies that bound to fluorescent markers expressed by the cancer cells to confirm that synapses go into malignant cells. "We saw very clear neuron-to-glioma synaptic structures," Monje said.

Using brain tissue from mice with human gliomas, the researchers measured the transmission of electrical signals into and through the tumors. They recorded two types of electrical signals: brief signals lasting four to five milliseconds, which are transmitted across a synaptic junction from a healthy neuron to a cancer cell by way of neurotransmitter molecules; and sustained electrical signals lasting one to two seconds that reflect electrical current propagated by a flux of potassium ions across the tumor cells' membranes. The potassium currents are caused by signals from neurons and are amplified by gap junctions that connect the cancer cells in an electrically coupled network.

The scientists also conducted experiments using a dye to visualize the gap-junction-connected cells, and used drugs capable of blocking gap junctions to confirm that this type of junction existed between the tumor cells and mediated their electrical coupling. Further experiments measuring changes in calcium levels

confirmed that the tumor cells are electrically coupled via gap junctions.

"The live calcium imaging made it strikingly clear that this cancer is an electrically active tissue," said Venkatesh, the lead author. "It was startling to see that in cancer tissue."

The researchers showed that about 5-10% of glioma cells receive synaptic signals, and about 40% exhibit prolonged potassium currents that are amplified by gap junction interconnections such that half of all tumor cells have some type of electrical response to signals from healthy neurons.

Possible drug therapies

In humans who were having the electrical activity in their brains measured before surgery to remove glioblastoma tumors, and in mice with human gliomas, the researchers saw hyper-excitability of healthy neurons near the tumors, a finding that could help explain why human glioma patients are prone to seizures.

Using optogenetic techniques, which relied on laser light to activate the cancer cells in mice implanted with human gliomas, the researchers demonstrated that increasing electrical signals into the tumors caused more tumor growth. Proliferation of the tumors was largely prevented when glioma cells expressed a gene that blocked transmission of the electrical signals.

Existing drugs that block electrical currents also reduced growth of high-grade gliomas, the research found. A seizure medication called perampanel, which blocks activity of neurotransmitter receptors on the receiving end of a synapse, reduced proliferation of pediatric gliomas implanted into mice by 50%. Meclofenamate, a drug that blocks the action of gap junctions, resulted in a similar decrease in tumor proliferation.

Monje's team plans to continue investigating whether blocking electrical signaling within tumors could help people with high-grade gliomas. "It's a really hopeful new direction, and as a clinician I'm quite excited about it," she said.

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Other Stanford co-authors of the paper are staff scientist Wade Morishita, PhD; postdoctoral scholars Anna Geraghty, PhD, Marlene Arzt, MD, and Kathryn Taylor, PhD; graduate student Shawn Gillespie; medical student Lydia Tam; staff scientist Cedric Espenel, PhD; research assistants Anitha Ponnuswami, Lijun Ni and Pamelyn Woo; Hannes Vogel, MD, professor of pathology and of pediatrics; and Robert Malenka, MD, PhD, professor of psychiatry and behavioral sciences.

Monje is a member of Stanford Bio-X, the Stanford Institute for Stem Cell Biology and Regenerative Medicine, the Stanford Maternal & Child Health Research Institute, the Stanford Cancer Institute and the Wu Tsai Neurosciences Institute at Stanford.

Scientists from Massachusetts General Hospital, Harvard Medical School, the Massachusetts Institute of Technology, Johns Hopkins University, the University of Michigan and the University of California-San Francisco also contributed to the research.

The research was funded by the National Institutes of Health (grant DP1 NS111132), the National Institute of Neurological Disorders and Stroke (grant NINDS R01NS092597), the National Cancer Institute (grant F31CA200273), the Michael Mosier Defeat DIPG Foundation, the ChadTough Foundation, the V Foundation, Ian's Friends Foundation, the Department of Defense, the Mckenna Claire Foundation, Alex's Lemonade Stand Foundation, The Cure Starts Now Foundation and DIPG Collaborative, the Lyla Nsouli Foundation, Unravel Pediatric Cancer, the California Institute for Regenerative Medicine, the Joey Fabus Childhood Cancer Foundation, the N8 Foundation, the Sam Jeffers Foundation, Cancer Research UK, the Virginia and D.K. Ludwig Fund for Cancer Research, and the Stanford Maternal & Child Health Research Institute's Anne T. and Robert M. Bass Endowed Faculty Scholarship in Pediatric Cancer and Blood Diseases.

Stanford's Department of Neurology and Neurological Sciences also supported the work.

A second paper showing similar findings by another team of researchers will be published simultaneously in Nature.

http://bit.ly/2kn1OY2

University of Minnesota researchers find new ways to improve CPR

Likely an optimal combination of chest compression frequency and depth when performing CPR

MINNEAPOLIS, MN - An international research consortium, which included faculty members from the University of Minnesota Medical School, was able to identify what is likely an optimal

combination of chest compression frequency and depth when performing CPR.

The investigation was led by Sue Duval, PhD, Associate Professor of Medicine and Biostatistics at the U of M Medical School, assisted by an international team of resuscitation investigators based at UT Southwestern, Medical College of Wisconsin, University of Oklahoma School of Community Medicine, the University Hospital of Grenoble Alpes in France, and Toho University in Tokyo, Japan.

The findings, published in *JAMA Cardiology*, suggest the combination of 107 compressions per minute and a depth of 4.7 cm (about 2 inches) in the first five minutes of CPR can be associated with significantly improved outcomes when Emergency Medical Services (EMS) rescuers are treating cardiac arrest outside the hospital.

In addition, the optimal combination identified did not seem to significantly vary when analyzed according to age, sex, presenting cardiac rhythm or the use of a specialized device attached to the airway during CPR. Moreover, the investigators showed that the use of the device significantly improved outcomes when the target combination of rate and depth was utilized.

The researchers found that even when CPR was performed within 20% of those chest compression values, neurologically intact survival was significantly higher -- 6% vs. 4.3% outside that range. Considering an estimated 300,000 or more out-of-hospital cardiac arrests occur each year nationally, this could translate into thousands of additional lives being saved annually in the United States alone and perhaps more if the target combination could be achieved routinely.

"What also makes this particular study especially novel for the resuscitation research community is the presentation of the data using contour plots -- graphical representation similar to a temperature map -- where the hottest points correspond to the best chance for neurologically intact survival," said Duval. "I believe this was another pivotal step in the continuum of research efforts to further save lives through robust data analysis."

The premise for this work stemmed in large part from prior National Institutes of Health (NIH) studies in which improved outcomes were observed when CPR was performed within a specified range of compression rates (100 to 120 per minute). Soon garnering the moniker the "sweet spot" of CPR, similar studies were performed showing improved outcomes within a range of compression depth as well. But because variations in rate can affect depth, and vice versa, the current investigators sought to take the next step to identify the optimal combination of the two, a "sweeter spot," to better guide rescuers in the future.

"The findings here not only emphasize the importance of quality CPR performance, but they will likely help paramedics and others on the frontlines save many more lives," said Paul Pepe, MD, Professor of Emergency Medicine at UT Southwestern. "We knew that both the depth and frequency of chest compressions could each affect outcomes, but we still had yet to better identify the optimal combination of the two - and, perhaps more importantly, whether that optimal target would vary if you were a man or woman, or if you were older or had a longer period of cardiac arrest before rescuers reached you. This study provided critical new knowledge toward that end."

Whether the findings would be universally applicable in all EMS systems has yet to be confirmed, but this study, conducted across 150 different EMS agencies in the U.S. and Canada, may be the best available findings to date. The researchers still advise that further validation of this target combination is recommended, especially when new devices, procedures or mechanical CPR tools are being introduced into the situation.

The study reviewed data from more than 3,600 patients who experienced cardiac arrest outside the hospital. Compression rate and depth were being recorded as part of a clinical trial conducted by the NIH Resuscitation Outcomes Consortium, with the use of a specific CPR device called the impedance threshold device (ITD). It was the first multicenter trial to use electronically documented measurements of both chest compression rates and chest compression depth.

The Resuscitation Outcomes Consortium (ROC), supported by the National Institutes of Health and other federal and Canadian agencies, provided the key information for this study. The ROC has enrolled tens of thousands of patients in scientific evaluations of prehospital interventions to improve outcomes in severely ill or injured patients before they are transported to a hospital, and it maintains a large registry of such cases.

http://bit.ly/2ksYoTF

Viking berserkers may have used henbane to induce trance-like state

Ethnobotanist argues the plant is a better fit than hallucinogenic mushrooms.

Jennifer Ouellette

The legendary Viking warriors known as berserkers were renowned for their ferocity in battle, purportedly fighting in a trance-like state of blind rage (*berserkergang*), howling like wild animals, biting their shields, and often unable to distinguish between friend and foe in the heat of battle.

***Enlarge** / Sixth century Viking matrix used in the manufacture of helmet plaques, depicting Odin accompanied by a Berserker.* **Werner Forman/Universal Images Group/Getty Images**

But historians know very little about the berserkers apart from scattered Old Norse myths and epic sagas. One intriguing hypothesis as to the source of their behavior is that the berserkers ingested a specific kind of mushroom with psychoactive properties. Now an ethnobotanist is challenging that hypothesis, suggesting in a recent paper in the Journal of Ethnopharmacology that henbane (*ヒヨス,天仙子*) is a more likely candidate.

Accounts of the berserkers date back to a late ninth-century poem to honor King Harald Fairhair. The 13th-century Icelandic historian/poet Snorri Sturluson described Odin's berserkers as being "mad as dogs or wolves" and "strong as bears or wild oxen," killing people with a single blow. Specific attributes can vary widely among the accounts, often veering into magic or mysticism. There are claims that berserkers were not affected by edged weapons or fire, but they could be killed with clubs. Other claims say they could blunt the blades of their enemies with spells or just by giving them the evil eye. Most accounts at least agree on the primary defining characteristic: a blind ferocious rage.

The onset of *berserkergang* purportedly began with bodily chills, shivering, and teeth chattering, followed by swelling and reddening of the face. Then the rage broke out, and once it abated, the berserker would experience both physical fatigue and emotional numbness for a few days. Several hypotheses have been proposed for why the warriors would have behaved this way, including self-induced hysteria—aided by biting their shields and howling—epilepsy, ergot poisoning, or mental illness. One of the more hotly contested hypotheses is that the berserkers ingested a hallucinogenic mushroom (*Amanita muscaria*), commonly known as fly agaric, just before battle to induce their trance-like state.

***Enlarge** / The mushroom* **Amanita muscaria** *is known to have hallucinogenic properties.* **Ak ccm/Wikimedia Commons**

A. muscaria has a distinctly *Alice in Wonderland* appearance, with its bright red cap and white spots. While it's technically toxic to humans, the mushrooms are apparently safe to ingest after parboiling them twice. *A. muscaria* was very popular as an intoxicant among Siberian tribes, possibly holding religious significance because of its psychoactive properties. The latter aspect is due to two compounds: ibotenic acid and muscimol, with muscarine (first discovered in 1869) most likely responsible for some of the more unpleasant side effects. The 'shroom typically induces a drunken state with auditory illusions and shifts in color vision. It can also induce vomiting, hyperthermia, sweating, reddening of the face, twitching and trembling, dilated pupils, increased muscle tone, delirium, and seizures.

Much of that is consistent with accounts of berserker behavior. But according to Karsten Fatur, an ethnobotanist at the University of Ljubljana in Slovenia, henbane (*Hyoscyamus niger*) is a much better candidate. It's been around since ancient Greece and has been used in various cultures throughout history as a narcotic, painkiller, cure for insomnia, and anesthetic. It's a common treatment for motion sickness and can produce short-term memory loss. It can knock out someone for 24 hours, and in rare cases henbane can lead to respiratory failure.

It's also been investigated as a possible truth serum. Henbane even found its way into early European beers, gradually being replaced with hops after the passage of the Bavarian Purity Law in 1516.

***Enlarge* / Hyoscyamus niger*, more commonly known as henbane, might be a better fit for the berserker symptoms.* K.B. Simoglou/Wikimedia Commons**

Fatur argues that while both the mushrooms and henbane could account for increases in strength, altered consciousness, delirium, jerking and twitching, and red face commonly associated with the berserkers, aggressive rage is not common with the mushroom. Fatur cites several cases involving angry behavior associated with plants related to henbane, containing the same alkaloids.

"This anger effect can range from agitation to full-blown rage and combativeness depending on the dosage and the individual's mental set," he wrote. "As this is perhaps the most defining component of the berserker state, this symptom is of central importance in identifying the potential causes and provides a very critical reason as to why *H. niger* is a more appropriate theoretical intoxicant for the berserkers than *A. muscaria*."

Henbane can also dull pain (hence the accounts of berserkers being nearly invulnerable), contribute to an inability to recognize faces, cause removal of clothing, and lower blood pressure, which Fatur suggests might account for the assertion that berserkers didn't lose much blood when injured with blades. And berserkers purportedly suffered from numerous side effects for several days following that battle high. The mushrooms typically don't produce lingering side effects; henbane does, including headache, dilated pupils, and blurred vision.

Fatur suggests that *A. muscaria* would have been much more rare in Scandinavia—it typically grows in forests since it flourishes in a symbiotic relationship with tree roots. Henbane, in contrast, grows rapidly as a weed and is known to have flourished in Scandinavia during the berserker era. And a woman's grave in Denmark, dating back to about 980, included a pouch of henbane seeds, along with clothing and jewelry, according to Fatur.

Naturally, a few caveats are in order. There are elements of berserker behavior that henbane cannot account for, such as the biting of shields and chattering teeth. And Fatur notes that much of this is speculative, since there simply isn't sufficient archaeological or historical evidence to prove or disprove his hypothesis. He

himself has no specific expertise in history or archaeology, so the ethnobotanist is calling on future research by those communities to confirm or disprove his unique ethnobotanical perspective.

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http://bit.ly/2lYG0CB

Did a common childhood illness take down the Neanderthals?

A 21st century nuisance for parents may have proved deadly to early man

BROOKLYN, NY - It is one of the great unsolved mysteries of anthropology. What killed off the Neanderthals, and why did Homo sapiens thrive even as Neanderthals withered to extinction? Was it some sort of plague specific only to Neanderthals? Was there some sort of cataclysmic event in their homelands of Eurasia that lead to their disappearance?

This illustration shows the structure of the Eustachian Tube in Neanderthal Man and it's similarity to the human infant. **Credit: SUNY Downstate Health Sciences University**

A new study from a team of physical anthropologists and head & neck anatomists suggests a less dramatic but equally deadly cause.

Published online by the journal, *The Anatomical Record*, the study, "Reconstructing the Neanderthal Eustachian Tube: New Insights on Disease Susceptibility, Fitness Cost, and Extinction"[1] suggests that the real culprit in the demise of the Neanderthals was not some exotic pathogen.

Instead, the authors believe the path to extinction may well have been the most common and innocuous of childhood illnesses - and the bane of every parent of young children - chronic ear infections.

"It may sound far-fetched, but when we, for the first time, reconstructed the Eustachian tubes of Neanderthals, we discovered that they are remarkably similar to those of human infants," said coinvestigator and Downstate Health Sciences University Associate Professor Samuel Márquez, PhD, "Middle ear infections are nearly ubiquitous among infants because the flat angle of an infant's Eustachian tubes is prone to retain the otitis media bacteria that cause these infections - the same flat angle we found in Neanderthals."

In this age of antibiotics, these infections are easy to treat and relatively benign for human babies. Additionally, around age 5, the Eustachian tubes in human children lengthen and the angle becomes more acute, allowing the ear to drain, all but eliminating these recurring infections beyond early childhood.

But unlike modern humans, the structure of the Eustachian tubes in Neanderthals do not change with age - which means these ear infections and their complications, including respiratory infections, hearing loss, pneumonia, and worse, would not only become chronic, but a lifelong threat to overall health and survival.

"It's not just the threat of dying of an infection," said Dr. Márquez. "If you are constantly ill, you would not be as fit and effective in competing with your Homo sapien cousins for food and other resources. "In a world of survival of the fittest, it is no wonder that modern man, not Neanderthal, prevailed."

"The strength of the study lies in reconstructing the cartilaginous Eustachian tube," said Richard Rosenfeld, MD, MPH, MBA, Distinguished Professor and Chairman of Otolaryngology at SUNY Downstate and a world-renowned authority on children's health. "This new and previously unknown understanding of middle ear function in Neanderthal is what allows us to make new inferences regarding the impact on their health and fitness."

"Here is yet another intriguing twist on the ever-evolving Neanderthal story, this time involving a part of the body that researchers had almost entirely neglected," said Ian Tattersall,

Ph.D., paleoanthropologist and Curator Emeritus of the American Museum of National History. "It adds to our gradually emerging picture of the Neanderthals as very close relatives who nonetheless differed in crucial respects from modern man."

[1]. *Reconstructing the Neanderthal Eustachian Tube: New Insights on Disease Susceptibility, Fitness Cost, and Extinction* The Anatomical Record
Anthony Santino Pagano, PhD, Samuel Márquez, PhD, Jeffrey T. Laitman, PhD
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Ancient DNA puts a face on the mysterious Denisovans, extinct cousins of Neanderthals

Clues from DNA enable researchers to piece together a rough composite of a young girl

By Michael Price

Many of us can picture the face of a Neanderthal, with its low forehead, beetled brows, and big nose. But until now, even scientists could only guess at the features of the extinct Denisovans, who once thrived across Asia. For more than 10 years, these close cousins of Neanderthals have been identified only by their DNA in a handful of scrappy fossils.

This artist's reconstruction, based on anatomical estimates from a new method, shows the face of a Denisovan girl from Siberia in Russia. **Maayan Harel**

Now, a new method has given the Denisovans a face. A recently developed way to glean clues about anatomy from ancient genomes enabled researchers to piece together a rough composite of a young girl who lived at Denisova Cave in Siberia in Russia 75,000 years ago. The results suggest a broad-faced species that would have looked distinct from both humans and Neanderthals.

Ludovic Orlando, a molecular archaeologist at the University of Copenhagen who wasn't involved in the work, calls the approach "clever." But he and others caution against making specieswide generalizations based on a single individual.

Perhaps 600,000 years ago, the lineage that led to modern humans split from the one that led to Neanderthals and Denisovans. Then about 400,000 years ago, Denisovans and Neanderthals themselves split into separate branches. Denisovans ranged from Siberia to Southeast Asia and may have persisted until as recently as 30,000 years ago, based on their genetic legacy in living Southeast Asians.

Hundreds of Neanderthal skeletons, including intact skulls, have been found over the years. But the only fossils conclusively linked to Denisovans are a pinkie bone from the girl plus three teeth, all from Denisova Cave, and a recently identified lower jaw from China's Baishiya Karst Cave.

Then in 2014, researchers introduced a novel method based on epigenetics—a set of molecular knobs that can turn gene expression up or down—to analyze gene regulation in long-extinct hominins. One such knob is a chemical modification called methylation, which silences gene expression. In methylated DNA, one nucleotide, cytosine, degrades over thousands of years into a different end product than usual. By tracking that degradation in an ancient genome, scientists can create a methylation "map."

Liran Carmel and David Gokhman, geneticists at the Hebrew University of Jerusalem, and their colleagues applied this method to DNA in the girl's pinkie from Denisova Cave. They compared the girl's methylation map with similar maps of modern humans, Neanderthals, and chimpanzees, focusing on areas where the degree of methylation differed by more than 50%.

To find out how Denisovans' unique methylation patterns might have influenced their physical features, the researchers consulted the Human Phenotype Ontology database of genes known to cause

specific anatomical changes in modern humans when they are missing or defective. Because methylated genes are "turned off," they may have effects comparable to those of the genes in the database, making it possible for researchers to infer Denisovan anatomy.

The method can't provide exact body measurements. "We can say [Denisovans had] longer fingers [than modern humans for example], but we cannot say 2 millimeters longer," Carmel explains. In total, the researchers discovered 56 Denisovan anatomical features that may have differed from humans or Neanderthals, 34 of them in the skull. As expected, the Denisovan girl looked fairly similar to a Neanderthal, with a similarly flat cranium, protruding lower jaw, and sloping forehead, the researchers report this week in *Cell*.

Yet she also had key differences. The reconstructed face was notably wider than that of a modern human or Neanderthal, and the arch of teeth along the jawbone was longer.

A test of the model came while *Cell*'s editors reviewed the paper. Another team concluded based on ancient proteins in the Baishiya jawbone that it belonged to a Denisovan. Carmel and colleagues eagerly matched their model Denisovan to the real thing, and found a close fit: The jawbone was wider than that of either humans or Neanderthals, and there were hints that it protruded about as much as in Neanderthals but more than in modern humans. "It almost perfectly matched our predictions, which was very nice for us," Carmel says. The team's predictions also match skull fragments from Xuchang, China, that some argue belong to a Denisovan, he adds, and the method may help identify additional Denisovan specimens.

Because the current study is based on a single individual and the technique only returns relative measurements, researchers caution that it's an imperfect reflection of what the species looked like. Only more Denisovan fossils can confirm whether this portrait is accurate, says Gabriel Renaud, a bioinformatician at the University of Copenhagen, who adds that he wishes the authors had publicly released their computational methods so that others could replicate the findings.

"If you were to find a single *Homo sapiens* fossil and it's an NBA basketball player, then you might conclude that *Homo sapiens* were 7 feet tall," he says. "It's an interesting approach, but we can't verify the predictions until several Denisovan skeletons are found."

Reconstructing Denisovan Anatomy Using DNA Methylation Maps - Gokhman, D. et al. Cell https://doi.org/10.1016/j.cell.2019.08.035 (2019).

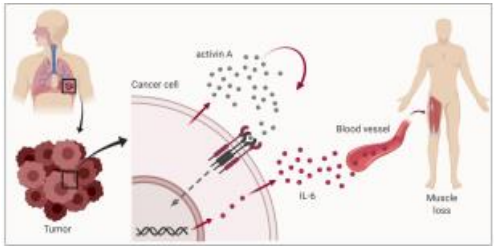
http://bit.ly/2kpf8Lw

How cancer breaks down your muscles

New research sheds light on how cancer tumors can take control of muscle cells and cause wasting.

A complicated metabolic syndrome called cachexia is a type of cancer-related muscle wasting disease that can be deadly. The name comes from the Greek words for "bad condition", which is quite descriptive of the health state of patients after a tumor has triggered muscle atrophy in their bodies over a long period.

"The tumor may be in a completely different place than where the affected muscle cells are," says Geir Bjørkøy, a professor at NTNU's Department of Biomedical Laboratory Science, in the Faculty of Natural Sciences.



Activin A and IL-6 are both key signalling factors and functionally linked.
Illustration: NTNU and biorender.com

"A small tumor hidden in your lungs or pancreas can cause your muscles to shrink and weaken. You may feel fatigue, shortness of breath or your tolerance to exercise may be impaired because your heart function may be reduced," says Kristine Pettersen, a

postdoctoral fellow at the Centre of Molecular Inflammation Research (CEMIR) at NTNU.

Senior engineer Sonja Andersen at NTNU's Department of Biomedical Laboratory Science says, "The distance from the tumor to the affected area means that there must be a connection between the tumour and the damaged muscle cells. One or more physical substances from the tumor have to be causing the muscle cells to self-degrade beyond what's normal."

Now, a research group at NTNU and several partners have identified a possible mechanism for how cancer cells may be sending these messages to the muscle cells. Their exciting results have just been published in the Journal of Cachexia, Sarcopenia and Muscle (JCSM).

Cachexia almost behaves like a disease of its own, in addition to the cancer itself. When you lose muscle mass, you not only become weaker, but your ability to tolerate the harsh side effects of cancer treatment is reduced as well. This may limit treatment options, and cachexia is associated with increased mortality rate.

People with cachexia may suffer drastic weight loss, and increased nutrient intake alone cannot compensate for it. Patients often feel both tired and nauseated.

Cachexia and not the cancer itself is the probable cause of about one in three cancer-related deaths. Currently, there is no effective treatment for cachexia.

Since the cancer cells must be secreting some signal that triggers the muscle wasting, researchers are investigating two different signalling factors.

The main suspects have been activin A and interleukin 6 (IL-6). Some studies indicate that activin A must be the central factor, while others suggest that IL-6 is a key signalling factor from the tumor that causes the loss of muscle tissue.

"Previously, we have shown that IL-6 can increase the wasting process in muscle cells and consequently may be important for the development of cachexia," says Pettersen.

But who is right? Those who blame activin A, or those who think IL-6 is the most important?

Bjørkøy says, "It turns out to be both. Activin A and IL-6 are both key signalling factors and functionally linked."

Here's the short version of what is going on:

1. First, the cancer cells produce the signalling factor activin A, which they secrete. Activin A can then have an effect on these same cancer cells through receptors on their surface that bind this signalling substance.

2. When activin A is bound and activates the surface receptor on the cancer cells, these cells start producing large amounts of the signalling factor IL-6, which is then released.

3. IL-6 works in several different ways, one of which is that it binds to muscle cells and instructs them to break down cell content.

So why do the cancer cells do this? Actually, they are merely increasing the speed of a process that's already happening. The cancer cells need the nutrients that are made available when the muscle cells break down proteins. In effect, the cancer cells abuse a fundamental mechanism that already exist in our cells and tissues.

When regulated, this breakdown is a completely normal process. The cells in the body degrade and build up cellular components all the time. This is important to keep all our cells functioning.

All the cells in our body contain lots of tiny organelles (cellular structures with specific functions) with digestive enzymes. These organelles, called lysosomes, absorb and degrade cellular components in a process called "autophagy," meaning "self-eating".

"Autophagy is important for all cells and is used to remove damaged or redundant cell contents," says Pettersen. "The process can also increase during periods where food is scarce."

"Autophagy releases amino acids, fats and sugars from the degraded cellular components to provide building blocks for new biomolecules or for cellular energy production. In this way, autophagy is an important mechanism for surviving starvation in the cells of all organisms - from fungi to mammals," she said.

Thus, the building blocks that make up our cells are broken down and can be released from the cells generating them and used by other cells in new places where they are needed next.

Our muscle cells are able to adjust the amount of certain proteins without compromising cell function. When some of these muscle proteins are degraded, amino acids are released that muscle cells either can use themselves or can release into the blood for the benefit of other cells in the body. For example, we can usually tolerate a slight reduction in muscle proteins in our arms or legs, especially if it helps our heart and lungs to function properly.

Andersen points out that cancer cells only cause a slight increase in autophagy. However, this small change in the overall balance is sufficient to cause a slight increase in muscle wasting that results in the loss of muscle mass over time.

Removing the tumor in patients with cachexia also reverses the cachexia, and muscle mass can return to normal.

Unfortunately, not all tumours can be removed by current treatments, either because the cancer has spread, the tumour is inaccessible or because the cancer treatment is not effective.

The research group at NTNU has shown that preventing the cancer cells from producing activin A or preventing activin A from binding to the receptor on the cancer cells restricts the production of IL-6 and reduces the cancer cells' ability to increase autophagy in other cells.

In cancerous mice, this has prevented them from developing cachexia, Pettersen says.

"However, we lack formal evidence to verify if the same mechanism operates similarly in humans. In patients, the picture may be more complicated even if we know that both signalling compounds that have been studied can be elevated in blood samples from cancer patients," she said.

"Other signalling factors and processes may also be involved in stimulating the increased autophagy of muscle cells, and all types of cancer that cause cachexia may not use the same signalling factors," Bjørkøy says. "It's also conceivable that there are differences between individual patients, even though they initially have the same type of cancer," says Andersen.

Pettersen notes that although the researchers believe the two signalling factors they have functionally linked to each other are often involved in cancer cachexia in patients, it is important to continue the search for other signalling candidates as well.

This research has helped to shed light on the cachexia puzzle and confirmed a link between two important signalling factors, but further research is needed to obtain a more complete picture. The hope is to find out if the typical cancers that cause cachexia - such as lung, pancreatic and intestinal cancers - use distinct or shared mechanisms to trigger muscle loss.

The goal is to develop tests that can measure the amount or activity of the relevant signalling substances, in order to provide patients with tailor-made treatments to block muscle wasting.

Documented cases already exist showing that individual patients with cachexia have greatly benefited from a drug that reduces the efficacy of IL-6. This drug is currently used to treat rheumatism. International researchers are now planning a clinical trial of the same drug in cancer patients with cachexia.

"So there's reason to be optimistic that we'll soon have biological drugs that can restrain this serious complication of cancer," says Bjørkøy.

Nevertheless, it will take some time before researchers can clarify how this will work in patients and how many patients can be helped with the drug that is currently being tested.

The new findings are the result of many years' work. Professor Bjørkøy says the project at NTNU has been going on for ten years, but that the ideas about this form of muscle wasting and the processes behind cancer cachexia have been around far longer.

The research group has worked closely with NTNU's Department of Biomedical Laboratory Science, the Centre for Molecular Inflammation Research (CEMIR) at NTNU and the biotechnology company Novartis in Switzerland.

Novartis' interest in the project revolves around expanding the knowledge about the disease mechanism and its potential to open up novel approaches to cachexia treatment methods.

http://bit.ly/2krAoQQ

No bones about it, this protein slows down fracture-healing

Abundance of ApoE may explain why older people have more trouble healing broken bones

DURHAM, N.C. -- Broken bones are a bigger deal the older you are: even after they've healed, the bones of older people are weaker and more likely to re-fracture. And since more than 6 million Americans break a bone each year, figuring out how to help people heal better would make a big difference.

In a paper published in JCI Insight on Sept. 19, Duke scientists found that a certain protein, which is more prevalent in older people, interferes with bone healing. They hope this discovery will lead to new treatments to help people heal after injuries or surgeries.

"When we decreased the protein level, aging was reversed," said senior author Gurpreet Baht, Ph.D. an assistant professor in the Duke Department of Orthopaedic Surgery. "Not only was there more bone and healing happened faster, but it was also structurally more sound."

Baht's team confirmed that older people have more Apolipoprotein E, ApoE for short, than younger people. (If that protein name rings a bell, it's because ApoE is also implicated in Alzheimer's and heart disease).

The team found that 75-85 year olds had twice as much ApoE in their bloodstreams as 35-45 year olds, then found the same was true for 24-month-old mice versus 4-month-old mice, which approximate the same human age ranges.

Next, they wanted to figure out if and how ApoE affects the multi-step process of bone healing. When you break a bone, your body sends signals through the bloodstream to recruit cells to fix it. Some of those recruits, specifically skeletal stem cells, build up cartilage as a temporary scaffolding to hold the fracture together.

In the next step, more recruited cells mature into osteoblasts, bone-building cells, which lay strong, dense bone cells on top of the cartilage scaffolding. Finally, a different kind of cell eats up the cartilage scaffolds and osteoblasts fill those holes with bone.

"Over time, this cartilage will continue to be resorbed and osteoblasts will continue to deposit new bone," Baht explained. "After a few months of your arm or leg healing, there will be almost no cartilage anymore. And if you were to look at it five years out, there'd be no sign of an injury anymore."

That's if the bone healing process works perfectly. But the researchers found that if they added ApoE to a petri dish with skeletal stem cells, fewer cells developed into osteoblasts and the osteoblasts were worse at building bones.

"We wanted to see if the cell population was more or less capable of becoming osteoblasts," Baht said. "[Normally,] you put these cells down in a petri dish for about a month and the dish becomes so hard that you can't even scratch the surface because they've made

two-dimensional bone there. ApoE-treated cells are still able to do this, they just don't do it as much or as well."

Next, the researchers created an intervention by injecting a virus which keeps mice from making ApoE protein. Circulating ApoE levels dropped by 75 percent and the healed bones contained one and a half-times more strong, hard bone tissue than bones of untreated mice.

The research was supported by the Duke Center for the Study of Aging and Human Development and Claude D. Pepper Older Americans Independence Center (AG028716 and K01AG056664), the Pathway to Stop Diabetes Initiator Award from the American Diabetes Association (1-16-INI-17) and a Borden Scholar Award.

Past researchers linked ApoE to Alzheimer's disease and atherosclerosis, a disease in which fatty plaques narrow the arteries. Too little ApoE, and fat builds up and can cause cardiovascular issues. The liver virus which turned off ApoE production in mice acts permanently, so Baht's next step is to investigate other interventions.

"You have to be careful," Baht said. "If a patient were to permanently decrease circulating ApoE levels, and then have a fatty meal, that fat might not get processed properly and could deposit in blood vessels. In our future studies, we're going to try to temporarily lower ApoE."

"As a treatment to improve bone healing, the patient could take a pill or an injection to lower ApoE for a short time rather than permanently, and there would be dietary restrictions during treatment. That would be probably a much safer model," Baht said.

CITATION: "Lowering Circulating Apolipoprotein E Levels Improves Aged Bone Fracture Healing," Rong Huang , Xiaohua Zong, Puviindran Nadesan, Janet L Huebner, Virginia B Kraus , James P White, Phillip J White, Gurpreet S Baht. JCI Insight, *19 Sept 2019. DOI: 10.1172/jci.insight.129144.*

http://bit.ly/2mr0vIh

Alzheimer's drug also treats parasitic Chagas disease

Memantine can diminish the number of parasites in mice with Chagas disease, and increase the survival rate

The drugs currently used to treat Chagas disease, a neglected tropical disease, have serious side effects and limited use in those with chronic disease. Now, researchers have reported in *PLOS Neglected Tropical Diseases* that memantine, a drug currently used to treat Alzheimer's disease, can diminish the number of parasites in mice with Chagas disease, and increase the survival rate of the animals.

Chagas disease, caused by the protozoan Trypanosoma cruzi affects 5 to 6 million people in the Americas. The disease can be divided into acute and chronic phases, with the clinical phase causing heart, esophagus or intestinal symptoms. The two drugs that have been used to treat Chagas for the last 50 years--nifurtimox and benznidazole--are highly effective in the acute phase but used sparingly in the chronic phase due to serious side effects that occur with long-term treatment.

In the new work, Ariel M. Silber of Universidade de São Paulo, Brazil, and colleagues studied memantine, which works on the central nervous system of animals but has also been shown to kill protozoa. The researchers first studied the effect of different concentrations of memantine on cultured macrophages-- a type of white blood cell--that were infected with T. cruzi. Next, they tested the drug in T. cruzi-infected mice.

The team found that memantine reduced the number of T. cruzi-infected macrophages in a dose-dependent way; more drug led to a greater reduction in the infection. In mice with Chagas disease, memantine lowered levels of the parasite by 40% and increased survival rates from 7.5% to 12.5%. The mice treated with

memantine also had 35.3% lower parasite levels in their hearts compared to control animals.

"All these findings point memantine as an interesting starting point for the development of an optimized alternative therapy for Chagas disease," the researchers say.

In your coverage please use this URL to provide access to the freely available paper: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0007226

Citation: Santos Souza HF, Rocha SC, Damasceno FS, Rapado LN, Pral EMF, et al. *(2019) The effect of memantine, an antagonist of the NMDA glutamate receptor, in in vitro and in vivo infections by Trypanosoma cruzi.* PLOS Neglected Tropical Diseases *13(9): e0007226. https://doi.org/10.1371/journal.pntd.0007226*

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These Gut Bacteria Brew Their Own Booze, and May Harm Livers in People Who Don't Drink

Super-strains of gut bacteria produce harmful amounts of alcohol, which may to contribute to fatty liver disease.

By Nicoletta Lanese - Staff Writer

It's common knowledge that drinking too much alcohol can lay waste to your liver. But now, researchers have spotted a strain of gut bacteria that produces its own booze in copious amounts — high enough to potentially pose a risk of liver problems in people who don't drink at all.

Although much more research is needed to confirm the results, they suggest that these boozy bacteria may contribute to nonalcoholic fatty liver disease (NAFLD), a condition in which fat builds up in the liver for reasons unrelated to alcohol consumption.

The researchers first stumbled upon this unusual microbe while they were studying a patient with a curious condition: The patient had so-called auto-brewery syndrome (ABS), an extremely rare condition that leaves people drunk after eating sugary food. In the week before he sought medical care, the unfortunate patient became inebriated each time he consumed a carbohydrate-rich meal and his blood-alcohol concentration had occasionally spiked to potentially lethal levels, around 0.4%. He was even suspected to be a "closet drinker" by his friends, according to the new study, published today (Sept. 19) in the journal Cell Metabolism.

ABS has been linked to yeast infections, wherein the fungus ferments alcohol in the intestines just as it brews beer in barrels; but in this case, yeast wasn't the culprit.

The researchers looked to their patient's poop for answers. They found, not yeast, but strains of alcohol-producing bacteria called *Klebsiella pneumonia.* This is the first time that a bacterium has been linked to ABS, study co-author Jing Yuan, a professor and director of the bacteriology laboratory at the Capital Institute of Pediatrics in Beijing, told Live Science in an email. Though the common gut bacteria poses no problem in healthy people, the microbe appeared to be producing four to six times the normal level of alcohol in the patient.

Besides becoming intoxicated, the patient also suffered from severe liver inflammation and scarring due to a buildup of fat in the organ, his doctors noted. The condition, called nonalcoholic steatohepatitis, is a progressive form of NAFLD, and the researchers wondered if others with the disorder might carry the same "super-strain" of boozy bacteria.

The team sampled the gut bacteria found in more than 40 people with NAFLD. Compared with about 50 healthy controls, the NAFLD patients hosted slightly more *K. pneumonia* in their guts than average. However, the alcohol-producing ability of those

bacteria appeared unusually strong. About 60% of sampled NAFLD patients had high- and medium-alcohol-producing bacteria in their gut, while only 6% of the controls carried these strains.

To test if the boozy bacteria could cause fatty liver disease, the researchers isolated high-alcohol producing strains and fed them to "germ-free" lab mice, which don't have their own gut bacteria. Another group of mice received ethanol, while a control group ate only normal food for three months. Mice that ate the boozy bacteria began accumulating fat in their livers after one month and developed scarring after two months, similar to the mice fed ethanol. The extent of the liver damage correlated with the amount of alcohol produced — the more alcohol, the more damage. But the condition could be reversed with the administration of antibiotics.

The results suggest that *K. pneumonia* can indeed drive the progression of fatty liver disease, at least in mice.

"That's something unique — that just changing one bacteria does it," said Rohit Loomba, director of the NAFLD Research Center at the University of California, San Diego. Loomba noted that *K. pneumonia* may be one of several bacteria that could inflict liver damage in animal models. Studies to confirm the findings in humans will be key to learning how and whether *K. pneumonia* mingles with other gut microbes to drive liver disease progression, he said.

This isn't the first study to tie gut bacteria to liver disease. In a study published this year, Loomba and his colleagues found that people with NAFLD host distinct bacterial communities in their guts, depending on how far their disease has progressed. By analyzing these microbial signatures, the scientists were able to diagnose those with the most advanced stage of NAFLD, called cirrhosis, with 92% accuracy. In a similar 2017 study, the team learned they could predict the extent of scarring, or fibrosis, present in a patient's liver based on the composition of their gut microbiome.

If microbes like *K. pneumonia* do indeed play a role in NAFLD in people, they might someday serve as targets for the treatment of the disease, Loomba added.

In follow-ups with their human participants, the study authors found that levels of the high-alcohol producing strains dipped or disappeared in many of those who had undergone standard treatment for the disease and lost weight. The result suggests that there's a strong association between *K. pneumonia* and NAFLD progression, but whether the bacteria truly help cause the disease remains unclear.

Yuan and his colleagues are now recruiting study participants for a larger, long-term study in adults and another study in children to learn "why some people have high-alcohol producing strains of *K. pneumonia* in their gut while others don't" and whether the bacteria actually contribute to disease.

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Human Testicles Contain Endocannabinoid System Components

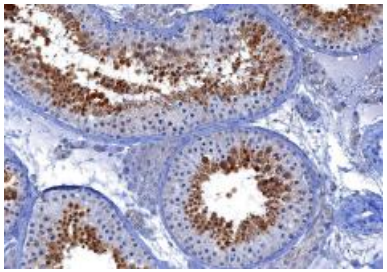
Proteins that synthesize, bind, and degrade endocannabinoids are present in the body's sperm factories, suggesting that the use of cannabis may directly affect them.

Ruth Williams

Heavy use of marijuana has been linked to low sperm counts and testicular germ cell cancers, but whether these conditions are actually caused by the drug or whether cannabinoids could even interact with these cells locally is unclear. A study in *Scientific Reports* today (September 19) reveals that the full toolbox of the endocannabinoid system is present in human testes, and therefore, in principal, cannabinoids could act directly on the male reproductive system.

"While the endocannabinoid system has been shown to play a major role in the physiology of the nervous system and shown to influence metabolism, its impact on reproductive organs has not been thoroughly elucidated. This paper adds valuable data to the growing evidences that the endocannabinoid system is an important component of male gonads," Polina Lishko, a reproductive biologist at the University of California, Berkeley, who was not involved in the study, writes in an email to *The Scientist.*

"It shows that the whole system is there, which [indicates] it has a physiological importance," adds endocrinologist Jorma Toppari of the University of Turku in Finland who also did not participate in the research. What that physiological function is, "we don't know" yet, he says.



Human testis stained for the endocannabinoid degrading enzyme FAAH
Niels Skakkebaek

Because marijuana is a well-known psychoactive drug with effects on mood and perception, the endocannabinoid system—the proteins and pathways that respond to cannabinoids in the plant and to the body's own endocannabinoids—has been mostly explored and characterized in the brain. But evidence exists that the system functions in other parts of the body and in other physiological processes, such as immunity, appetite, and reproduction.

The endocannabinoid 2-AG and the cannabinoid receptors CB1 and CB2 have been detected in human sperm. And, says Niels Skakkebæk of the University of Copenhagen, "we had seen that . . . young men who were smoking marijuana, they had lower sperm counts, so lower semen quality." There were, however, no studies of the endocannabinoid system in the human testes where spermatogenesis actually happens, he says.

To fill this gap, Skakkebæk and colleagues examined healthy testes tissue specimens from 15 men undergoing surgery for testicular cancer as well as from a number of multi-organ donors. They performed immunohistochemistry to detect the endocannabinoid receptors and the enzymes that synthesize and degrade endocannabinoids. For the endocannabinoids themselves, which are lipid-based molecules and therefore incompatible with immunohistochemistry, the team used a method called matrix-assisted laser desorption ionization (MALDI) imaging analysis—a type of mass spectrometry performed on thin tissue sections.

From these studies the researchers found that components of the system were present in both developing spermatozoa, and the supporting, hormone-secreting cells of the testes including Leydig and Sertoli cells.

"We were quite surprised that it was so fully expressed," says Skakkebæk. But "it's not evenly distributed," he adds. "In the germ cells, it appears that it is particularly strongly expressed in the later stages of cell division . . . indicating that it plays a specific role [at that point of sperm development]."

The results signal that cannabis users should beware, says infertility expert Sheena Lewis of Queens University in Belfast who was not involved in the research. "If you take recreational cannabis and you add enormously to the levels [of cannabinoids] that should be there, then obviously that is really bad news because that is going to be [potentially] . . . throwing the whole system into disarray."

As yet, the results are of "unknown significance" for fertility, so worrying too much would be "premature," says Raul Clavijo, a specialist in male reproductive medicine of the University of California, Davis, who was not part of the research team.

Certainly, "there is still a lot to learn about the system," says Skakkebæk "This is just the beginning." However, it is important "for all of us to realize that this system . . . is not only expressed in

the brain but is also widely expressed in the testes, so when a person smokes marijuana or takes cannabis we must assume that these drugs also react with [testes] cells."

J.E. Nielsen et al., "Characterisation and localization of the endocannabinoid system components in the adult human testis," Scientific Reports, 9:12866, 2019.

http://bit.ly/2m6zbPi

Antimicrobial resistance is rising drastically: study

The highest resistance rates were associated with the antimicrobials most frequently used in animals

by ETH Zurich

The world is experiencing unprecedented economic growth in low- and middle-income countries. An increasing number of people in India, China, Latin America and Africa have become wealthier, and this is reflected in their consumption of meat and dairy products. In Africa, meat consumption has risen by more than half; in Asia and Latin America it is up by two-thirds.

To meet this growing demand, animal husbandry has been intensified, with among other things, an increased reliance on the use of antimicrobials. Farmers use antimicrobials to treat and prevent infections for animals raised in crowded conditions but these drugs are also used to increase weight gain, and thus improve profitability.

This excessive and indiscriminate use of antimicrobials has serious consequences: the proportion of bacteria resistant to antimicrobials is rapidly increasing around the world. Drugs are losing their efficacy, with important consequences for the health of animals but also potentially for humans.

Mapping resistance hotspots

Low- and middle income countries have limited surveillance capacities to track antimicrobial use and resistance on farms. Antimicrobial use is typically less regulated and documented there than in wealthy industrialized countries with established surveillance systems.

The team of researchers led by Thomas Van Boeckel, SNF Assistant Professor of Health Geography and Policy at ETH Zurich, has recently published a map of antimicrobial resistance in animals in low- and middle-income countries in the journal *Science*.

The team assembled a large literature database and found out where, and in which animals species resistance occurred for the common foodborne bacteria Salmonella, E. coli, Campylobacter and Staphylococcus.

According to this study, the regions associated with high rates of antimicrobial resistance in animals are northeast China, northeast India, southern Brazil, Iran and Turkey. In these countries, the bacteria listed above are now resistant to a large number of drugs that are used not only in animals but also in human medicine. An important finding of the study is that so far, few resistance hotspots have emerged in Africa with the exception of Nigeria and the surroundings of Johannesburg.

The highest resistance rates were associated with the antimicrobials most frequently used in animals: tetracyclines, sulphonamides, penicillins and quinolones. In certain regions, these compounds have almost completely lost their efficacy to treat infections.

Alarming trend in multi-drug resistance

The researchers introduced a new index to track the evolution of resistance to multiple drugs: the proportion of drugs tested in each region with resistance rates higher than 50%. Globally, this index has almost tripled for chicken and pigs over the last 20 years. Currently, one third of drugs fail 50% of the time in chicken and one quarter of drugs fail in 50% of the time in pigs.

"This alarming trend shows that the drugs used in animal farming are rapidly losing their efficacy," Van Boeckel says. This will affect

the sustainability of the animal industry and potentially the health of consumers.

It is of particular concern that antimicrobial resistance is rising in developing and emerging countries because this is where meat consumption is growing the fastest, while access to veterinary antimicrobials remains largely unregulated. "Antimicrobial resistance is a global problem. There is little point in making considerable efforts to reduce it on one side of the world if it is increasing dramatically on the other side," the ETH researcher says.

Input from thousands of studies

For their current study, the team of researchers from ETH, Princeton University and the Free University of Brussels gathered thousands of publications as well as unpublished veterinary reports from around the world. The researchers used this database to produce the maps of antimicrobial resistance.

However, the maps do not cover the entire research area; there are large gaps in particular in South America, which researchers attribute to a lack of publicly available data. "There are hardly any official figures or data from large parts of South America," says co-author and ETH postdoctoral fellow Joao Pires. He said this surprised him, as much more data is available from some African countries , despite resources for conducting surveys being more limited than in South America.

Open-access web platform

The team has created an open-access web platform resistancebank.org (LINK) to share their findings and gather additional data on resistance in animals. For example, veterinarians and state-authorities can upload data on resistance in their region to the platform and share it with other people who are interested.

Van Boeckel hopes that scientists from countries with more limited resources for whom publishing cost in academic journal can be a barrier will be able to share their findings and get recognition for their work on the platform. "In this way, we can ensure that the data is not just stuffed away in a drawer" he says, "because there are many relevant findings lying dormant, especially in Africa or India, that would complete the global picture of resistance that we try to draw in this first assessment. The platform could also help donors to identify the regions most affected by resistance in order to be able to finance specific interventions.

As meat production continues to rise, the web platform could help target interventions against AMR and assist a transition to more sustainable farming practices in low- and middle-income countries. "The rich countries of the Global North, where antimicrobials have been used since the 1950s, should help make the transition a success," says Van Boeckel.

The study titled, "Global Trends in Antimicrobial Resistance in Animals in Low- and Middle-Income Countries," is published September 20, 2019 in *Science*.

Explore further

Tracking global trends in the effectiveness of antibiotic therapy using the Drug Resistance Index

More information: *T.P. Van Boeckel el al., "Global trends in antimicrobial resistance in animals in low- and middle-income countries," Science (2019). science.sciencemag.org/cgi/doi … 1126/science.aaw1944*

"Changes in antibiotic resistance in animals," Science (2019). science.sciencemag.org/cgi/doi … 1126/science.aay9652

http://bit.ly/2krI6dK

Eating Urchins: Can Gourmet Diners Reverse the Collapse of an Ecosystem?

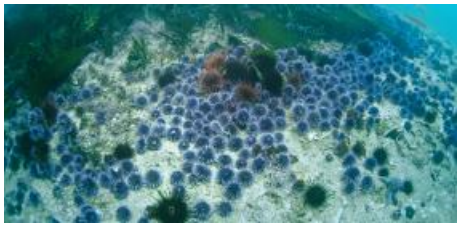
A company wants to take urchins from the wild, then fatten them up for sale.

by Alastair Bland

B-movie screenwriters could hardly have produced a campier story: the world turns to dust as an army of tiny, pincushion-like invaders ever so slowly takes over. They devour whatever lies in their path, then live on for decades without eating. The ecosystem collapses,

and while humanity despairs, a few bright scientists hatch a plan to save the day.

But fact can be as strange as science fiction and this zany plot is unfolding around the world as sea urchins proliferate. In places such as Tasmania, Japan, Norway, Canada, and California, urchins are mowing down seaweed, including giant kelp. In the bleak, sometimes almost lifeless environments that result, the seafloor is carpeted with urchins. And though they prefer seaweed, urchins will resort to gnawing on the coralline algae that encrusts many underwater rocks, emptying abalone shells, and even cannibalizing one another if there is nothing better to eat.



In Northern California, purple sea urchins are decimating kelp forests. Though the species of urchin causing problems may vary by region, the damage is the same. **Photo by Norbert Wu/Minden Pictures**

These urchin barrens can last for decades. Off Hokkaido, Japan, barrens have persisted for 80 years and counting. In Alaska's Aleutian Islands, they've lasted for more than 25. Unless disrupted by a powerful environmental disturbance, like a disease outbreak or the appearance of a predator, urchin barrens will not shift back to a kelp-dominated system.

Off California, where the concentration of purple urchins has increased 60 to 100 times since their takeover began around 2014, local divers, ecologists, and entrepreneurs are hoping to avert such a grim future. Their plan is to develop a new fishery for the overpopulated urchins, which number in the tens of millions, turning a scourge into an opportunity while creating clearings in the urchin barrens where kelp may have a chance to regrow.

Sea urchins—or more specifically, their gonads, which are marketed as *uni*—are a valued delicacy. But the urchins living in barren environments have little to eat so their insides, including their prized golden gonads, are shriveled and commercially worthless. Historically, commercial urchin divers in the northeast Pacific have overlooked purple urchins because of their small size, preferring the much larger red urchins. But even red urchins have been starved to commercial worthlessness by the scourge of purple urchins, bringing the once lucrative fishery to a standstill.

A small Norwegian company called Urchinomics, however, has a plan to restore the lost kelp forests and give urchin divers back their livelihoods. Their venture involves gathering large numbers of purple urchins from overrun areas, fattening them up in tanks, and then selling them to restaurants. They call this process urchin ranching.

Urchinomics, which launched several years ago, is currently piloting a small-scale ranching operation in Japan, and has research facilities in Norway and on both coasts of Canada. Now they're running laboratory trials with scientists in California.

At San Diego State University, Renee Angwin, manager of the school's Coastal and Marine Institute Laboratory, is helping rear urchins taken from the barrens. She feeds them dried seaweed pellets and watches as the animals rapidly rebound from a starvation state to marketable condition. According to Angwin, it takes about two months for shrunken and worthless gonads to swell into fat, pinky-sized uni slabs.

"We're letting nature do all the work—nature's growing it to market size and then we're just enhancing what nature's already done," Angwin says.

Denise MacDonald, Urchinomics's director of global marketing, says the business's plan is to create a local specialty dining market for purple urchin uni, modeled after the oyster bar. She describes an experience where "the shucker will open the urchin, clean it out, and you get your urchin with the roe inside," ripe and ready for a

drizzle of lime juice or soy sauce. Uni is a richly flavored food and MacDonald says that three purple urchins are likely plenty for a table of five people. Because eating uni is a high-end foodie experience, the market for urchin will be small. It's hard to picture the finicky pace of gourmet dining undoing the creatures' environmental takeover.

***Known as* uni*, urchin gonads are a delicacy.* Photo by Bamboofox/Alamy Stock Photo**

"I can't imagine this program fully restoring the miles and miles of urchin barren along the North Coast [of California] right now," says Kyle Cavanaugh, a geographer at the University of California, Santa Barbara.

After all, urchin barrens are tenaciously persistent. Sea urchins can live for decades without solid food, and the blighted underwater landscapes they create are just as long-lasting. "Urchins can persist in this starvation state for a very long time," Cavanaugh says.

Craig Johnson, who studies urchin barrens at the University of Tasmania in Australia, is marginally optimistic about Urchinomics's plan. He believes there is sufficient demand for uni—mainly in Japan—to support a purple urchin ranching industry. In fact, providing enough uni to sate the market is a continuous problem, he says. Given that many wild urchin fisheries have been depleted, it makes the California purple urchins a potentially valuable new resource.

But to restore kelp forests, Urchinomics's efforts must be aggressive and thorough. The problem, says Johnson, is that while converting a thriving kelp forest into an urchin barren requires a huge incursion of urchins, it only takes a relatively small number of urchins to maintain that barren in perpetuity. That means urchins must be almost entirely eradicated in order to shift a barren back to a healthy, kelp-filled state. "The key thing," says Johnson by email, "is that they'll need to remove around 90 percent (and possibly more) of the urchins to see kelp recovery."

For now, it remains to be seen if divers can harvest urchins so efficiently and thoroughly that they can help restore kelp beds while still turning a profit. "It might not be economically viable to mop up those last animals," he adds.

http://bit.ly/2ktfqB5

When natural disaster strikes, men and women respond differently

Women are quicker to take cover or prepare to evacuate during an emergency, but often have trouble convincing the men in their life to do so, suggests a new CU Boulder study of how gender influences natural disaster response.

by Lisa Marshall, University of Colorado at Boulder

The research also found that traditional gender roles tend to resurface in the aftermath of disasters, with women relegated to the important but isolating role of homemaker while men focus on finances and lead community efforts.

Even agencies charged with providing assistance still, at times, ask to speak to the "man of the house," the researchers found.

"We found that there are many barriers that disadvantage women in the event of a disaster, leaving them behind when it comes to decision-making and potentially slowing down their recovery," said lead author Melissa Villarreal, a doctoral student in the Department of Sociology and research assistant at the Natural Hazards Center.

For the study, co-authored by Texas A&M University Assistant Professor Michelle Meyer and published in the journal Disasters, the researchers analyzed in-depth interviews with 33 women and 10 men across two Texas towns. Some were from Granbury, which in 2013 was hit by an EF-4 tornado that killed six and cut a mile-wide swath of destruction, damaging 600 homes. Others were from West,

where an explosion at a fertilizer company that same year killed 15 and destroyed 100 homes.

Residents were asked about their experiences in the midst of and the year after the disaster. While the circumstances surrounding the events were very different, common gender-influenced patterns emerged.

"We often assume that men and women are going to respond the same way to these kinds of external stimuli but we are finding that's not really the case," said Meyer, director of the Hazard Reduction and Recovery Center at Texas A&M.

In one interview, a Granbury woman recounted hunkering down in the closet with her children, pleading with her husband—who was looking out the window at the tornado—to come in and join them.

In another case, a woman resisted her husband's plan to get in the car and drive away from the storm, preferring to shelter in place. She ultimately deferred, and they ended up stuck in the car, the children in the back seat, being jostled by the wind as the tornado whipped through.

"Women seemed to have a different risk perception and desire for protective action than the men in their lives, but men often determined when and what type of action families took," Villareal wrote. "In some cases, this put women and their families in greater danger."

The findings are the latest in a series of studies that have found that women tend to have a higher perception of risk, but because they are framed as "worriers," they are sometimes not taken seriously.

Women in the new study also complained that recovery organizations tended to call the men of the household to find out where to direct aid, even when women had filled out the forms requesting it.

"Eliminating the male head-of-household model is crucial for speeding overall household recovery," the authors conclude.

During recovery, women were often charged with "private sphere" tasks like putting the house back together and caring for children while schools were closed, but they often felt excluded from leadership roles in community recovery projects."If your perspective is not taken into consideration and you feel isolated, that can impede your mental health recovery," said Villareal.

She recently embarked on a separate study, set in Houston, looking at the unique challenges Mexican immigrant populations are facing in the aftermath of Hurricane Harvey, which hit the region in 2017.

Ultimately, she would like to see government agencies consider gender differences when crafting disaster warnings and prioritize providing childcare post-disaster so that women can play a greater role in community efforts.

"If we can put racial and gender forms of bias aside and listen to all the people tell their stories about what is affecting them, that could go a long way in helping communities recover," said Villarreal.

More information: *Melissa Villarreal et al. Women's Experiences Across Disasters – A Study of Two Towns in Texas∗, Disasters (2019).* DOI: 10.1111/disa.12375

https://go.nature.com/2muRU7H

Why midday might be a golden hour for vaccinations

Immune cells' built-in timepieces affect response to inoculation.

The biological clock ticking within some immune cells can influence how well they respond to vaccination, a study in mice has found.

Cells have molecular clocks that dial gene activity up or down in a daily cycle. These clocks can affect immunity. Nathalie Labrecque at the Maisonneuve-Rosemont Hospital Research Centre in Montreal, Canada, and Nicolas Cermakian at the Douglas Mental Health University Institute, also in Montreal, and their colleagues investigated how the circadian clock affects the way that immune cells called CD8 T cells respond to vaccination.

The team found that vaccination stimulated the production of more CD8 T cells during the middle of the day than at other time points. Genes associated with the activation of these T cells were also expressed at higher levels at the middle of the day than at night. Mice that lacked the key clock gene *Bmal1* within CD8 T cells did not show this rhythmic response.

Proc. Natl Acad. Sci. USA (2019)

https://wb.md/2kYHAEe

Brutal Toll of Osteoporotic Fractures Revealed in New NOF Report

"Osteoporotic fractures are responsible for more hospitalizations than heart attacks, strokes, and breast cancer combined."

Nancy A. Melville

A new report provides striking details about the toll osteoporotic fractures take on the individual and at a societal level in the United States, showing that as many as 2 million Medicare beneficiaries sustained 2.3 million osteoporotic fractures in 2015.

Moreover, nearly one in five died within 12 months of a new fracture.

This latest report from the National Osteoporosis Foundation (NOF) "provides real-world data from Medicare claims that shows how the healthcare system is failing the 55 million Americans who have or who are at high risk of osteoporosis," Elizabeth Thompson, CEO of the NOF, told *Medscape Medical News*.

The data show that, remarkably, "osteoporotic fractures are responsible for more hospitalizations than heart attacks, strokes, and breast cancer combined." "The biggest surprise from this report is that things are worse than we thought," Bart Clarke, MD, president of the American Society for Bone and Mineral Research (ASBMR), told *Medscape Medical News*.

"We've known the risk of a secondary fracture is high, that if people don't take therapy they will continue to have fractures and that many people don't get bone density testing after their first fracture," said Clarke, who is a clinician and researcher with the Division of Endocrinology, Metabolism, Diabetes, and Nutrition at the Mayo Clinic College of Medicine in Rochester, Minnesota.

Now, it's obvious from these new figures that "in some cases, these rates are worsening, so this is...of great interest," he added.

The findings send the message that fractures can have more detrimental implications than many realize, Clarke stressed.

"People tend to think 'this is normal for me — my mother had a fracture, as did my grandmother, and now I have one,' and so they're not overly concerned," he explained.

"But we, as clinicians, see these as sentinel events for future fractures."

"We know that when you break a bone, your risk of having a second fracture in the next 2 years is at least double the risk for the first fracture," he emphasized. "This not something I think a lot of patients or even physicians realize."

Those With a Hip Fracture Had Highest Mortality Rate a Year Later

The report focused on "new" osteoporotic fractures by excluding beneficiaries who had another osteoporotic fracture in the prior 6- to 12- months.

According to the analysis, female beneficiaries had a 79% higher rate of osteoporotic fracture than males, after adjusting for age, and the most common fractures involved the spine and hip, representing 40% of all osteoporotic fractures in the Medicare population in 2015.

The rates are alarming because hip fractures are in fact among the most detrimental of osteoporotic fractures, and the analysis supports that, showing hospitalization rates were more than 90% among those sustaining a hip fracture.

Overall, nearly 20% of patients died within 12 months of a new osteoporotic fracture, and those with a hip fracture had the highest mortality, with 30% dying within 12 months.

In addition, approximately 15% of those who experienced a new osteoporotic fracture had one or more subsequent fractures within 12 months of the initial fracture.

And clinical follow-up after a first fracture — seen as critical in the prevention of a secondary fracture — is low, as supported by the finding of the analysis that only 9% of women who suffered an osteoporotic fracture were screened for osteoporosis with a bone mineral density test within 6 months following their initial fracture.

Prevention Efforts Could Be Boosted by Fracture Liaison Service

Indeed, NOF's Thompson noted, patients sometimes don't even report fractures to their primary care physician.

"One of the things we learn over and over again is people will present at the emergency room with a fracture such as a broken wrist, toe, or shoulder, and they will have it fixed there, but may never even tell their primary care doctor about it, and right now the onus is not on that hospital or orthopedic surgeon to initiate or provide osteoporosis care," she explained.

But introducing fracture liaison services could substantially improve matters, the experts say. As part of these services, dedicated staff follow-up with patients to make sure their primary care provider is informed of the fracture and that proper preventive measures, such as a bone density evaluation, are being offered.

Centers reporting success with such programs include the Geisinger Health System's High-Risk Osteoporosis Clinic (HiROC), which in a recent study reported increases in bone density tests in women over age 65 years, from 40% to 74%, in their program, so as many as 75% of eligible patients received prescriptions for osteoporosis drugs compared with just 13.8% in the primary care population as a whole.

Thompson added that "Medicare needs to incentivize the use [of programs such as fracture liaison services] by helping to defray any upfront costs and/or creating a bundled payment model."

Key measures could also make an important difference at the primary level, Thompson asserted.

"We recommend physicians put a check-off box in their chart asking patients questions, including whether they have had a fracture, if so, when? What body part?" she said.

"We also recommend a check-off box asking if the patient has had a bone density test. It's recommended that every woman starting at age 65 and man at age 70 should have a baseline bone mineral density," Thompson explained.

Extensive details for the prevention of secondary fractures are outlined in new consensus guidelines published by the ASBMR.

Costs of Second Fractures Are Substantial

In addition to the health effects, the economic costs associated with second fractures are also substantial.

According to the report, the incremental medical cost to Medicare of a subsequent fracture over the 180-day period following a new osteoporotic fracture was more than $20,700.

Translated to the estimated 307,000 Medicare Fee For Service (FFS) beneficiaries who suffered a subsequent fracture during a follow-up of 2- to 3 years and survived at least 180 days after the second fracture, the amount would exceed $6.3 billion in allowed cost to Medicare FFS, the authors note.

However, reductions of just 5% to 20% in the rate of subsequent fractures could have led to savings of $310 million to $1.2 billion, respectively, they estimate.

Thompson is the CEO of the NOF. Clarke is the president of the ASBMR and has reported no relevant financial relationships.

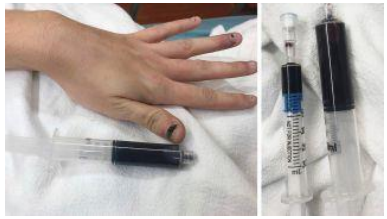
NOF. Published September 11, 2019. Full text

http://bit.ly/2kXpqmu

Woman's Blood Turns a Shocking Shade of Blue After She Used Tooth-Numbing Gel

A young woman turned up in the emergency room after her blood turned navy blue.

By Nicoletta Lanese - Staff Writer



***The woman's skin had a bluish tint, and her drawn blood appeared a deep blue color.* (Image: © The New England Journal of Medicine 2019)**

A woman in Rhode Island went to the emergency room when her skin and blood took on an odd hue: She was turning blue, according to a new report of the case.

"I'm weak and I'm blue," the 25-year-old told her doctors, according to Otis Warren, a physician at Miriam Hospital who treated the woman and spoke to NBC News. The patient reported applying "large amounts" of topical benzocaine, a numbing medication, on an aching tooth the night before, Warren and colleagues wrote in the report about the woman's case, published Sept. 19 in The New England Journal of Medicine.

The medication can have an unusual and potentially dangerous side effect: Benzocaine can cause iron in the blood to give up electrons, change form and no longer bind properly to oxygen, according to NBC. The body relies on sturdy bonds between iron and oxygen to move the life-sustaining element through the body. Without adequate oxygen, normally red blood can turn blue, and the skin and nails soon follow.

The condition, called methemoglobinemia, essentially suffocates the body's tissues and can cause serious damage if blood oxygen levels drop below 70%, according to Medscape.

http://bit.ly/2ktX56Z

Man's 'Bug Bite' Was Really a Sign of Leukemia

The swollen lump on the man's foot wouldn't go away.

By Rachael Rettner - Senior Writer

When a man in Ohio developed a swollen lump on his foot, he thought it was just a particularly painful and stubborn bug bite. So he was stunned to find out that it was actually a sign of leukemia, according to news reports.

The man, 46-year-old Mike Balla, first noticed the lump on his foot last August, according to NBC Today. He thought it was a mosquito or spider bite, but soon, it got bigger and more uncomfortable. After going to the doctor, he was told the lump was likely an infected bug bite, and treated with antibiotics.

But the treatment didn't seem to work, so he was given another antibiotic. When that failed as well, Balla ended up in the emergency room (ER).

That's when an ER doctor came into his room and told him they were waiting for a consult from an oncologist. Balla at first assumed they had him mixed up with another patient.

"I said, 'I think you have the wrong person. I have a bite on my foot that's infected,'" Balla told Today.

But doctors told him that blood tests revealed he had acute myeloid leukemia, a cancer of the blood and bone marrow cells. It is a rapidly progressing cancer that requires immediate treatment.

Symptoms can include fatigue, bone pain, easy bruising and bleeding and an increased susceptibility to infections, according to the Mayo Clinic.

It is rare for leukemia to look like a bug bite, Dr. Alice Mims, a hematologist at The Ohio State University Comprehensive Cancer Center who wasn't involved with Balla's case, told Prevention magazine. But sometimes, cancer cells can get into the skin and result in something that looks like a bug bite, Prevention reported.

Balla was treated with chemotherapy and a bone marrow transplant. He later experienced a cancer relapse, but is now in remission again, according to a statement from the Cleveland Clinic, where Balla was treated.

Balla now advises men not to put off going to the doctor if they think something might be wrong. "The hour it takes to go get a checkup could help prevent months of health problems," he said in the statement. "You may think you don't have time for that. But it's not true. If you don't go to the doctor, you may have a much bigger problem."

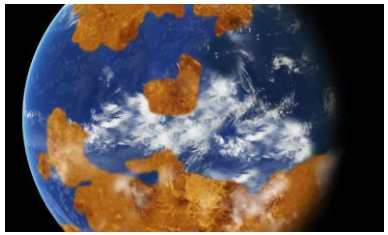
http://bit.ly/2kNtoy8

Could Venus have been habitable?

Venus may have been a temperate planet hosting liquid water for 2-3 billion years

Venus may have been a temperate planet hosting liquid water for 2-3 billion years, until a dramatic transformation starting over 700 million years ago resurfaced around 80% of the planet.

A study presented today at the EPSC-DPS Joint Meeting 2019 by Michael Way of The Goddard Institute for Space Science gives a new view of Venus's climatic history and may have implications for the habitability of exoplanets in similar orbits.



Artist's representation of Venus with water. **Credit: NASA**

Forty years ago, NASA's Pioneer Venus mission found tantalising hints that Earth's 'twisted sister' planet may once have had a shallow ocean's worth of water. To see if Venus might ever have had a stable climate capable of supporting liquid water, Dr. Way and his colleague, Anthony Del Genio, have created a series of five simulations assuming different levels of water coverage.

In all five scenarios, they found that Venus was able to maintain stable temperatures between a maximum of about 50 degrees Celsius and a minimum of about 20 degrees Celsius for around three billion years. A temperate climate might even have been maintained on Venus today had there not been a series of events that caused a release, or 'outgassing', of carbon dioxide stored in the rocks of the planet approximately 700-750 million years ago.

"Our hypothesis is that Venus may have had a stable climate for billions of years. It is possible that the near-global resurfacing event is responsible for its transformation from an Earth-like climate to the hellish hot-house we see today," said Way.

Three of the five scenarios studied by Way and Del Genio assumed the topography of Venus as we see it today and considered a deep ocean averaging 310 metres, a shallow layer of water averaging 10 metres and a small amount of water locked in the soil. For comparison, they also included a scenario with Earth's topography and a 310-metre ocean and, finally, a world completely covered by an ocean of 158 metres depth.

To simulate the environmental conditions at 4.2 billion years ago, 715 million years ago and today, the researchers adapted a 3-D general circulation model to account for the increase in solar radiation as our Sun has warmed up over its lifetime, as well as for changing atmospheric compositions.

Although many researchers believe that Venus is beyond the inner boundary of our Solar System's habitable zone and is too close to the Sun to support liquid water, the new study suggests that this might not be the case.

"Venus currently has almost twice the solar radiation that we have at Earth. However, in all the scenarios we have modelled, we have found that Venus could still support surface temperatures amenable for liquid water," said Way.

At 4.2 billion years ago, soon after its formation, Venus would have completed a period of rapid cooling and its atmosphere would have been dominated by carbon-dioxide. If the planet evolved in an

Earth-like way over the next 3 billion years, the carbon dioxide would have been drawn down by silicate rocks and locked into the surface. By the second epoch modelled at 715 million years ago, the atmosphere would likely have been dominated by nitrogen with trace amounts of carbon dioxide and methane—similar to the Earth's today—and these conditions could have remained stable up until present times.

The cause of the outgassing that led to the dramatic transformation of Venus is a mystery, although probably linked to the planet's volcanic activity. One possibility is that large amounts of magma bubbled up, releasing carbon dioxide from molten rocks into the atmosphere. The magma solidified before reaching the surface and this created a barrier that meant that the gas could not be reabsorbed. The presence of large amounts of carbon dioxide triggered a runaway greenhouse effect, which has resulted in the scorching 462 degree average temperatures found on Venus today.

"Something happened on Venus where a huge amount of gas was released into the atmosphere and couldn't be re-absorbed by the rocks. On Earth we have some examples of large-scale outgassing, for instance the creation of the Siberian Traps 500 million years ago which is linked to a mass extinction, but nothing on this scale. It completely transformed Venus," said Way.

There are still two major unknowns that need to be addressed before the question of whether Venus might have been habitable can be fully answered. The first relates to how quickly Venus cooled initially and whether it was able to condense liquid water on its surface in the first place. The second unknown is whether the global resurfacing event was a single event or simply the latest in a series of events going back billions of years in Venus's history.

"We need more missions to study Venus and get a more detailed understanding of its history and evolution," said Way. "However, our models show that there is a real possibility that Venus could have been habitable and radically different from the Venus we see today. This opens up all kinds of implications for exoplanets found in what is called the 'Venus Zone', which may in fact host liquid water and temperate climates."

http://bit.ly/2mnFa2n

Russia Says It Will Keep Source of Hole (and Air Leak) on Soyuz Secret— But NASA Wants to Know: Report

NASA Administrator Jim Bridenstine wants answers.

By Elizabeth Howell - Live Science Contributor

Amid reports that the Russians will keep the cause of an air leak discovered at the International Space Station in 2018 secret, NASA Administrator Jim Bridenstine has promised to speak personally with the head of the Russian space agency.

"They have not told me anything," Bridenstine said during a Houston energy conference question session Thursday (Sept. 19), according to the Houston Chronicle. But he emphasized that he wants to keep good relations with the Russians, one of the two chief partners on the orbiting complex.

"I don't want to let one item set [the relationship] back, but it is clearly not acceptable that there are holes in the International Space Station," he said, referring to the 2-millimeter (0.08 inches) hole that the Expedition 56 crew found in the Soyuz MS-09 spacecraft, a crew vehicle that was docked to the station.

Bridenstine's comments came in the wake of a report by Russia's state-run international news agency RIA Novosti, in which Dmitry Rogozin, head of Roscosmos (the Russian space agency), suggested his agency found what created the hole last year, but would not disclose the results outside of Roscosmos.

"What happened is clear to us, but we won't tell you anything," Rogozin said at a meeting with participants at a science conference, according to a computer-translated page from RIA Novosti's Russian-language report on Wednesday (Sept. 18).

After NASA reported a slow drop in cabin pressure at the station on Aug. 29, 2018, the crew of Expedition 56 located the cause of the air leak in the orbital compartment of the Soyuz MS-09 spacecraft, nearly three months after the vessel arrived at the International Space Station with three new crewmembers on board.

The astronauts plugged the hole using epoxy, gauze and heavy-duty tape, and the Russians launched an investigation. In the first few weeks, Roscosmos director Dmitry Rogozin first speculated that a micrometeoroid might have punched the hole, then suggested the hole could have been drilled by a human either accidentally or deliberately.

NASA and Roscosmos, however, issued a joint statement in mid-September 2018 after the two agency chiefs spoke by phone. The agencies "agreed on deferring any preliminary conclusions and providing any explanations until the final investigation has been completed," Roscosmos and NASA said in their statement.

Roscosmos is currently the only agency capable of launching crew members to space since NASA retired the space shuttle in 2011. NASA is readying American commercial crew vehicles from Boeing and SpaceX and expects to start running crewed test flights as early as this year. But for now, the Soyuz is the only way astronauts can fly to and from the International Space Station.

The two agencies are the chief partners on the space station, and have been working together to build and maintain the 21-year-old orbiting complex since the early 1990s. Bridenstine and other NASA officials have thus repeatedly emphasized the level of trust between their agency and Roscosmos, which includes several missions before ISS. NASA and the Soviet Union ran a joint mission in 1975 called Apollo-Soyuz, and the new Russian nation partnered with NASA for shuttle flights to the space station Mir between 1994 and 1998.