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People with untreated 'white coat hypertension' twice as likely to die from heart disease

Researchers at Penn Medicine say findings underscore the need for increased out-of-office blood pressure monitoring

PHILADELPHIA - White coat hypertension, a condition in which a patient's blood pressure readings are higher when taken at the doctor's office compared to other settings, was originally attributed to the anxiety patients might experience during medical appointments.

However, over the years, research has suggested the elevated readings might be a sign of underlying risk for future health problems. A new study led by researchers from Penn Medicine, published today in the Annals of Internal Medicine, revealed that patients with untreated white coat hypertension not only have a heightened risk of heart disease, but they are twice as likely to die from heart disease than people with normal blood pressure.

Researchers also found that patients with white coat hypertension who were taking medication to treat their high blood pressure, called antihypertensives, did not have an increased risk of heart disease or cardiovascular-related death compared to those with normal blood pressure readings.

"Studies suggest that about one in five adults may have white coat hypertension. Our findings underscore the importance of identifying people with this condition," said the study's lead author Jordana B. Cohen, MD, MSCE, an assistant professor in the division of Renal-Electrolyte and Hypertension and a senior scholar in the Center for Clinical Epidemiology and Biostatistics.

"We believe individuals with isolated in-office hypertension - those who are not taking blood pressure medication - should be closely monitored for transition to sustained hypertension, or elevated blood pressure both at home and the doctor's office."

High blood pressure, or hypertension, is a defined as a top reading of at least 130 or a bottom one of 80. The condition affects nearly a third of American adults and, if left untreated, increases one's risk for severe complications, including heart attack and stroke.

To diagnose and manage the condition, recent hypertension guidelines strongly recommend out-of-office blood pressure monitoring, such as at-home monitoring and ambulatory blood pressure monitoring, which requires patients to wear a portable device that records blood pressure readings over a 24-hour period. However, providers have been slow to adopt this practice due, in part, to skepticism over the usefulness of screening for white coat hypertension given the inconsistent findings - from past studies - and uncertainty around its association with heart disease and death.

To identify the cardiovascular risks of white coat hypertension, the researchers conducted a meta-analysis of 27 studies, comprising more than 60,000 patients, that evaluated the health risks associated with the condition.

They found that patients with untreated white coat hypertension had a 36 percent increased risk of heart disease, 33 percent increased risk of death and 109 percent increased risk of death from heart disease.

"Our findings support the pressing need for increased out-of-office blood pressure monitoring nationwide, as it's critical in the diagnosis and management of hypertension," Cohen said. "Simultaneously, we advise individuals with untreated white coat hypertension to engage in lifestyle modifications, including smoking cessation, reduction in their alcohol intake, and making improvements to their diet and exercise regimens. We also caution providers not to over-treat individuals with white coat hypertension who are already on blood pressure medication, as this could lead to dangerously low blood pressures outside of the office and unnecessary side effects from medication."

Researchers noted that future studies are needed to investigate interventions to reduce the cardiac risk of white coat hypertension.

This work was supported, in part, by a grant from the National Institutes of Health (K23-HL133843). Additional Penn authors on the study include Matthew G. Denker, Debbie L. Cohen and Raymond R. Townsend.

http://bit.ly/2Rq43bI

Our brains appear uniquely tuned for musical pitch

Results of study involving primates suggest that speech and music may have shaped the human brain's hearing circuits

In the eternal search for understanding what makes us human, scientists found that our brains are more sensitive to pitch, the harmonic sounds we hear when listening to music, than our evolutionary relative the macaque monkey.

The study, funded in part by the National Institutes of Health, highlights the promise of Sound Health, a joint project between the NIH and the John F. Kennedy Center for the Performing Arts that aims to understand the role of music in health.

"We found that a certain region of our brains has a stronger preference for sounds with pitch than macaque monkey brains," said Bevil Conway, Ph.D., investigator in the NIH's Intramural Research Program and a senior author of the study published in Nature Neuroscience. "The results raise the possibility that these sounds, which are embedded in speech and music, may have shaped the basic organization of the human brain."

The study started with a friendly bet between Dr. Conway and Sam Norman-Haignere, Ph.D., a post-doctoral fellow at Columbia University's Zuckerman Institute for Mind, Brain, and Behavior and the first author of the paper.

At the time, both were working at the Massachusetts Institute of Technology (MIT). Dr. Conway's team had been searching for differences between how human and monkey brains control vision only to discover that there are very few.

Their brain mapping studies suggested that humans and monkeys see the world in very similar ways. But then, Dr. Conway heard about some studies on hearing being done by Dr. Norman-Haignere, who, at the time, was a post-doctoral fellow in the laboratory of Josh H. McDermott, Ph.D., associate professor at MIT.

"I told Bevil that we had a method for reliably identifying a region in the human brain that selectively responds to sounds with pitch," said Dr. Norman-Haignere,

That is when they got the idea to compare humans with monkeys. Based on his studies, Dr. Conway bet that they would see no differences.

To test this, the researchers played a series of harmonic sounds, or tones, to healthy volunteers and monkeys. Meanwhile, functional magnetic resonance imaging (fMRI) was used to monitor brain activity in response to the sounds. The researchers also monitored brain activity in response to sounds of toneless noises that were designed to match the frequency levels of each tone played.

At first glance, the scans looked similar and confirmed previous studies. Maps of the auditory cortex of human and monkey brains had similar hot spots of activity regardless of whether the sounds contained tones.

However, when the researchers looked more closely at the data, they found evidence suggesting the human brain was highly sensitive to tones. The human auditory cortex was much more responsive than the monkey cortex when they looked at the relative activity between tones and equivalent noisy sounds.

"We found that human and monkey brains had very similar responses to sounds in any given frequency range. It's when we added tonal structure to the sounds that some of these same regions of the human brain became more responsive," said Dr. Conway.

"These results suggest the macaque monkey may experience music and other sounds differently. In contrast, the macaque's experience of the visual world is probably very similar to our own. It makes one wonder what kind of sounds our evolutionary ancestors experienced."

Further experiments supported these results. Slightly raising the volume of the tonal sounds had little effect on the tone sensitivity observed in the brains of two monkeys.

Finally, the researchers saw similar results when they used sounds that contained more natural harmonies for monkeys by playing recordings of macaque calls. Brain scans showed that the human auditory cortex was much more responsive than the monkey cortex when they compared relative activity between the calls and toneless, noisy versions of the calls.

"This finding suggests that speech and music may have fundamentally changed the way our brain processes pitch," said Dr. Conway. "It may also help explain why it has been so hard for scientists to train monkeys to perform auditory tasks that humans find relatively effortless."

Earlier this year, other scientists from around the U.S. applied for the first round of NIH Sound Health research grants. Some of these grants may eventually support scientists who plan to explore how music turns on the circuitry of the auditory cortex that make our brains sensitive to musical pitch.

Norman-Haignere et al., fMRI Responses to Harmonic Tones and Noises Reveal Divergence in the Functional Organization of Human and Macaque Auditory Cortex. Nature Neuroscience, June 10, 2019 DOI: 10.1038/s41593-019-0410-7

This study was supported by the NINDS, NEI, NIMH, and NIA Intramural Research Programs and grants from the NIH (EY13455; EY023322; EB015896; RR021110), the National Science Foundation (Grant 1353571; CCF-1231216), the McDonnell Foundation, the Howard Hughes Medical Institute.

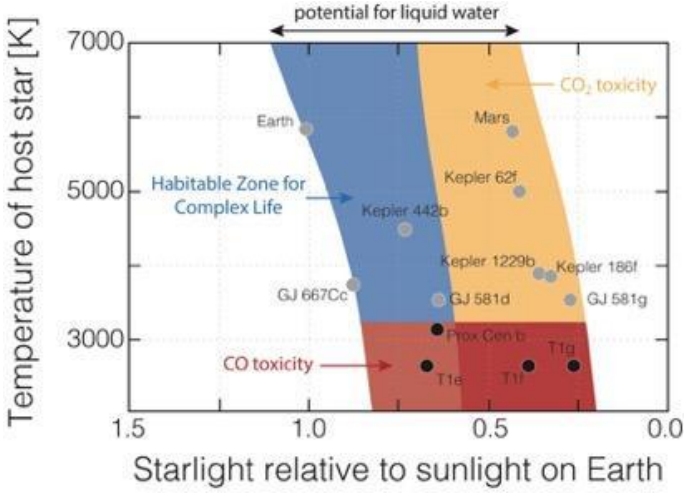
http://bit.ly/2IftOpy

New study dramatically narrows the search for advanced life in the universe

Toxic gases limit the types of life we could find on habitable worlds

RIVERSIDE, CA - Scientists may need to rethink their estimates for how many planets outside our solar system could host a rich diversity of life. In a new study, a UC Riverside-led team discovered that a buildup of toxic gases in the atmospheres of most planets makes them unfit for complex life as we know it.

Traditionally, much of the search for extraterrestrial life has focused on what scientists call the "habitable zone," defined as the range of distances from a star warm enough that liquid water could exist on a planet's surface. That description works for basic, single-celled microbes -- but not for complex creatures like animals, which include everything from simple sponges to humans.



The habitable zone for complex life (blue) is highly restricted relative to the zone defined by the potential for liquid water, due to toxic buildup of carbon dioxide (yellow) and carbon monoxide (red). This narrower zone excludes many exoplanets including Proxima Centauri b and TRAPPIST-1 planets e, f and g (black dots). **(Graphic courtesy of Christopher Reinhard/Georgia Tech)**

The team's work, published today in The Astrophysical Journal, shows that accounting for predicted levels of certain toxic gases

narrows the safe zone for complex life by at least half -- and in some instances eliminates it altogether.

"This is the first time the physiological limits of life on Earth have been considered to predict the distribution of complex life elsewhere in the universe," said Timothy Lyons, one of the study's co-authors, a distinguished professor of biogeochemistry in UCR's Department of Earth and Planetary Sciences, and director of the Alternative Earths Astrobiology Center, which sponsored the project.

"Imagine a 'habitable zone for complex life' defined as a safe zone where it would be plausible to support rich ecosystems like we find on Earth today," Lyons explained. "Our results indicate that complex ecosystems like ours cannot exist in most regions of the habitable zone as traditionally defined."

Using computer models to study atmospheric climate and photochemistry on a variety of planets, the team first considered carbon dioxide. Any scuba diver knows that too much of this gas in the body can be deadly. But planets too far from their host star require carbon dioxide -- a potent greenhouse gas -- to maintain temperatures above freezing. Earth included.

"To sustain liquid water at the outer edge of the conventional habitable zone, a planet would need tens of thousands of times more carbon dioxide than Earth has today," said Edward Schwieterman, the study's lead author and a NASA Postdoctoral Program fellow working with Lyons. "That's far beyond the levels known to be toxic to human and animal life on Earth."

The new study concludes that carbon dioxide toxicity alone restricts simple animal life to no more than half of the traditional habitable zone. For humans and other higher order animals, which are more sensitive, the safe zone shrinks to less than one third of that area.

What is more, no safe zone at all exists for certain stars, including two of the sun's nearest neighbors, Proxima Centauri and TRAPPIST-1. The type and intensity of ultraviolet radiation that these cooler, dimmer stars emit can lead to high concentrations of carbon monoxide, another deadly gas. Carbon monoxide binds to hemoglobin in animal blood -- the compound that transports oxygen through the body. Even small amounts of it can cause the death of body cells due to lack of oxygen.

Carbon monoxide cannot accumulate on Earth because our hotter, brighter sun drives chemical reactions in the atmosphere that destroy it quickly. Although the team concluded recently that microbial biospheres may be able to thrive on a planet with abundant carbon monoxide, Schwieterman emphasized that "these would certainly not be good places for human or animal life as we know it on Earth."

Scientists have confirmed nearly 4,000 planets orbiting stars other than the sun, but none of them will be possible to visit in person. They are simply too far away. Closest is Proxima Centauri b, which would take 54,400 years for current spacecraft to reach. Using telescopes to detect abundances of certain gases in their atmospheres is one of the only ways to study these so-called exoplanets.

"Our discoveries provide one way to decide which of these myriad planets we should observe in more detail," said Christopher Reinhard, a former UCR graduate student now an assistant professor at the Georgia Institute of Technology, co-author of this study, and co-leader of the Alternative Earths team. "We could identify otherwise habitable planets with carbon dioxide or carbon monoxide levels that are likely too high to support complex life."

Findings from the team's previous work is already informing next-generation space missions such as NASA's proposed Habitable Exoplanet Observatory. For example, because oxygen is essential to complex life on Earth and can be detected remotely, the team has

been studying how common it may be in different planets' atmospheres.

Other than Earth, no planet in our solar system hosts life that can be characterized from a distance. If life exists elsewhere in the solar system, Schwieterman explained, it is deep below a rocky or icy surface. So, exoplanets may be our best hope for finding habitable worlds more like our own.

"I think showing how rare and special our planet is only enhances the case for protecting it," Schwieterman said. "As far as we know, Earth is the only planet in the universe that can sustain human life."

In addition to Schwieterman, Lyons, and Reinhard, the paper's authors are Stephanie Olson from the University of Chicago and Chester E. Harman from Columbia University. This project was funded by the NASA Astrobiology Institute.

http://bit.ly/31xarQH

Severed Head of a Giant 40,000-Year-Old Wolf Discovered in Russia

Dated to over 40,000 years ago, or the end of the Pleistocene epoch

By Yasemin Saplakoglu, Staff Writer

Last summer, a Russian man was strolling along the shore of the local Tirekhtyakh River in Yakutia when he came upon a grisly sight: the severed head of an ancient wolf. The head had been well preserved by the permafrost and still sported a full head of hair and sharp fangs.

A local man discovered the severed head of a wolf that lived over 40,000 years ago. **Albert Protopopov/The Siberian Times**

The man, Pavel Efimov, handed the ancient head over to scientists, who dated it to over 40,000 years ago, or the end of the Pleistocene epoch, according to The Siberian Times. Their analysis also revealed that the wolf was fully grown and was between 2 and 4 years old when it died. The severed head is 16 inches (40 centimeters) long. That's about half the size of a modern wolf's body, which can range from 26 inches (66 cm) to 34 inches (86 cm) long, according to The Siberian Times.

These are the first remains to be found of a well-preserved, fully grown wolf from the Pleistocene, according to the Times. But people have previously found other remains of ancient wolves, such as a mummified wolf pup that lived over 50,000 years ago in Canada. Back in 2015, scientists analyzed the evolutionary split between dogs and wolves using DNA from a 35,000-year-old wolf rib bone discovered in Siberia, Live Science previously reported.

Now, scientists at the Swedish Museum of Natural History will examine the DNA from the newly discovered wolf head and compare the genetic information to that of modern wolves, The Siberian Times reported. The wolf head went on display in Tokyo as part of an exhibition on woolly mammoths and other frozen creatures.

http://bit.ly/2MMCXKF

Type A blood converted to universal donor blood with help from bacterial enzymes

Gut microbes produce enzymes that can convert the common type A into a more universally accepted type

By Elizabeth Pennisi

On any given day, hospitals across the United States burn through some 16,500 liters (35,000 pints) of donated blood for emergency surgeries, scheduled operations, and routine transfusions. But recipients can't ***take*** just any blood: For a transfusion to be successful, the patient and donor blood types must be compatible. Now, researchers analyzing bacteria in the human gut have discovered that microbes there produce two enzymes that can convert the common type A into a more universally accepted type.

If the process pans out, blood specialists suggest it could revolutionize blood donation and transfusion.

"This is a first, and if these data can be replicated, it is certainly a major advance," says Harvey Klein, a blood transfusion expert at the National Institutes of Health's Clinical Center in Bethesda, Maryland, who was not involved with the work.

People typically have one of four blood types—A, B, AB, or O—defined by unusual sugar molecules on the surfaces of their red blood cells. If a person with type A receives type B blood, or vice versa, these molecules, called blood antigens, can cause the immune system to mount a deadly attack on the red blood cells. But type O cells lack these antigens, making it possible to transfuse that blood type into anyone. That makes this "universal" blood especially important in emergency rooms, where nurses and doctors may not have time to determine an accident victim's blood type.

"Around the United States and the rest of the world, there is a constant shortage," says Mohandas Narla, a red blood cell physiologist at the New York Blood Center in New York City.

To up the supply of universal blood, scientists have tried transforming the second most common blood, type A, by removing its "A-defining" antigens. But they've met with limited success, as the known enzymes that can strip the red blood cell of the offending sugars aren't efficient enough to do the job economically.

After 4 years of trying to improve on those enzymes, a team led by Stephen Withers, a chemical biologist at the University of British Columbia (UBC) in Vancouver, Canada, decided to look for a better one among human gut bacteria. Some of these microbes latch onto the gut wall, where they "eat" the sugar-protein combos called mucins that line it. Mucins' sugars are similar to the type-defining ones on red blood cells.

So UBC postdoc Peter Rahfeld collected a human stool sample and isolated its DNA, which in theory would include genes that encode the bacterial enzymes that digest mucins. Chopping this DNA up and loading different pieces into copies of the commonly used lab bacterium *Escherichia coli*, the researchers monitored whether any of the microbes subsequently produced proteins with the ability to remove A-defining sugars.

At first, they didn't see anything promising. But when they tested two of the resulting enzymes at once—adding them to substances that would glow if the sugars were removed—the sugars came right off. The enzymes also worked their magic in human blood. The enzymes originally come from a gut bacterium called *Flavonifractor plautii*, Rahfeld, Withers, and their colleagues report today in *Nature Microbiology*. Tiny amounts added to a unit of type A blood could get rid of the offending sugars, they found. "The findings are very promising in terms of their practical utility," Narla says. In the United States, type A blood makes up just under one-third of the supply, meaning the availability of "universal" donor blood could almost double.

But Narla says more work is needed to ensure that all the offending A antigens have been removed, a problem in previous efforts. And Withers says researchers need to make sure the microbial enzymes have not inadvertently altered anything else on the red blood cell that could produce problems. For now, the researchers are focusing on only converting type A, as it's more common than type B blood. Having the ability to transform type A to type O, Withers says, "would broaden our supply of blood and ease these shortages."

http://bit.ly/2KfkJzm

A Medieval Grape Is Still Used to Make Wine

It's been genetically unchanged for at least 900 years.

Sarah Zhang

In a medieval cesspit in central France, archaeologists dug up a small, hard grape seed. They believed it to be 900 years old, based on the artifacts found nearby. When geneticists crushed up the

grape seed, extracted its DNA, and compared it with modern grapes, they found a perfect genetic match in Savagnin Blanc—a grape still grown, still picked, and still made into wine in Europe today.

This grape, it turns out, has survived unchanged for almost a millennium. In a time that has spanned the Hundred Years' War, the Enlightenment, the French Revolution, Napoleon, and two world wars, someone has always thought to take cuttings of Savagnin Blanc to keep planting into the ground anew.

This technique is called vegetative or clonal propagation, and it's a way to take a desirable variety and "freeze it across space and time," says Sean Myles, an agricultural geneticist at Dalhousie University, who was not involved in the Savagnin Blanc study. Historical evidence suggests that viticulturists have been propagating grapevines this way for thousands of years, and the genetics now bears this out.

Nathan Wales, an ancient-DNA researcher at the University of York, and his collaborators came across the 900-year-old Savagnin Blanc among 28 grape seeds excavated from nine different archaeological sites around France. The seeds dated back to the medieval period, the Roman era (100 B.C. to 500 A.D.), and in one case even the Iron Age (500 B.C.). The team found six separate pairs or groups of genetically identical seeds, sometimes hundreds of miles apart. The clones had almost certainly spread through vegetative propagation by humans.

One group of these Roman-era grape seeds were genetically similar, but not identical, to a modern variety called Mondeuse Blanche. In fact, Mondeuse Blanche appears to be the direct offspring of the Roman-era grapes. In other words, Wales says, "in 2000 years, there's been one reproductive cycle between the Romans and today." Grapevine varieties have stayed remarkably stable over the centuries.

The 900-year-old Savagnin Blanc—not to be confused with the more famous variety Sauvignon Blanc—is also notable because it is related to and probably even the parent of many modern varieties: Pinot Noir, Riesling Bleu, Verdejo, Sylvaner, Trousseau, and so on. "Savagnin, which to the general wine drinker is a very obscure minor grape, has this really important genetic history, and now we can take it back 1,000 years and put it in the middle of France," says Jon Bonné, a wine writer and the author of the forthcoming *The New French Wine*. He likens the variety to the "Johnny Appleseed of all these other varieties."

Savagnin Blanc is also known as Traminer Weiss, and it is still grown in a few European countries. But it is perhaps most famously used to make *vin jaune* or "yellow wine" from Jura in France. *Vin jaune* comes in a squat bottle called a clavelin and it has taken on a bit of a cult status. "It is probably the weirdest wine you'll ever have," Bonné says. "It is intensely yellow-colored. The best way I can describe it, it has almost no fruit characteristics. It's nuts, almonds, and walnuts, and this very distinct, slightly acidic tang, too."

While the grapes are genetically identical, Bonné says *vin jaune* is almost certainly not the same as the wine being made from Savagnin Blanc 900 years ago. The wine's exact origins are lost to history, and *vin jaune* only became an official designation in the 20th century. "Despite some crafty marketing by the Jurassiens"—people of the Jura region of France—"it's just hard to know what the historic expression of the wines really was," Bonné added in an email.

The art of wine making—or perhaps wine selling—rests on the appeal of tradition. This is why grape varieties have continued to be propagated, frozen in name, time, and evolution. Meanwhile, the pathogens that prey on grapes have continued to evolve, leading to major pesticide use. "We could probably be breeding new grape

varieties and not just relying on 1,000-year-old grape varieties," Myles says. But, he adds, "it's hard to go to Burgundy and say, 'Here's Sean's new super grape.' Are you going to strip out all your Pinot Noir and start planting Sean's new super grape?" What's the romance in that?

http://bit.ly/2wVqGZI

Cardiovascular diseases -- Promoting self-healing after heart attack

Many novel post-infarct therapies are designed to inhibit the inflammation

Myocardial infarction (MI) results in the localized death of the muscle cells that are essential for the heart's pumping function. Depending on the extent of the damage, MI may initiate a progressive deterioration of cardiac function that ultimately leads to heart failure. Following an acute infarction, cells of the immune system induce an inflammatory reaction in the heart muscle, which promotes clearance of the damaged tissue. "Many novel post-infarct therapies are designed to inhibit the inflammation," says Professor Oliver Söhnlein of the Institute for Cardiovascular Prevention at LMU. "However, inflammatory reactions everywhere in the body are normally self-limiting. So we set out to develop a therapeutic approach which makes use of the endogenous processes that enable the inflammation to be turned off," he explains. A new study, which appears in the Journal of the American College of Cardiology, reports how much progress Söhnlein and his team have made so far. At the core of their strategy is the protein annexin A1 (AnxA1), which plays an important role in the regulation of the innate immune response - in particular in the switch from the damage-disposal phase of inflammation to the restorative processes that lead to its resolution and healing. In the new study, the authors used two strains of mice. One lacked the ability to synthesize AnxA1, while the other served as the positive control. In mice that were unable to produce AnxA1, the inflammatory reaction induced by MI was more widespread and persistent, and the degree of impairment of cardiac function was greater, than in the control mice. Furthermore, therapeutic administration of AnxA1 following heart damage was found to promote myocardial repair in wild type mice.

The protein causes immune cells called macrophages to secrete the signal protein VEGF-A, which stimulates the formation of new blood vessels. "This in turn helps to increase blood flow, which is a crucial factor in the healing process after myocardial infarction," says Söhnlein. He and his colleagues have observed similar positive effects of AnxA1 on the repair of heart damage in pigs. "So the annexin A1-based therapy looks like a promising approach to mitigating the effects of acute heart attacks."

http://bit.ly/2wTIt3q

Checkmate for hepatitis B viruses in the liver

T-cell therapy can provide a permanent cure

Researchers at Helmholtz Zentrum München and the Technical University of Munich, working in collaboration with researchers at the University Medical Center Hamburg-Eppendorf and the University Hospital Heidelberg, have for the first time succeeded in conquering a chronic infection with the hepatitis B virus in a mouse model. The team showed in its publication, that T-cell therapy can provide a permanent cure. Up to now it has not been possible to fully control the virus. Their findings have now been published in the Journal of Clinical Investigation.

Infections with the hepatitis B virus (HBV) are a global health problem. According to the World Health Organisation (WHO), more than 260 million people worldwide are chronically infected with the virus. Vaccination prevents new HBV infections, but for people who are chronic carriers of the virus, a cure has not yet been found. Available drugs only prevent the virus from continuing to replicate in liver cells, but they cannot eliminate it. In the long term,

this can lead to complications such as liver cancer or liver cirrhosis, whereby functional liver tissue is replaced by fibrous connective tissue.

"Currently, chronic hepatitis B cannot be cured. We have now been able to show that T-cell therapy exploiting new technologies presents an encouraging solution for the treatment of chronic HBV infection and liver cancer that is triggered by the virus. That is because these 'living drugs' are the most potent therapy we have at our disposal at present," explains Prof. Ulrike Protzer. She is Director of the Institute of Virology at the Helmholtz Zentrum München and at the Technical University of Munich, both members of the German Center for Infection Research (DZIF).

T cells eliminate hepatitis B

According to Dr. Karin Wisskirchen, first author of the study and scientist in the group of Ulrike Protzer, the new T-cell therapy was specifically developed as an approach to fighting HBV infection and HBV-associated liver cancer. It is known that in chronically infected patients, virus-specific T cells either cannot be detected or they demonstrate decreased activity. However, if patients are able to keep the virus under control by themselves, a strong T-cell response becomes detectable. "The obvious answer is therefore to use virus-specific T cells to make up for this deficit," Dr. Wisskirchen says. The genetic information for HBV-specific T-cell receptors was obtained from patients with resolved infection. In the laboratory, it can then be introduced into T cells from the blood of patients with chronic hepatitis B. This leads to the formation of new, active T cells, which fight the virus or virus-induced cancer cells. T cells created in this way were able to completely eliminate HBV-infected cells in the cell culture.

In cooperation with the group led by Prof. Maura Dandri, Hamburg the immune cells were then tested in a humanized mouse model**. A single dose of the receptor-modified T-cells was sufficient to control the virus in the liver. Hereby, the T-cells only attacked infected liver cells and spared healthy tissue. Myrcludex B***, an experimental drug developed by Prof. Stephan Urban, Heidelberg, was then administered to prevent the virus from infecting healthy liver cells again as soon as the T-cells had stopped circulating. As a result, the infection was completely cured.

Preparations for a clinical study

"The promising results of this study will help us to further investigate the potential of T-cell therapy and go ahead with clinical trials along with our partners. We are thus taking a decisive step towards establishing this form of personalized medicine," Prof. Protzer says. Her group will therefore continue to explore ways of applying the therapy to the widest possible group of patients. The Helmholtz Zentrum München has out-licensed parts of its T-cell therapy to SCG Cell therapy Pte. Ltd. "Together with our partner we are planning a clinical trial to study the treatment of patients with HBV-associated hepatocellular carcinoma," Dr. Wisskirchen explains. T-cell therapy is a highly innovative area that has gained momentum thanks to the significant success of clinical trials in the treatment of lymphoma. Prof. Dandri stresses: "Such progress would not be possible without the close cooperation that we have within the German Center for Infection Research."

Further information

- ***T cells (T-lymphocytes) are a group of white blood cells, and are thus an important component of the body's immune system. They mature in the thymus gland, hence the abbreviation to "T" cells.***
- ***These investigations were carried out using a highly complex "humanized" mouse model that can be reconstituted with human liver cells, thus enabling the investigation of HBV and the preclinical evaluation of antiviral drug candidates. Prof. Dandri, who co-developed the model, heads the Virus Hepatitis Research Group at the I. Medical Clinic of the UKE, a partner institution of the German Centre for Infection Research (DZIF).***

- ***Myrcludex B is an inhibitor of the entry of HB viruses into liver cells. It is currently in a pivotal phase III clinical trial for the treatment of chronic hepatitis D. Mycludex B was developed by Prof. Stephan Urban at the University Hospital of Heidelberg, a partner institution of the German Centre for Infection Research (DZIF).***

Original publication:

Wisskirchen K, Kah J et al (2019), T cell receptor grafting allows virological control of hepatitis B virus infection. JCI. DOI: 10.1172/JCI120228;

Further articles on this subject *The article is the following publication describes how the T-cell receptors were isolated and characterized:*

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0182936

Hepatitis B virus infection: Degradation of viral DNA in the cell nucleus is opening up new treatment possibilities

http://bit.ly/2WCLpf7

Almost 400 medical practices found ineffective in analysis of 3,000 studies

New research could help eliminate medical practices that are no more effective than existing standards of care, reducing costs for patients and practitioners

Scientists have identified nearly 400 established medical practices that have been found to be ineffective by clinical studies published across three top medical journals.

Writing in the open-access journal *eLife*, the team hope their findings will encourage the de-adoption of these practices, also known as medical reversals, ultimately making patient care more efficient and cost effective.

Medical reversals are practices that have been found to be no better than prior or lesser standards of care, through randomised controlled trials (RCTs: studies that aim to reduce certain types of bias when testing new treatments). But it can be difficult to identify these practices. For example, Cochrane Reviews provide high-quality evidence on medical practices, but only one practice is covered in each review and many have not been reviewed in this way. Additionally, the Choosing Wisely initiative in the US aims to maintain a list of low-value medical practices, but it relies on medical organisations to report them.

"We wanted to build on these and other efforts to provide a larger and more comprehensive list for clinicians and researchers to guide practice as they care for patients more effectively and economically," says lead author Diana Herrera-Perez, Research Assistant at the Knight Cancer Institute at Oregon Health & Science University (OHSU), US.

To do this, Herrera-Perez and her team conducted a search of RCTs published over 15 years in three leading general medical journals: the Journal of the American Medical Association, the Lancet and the New England Journal of Medicine.

Their analysis revealed 396 medical reversals from 3,000 articles. Of these, most were conducted on people in high-income countries (92%), likely because the majority of randomised trials are performed in this setting. Meanwhile, 8% were done in low or middle-income countries, including China, India, Malaysia and Ethiopia.

Cardiovascular disease was the most commonly represented medical category among the reversals (20%), followed by public health/preventive medicine (12%) and critical care (11%). In terms of the type of intervention, medication was the most common (33%), followed by a procedure (20%) and vitamins and/or supplements (13%).

"There are a number of lessons that we can take away from our set of results, including the importance of conducting RCTs for both novel and established practices," explains senior author Vinay Prasad, Associate Professor at the OHSU Knight Cancer Institute. "Once an ineffective practice is established, it may be difficult to convince practitioners to abandon its use. By aiming to test novel treatments rigorously before they become widespread, we can

reduce the number of reversals in practice and prevent unnecessary harm to patients.

"We hope our broad results may serve as a starting point for researchers, policy makers and payers who wish to have a list of practices that likely offer no net benefit to use in future work."

Prasad adds that some limitations need to be taken into account with the results, including the fact that only three general medical journals were studied. This means the findings may not be broadly generalisable to all journals or fields. Additionally, other researchers may categorise results differently, depending on their expertise. To help overcome this issue, the team invited physicians from a range of backgrounds to review and comment on the practices identified as reversals.

"Taken together, we hope our findings will help push medical professionals to evaluate their own practices critically and demand high-quality research before adopting a new practice in future, especially for those that are more expensive and/or aggressive than the current standard of care," concludes co-lead author Alyson Haslam, PhD, also at the OHSU Knight Cancer Institute.

References

The paper 'A comprehensive review of randomized clinical trials in three medical journals reveals 396 medical reversals' can be freely accessed online at https://doi.org/10.7554/eLife.45183.

http://bit.ly/2IfqxgQ

Dogs Mirror Stress Level of Their Owners, Study Suggests

***A team of scientists from Linköping University, Sweden, has examined how stress levels in dogs are influenced by their owners and lifestyle factors. The results were published in the June 6 issue of the journal* Scientific Reports.**

"We found that the long-term levels of the stress hormone cortisol in the dog and its owner were synchronised, such that owners with high cortisol levels have dogs with high cortisol levels, while owners with low cortisol levels have dogs with low levels," said Dr. Ann-Sofie Sundman, first author of the study.

The researchers examined 25 border collies and 33 Shetland sheepdogs, all of them owned by women. The owners and the dogs provided hair samples on two occasions separated by a few months. Since physical activity can increase cortisol levels, the team also wanted to compare companion dogs with dogs that competed in obedience or agility. The physical activity levels of the dogs were therefore recorded for a week using an activity collar.

The authors found that physical activity in dogs didn't affect the long-term cortisol in their hair.

On the other hand, the stress level of competing dogs seems to be linked more strongly with that of the owner. "This may be associated with a higher degree of active interaction between the owner and the dog when they train and compete together," they said. The dog owners were also asked to complete two validated questionnaires related to their own and their dog's personality.

The scientists investigated whether stress levels are correlated with personality traits.

"Surprisingly enough, we found no major effect of the dog's personality on long-term stress," said Dr. Lina Roth, senior author of the study. "The personality of the owner, on the other hand, had a strong effect. This has led us to suggest that the dog mirrors its owner's stress." "The results suggest that the match between an owner and a dog affects the dog's stress level," the researchers said. "However, further studies are needed before we can draw any conclusions about the cause of the correlation."

Ann-Sofie Sundman et al. *2019. Long-term stress levels are synchronized in dogs and their owners.* Scientific Reports *9, article number: 7391; doi: 10.1038/s41598-019-43851-x*

http://bit.ly/2Fb2FCz

Study shows more effective method for detecting prostate cancer

Combining biopsy strategies allowed doctors to find up to 33% more cancers

Each year, 1 million men in the U.S. undergo biopsies to determine whether they have prostate cancer. The biopsy procedure traditionally has been guided by ultrasound imaging, but this method cannot clearly display the location of tumors in the prostate gland.

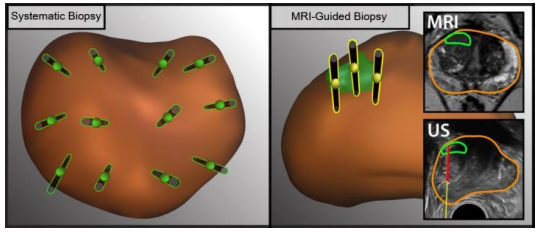


Illustration depicts how different biopsy methods take tissue samples (the black needles) from different regions in the prostate (brown oval object). MRI allows doctors to detect lesions (green oval object on right-hand image) and take tissue samples from such lesions specifically. Credit: UCLA Health

A multidisciplinary team of UCLA physicians has found that a new method, which includes biopsy guided by magnetic resonance imaging, or MRI, can be used together with the traditional method to increase the rate of prostate cancer detection.

Ultrasound has been used to visualize the prostate in order to take a representative sampling of tissue to biopsy. The introduction of MRI has allowed doctors to see specific lesions in the prostate and only take tissue samples from those spots. But the two sampling methods often aren't used in combination.

In the three-year study, published in *JAMA Surgery*, a strategy combining both sampling methods led to the detection of up to 33 percent more cancers than standard methods. According to senior author Dr. Leonard Marks, the findings could help lead to an important change in how prostate biopsies are performed.

"Our research suggests that the different biopsy methods identify different tumors," said Marks, who holds the Jean B. deKernion Chair in the department of urology at the David Geffen School of Medicine at UCLA. "To maximize our ability to identify prostate cancer, we need to take advantage of all the information we can. Our cancer detection rate, while using different methods in tandem, surpasses that from using either method alone. In this case, one plus one equals three."

The study is the first to directly compare the different biopsy sampling methods in the same group of men. Previous research demonstrated the advantages of MRI-guided biopsy, but exactly how to employ the new technology has not been clear. This trial establishes that lesion-targeted and systematic sampling are both required to maximize the accuracy of prostate biopsy.

In the past decade, MRI-guided biopsy methods, which are more targeted because they can precisely show the locations of lesions in the prostate, have been used more commonly. However, some tumors are not visible as lesions on MRIs, so such cancers may not be detected.

In the 300-person study, 248 men had a prostate lesion visible on MRI. By using all available biopsy information and methods together, the researchers detected cancer in 70 percent of those men. An additional 52 men in the trial had no lesion visible on MRI, yet 15 percent of those men were found to have cancer via the traditional ultrasound method, confirming that MRI does not identify all tumors.

"Men being assessed for prostate cancer should first receive an MRI before biopsy," said Marks, who is a member of the UCLA Jonsson Comprehensive Cancer Center. "When there's a lesion on MRI, physicians should take systematic and targeted biopsies together for the best chance at finding cancer. Even if the MRI is negative for lesions, men at risk -- including those with elevated levels of

prostate-specific antigen, a prostate nodule, or family history -- should still receive a traditional, systematic biopsy."

Identifying the precise location of cancerous tissue in the prostate is especially important as treatments become increasingly targeted. While the surgical removal of the entire gland, known as prostatectomy, is a common method of treatment, emerging treatments like focal therapy aim to eliminate only cancerous tissue in the gland while sparing healthy tissue.

"Improving our ability to see the location of cancer in the prostate in real time opens up the door for treatment innovations," Marks said. "If we can identify the location of tumors and put biopsy needles directly into them, why not find a way to destroy the tumor on the spot?"

Dr. Fuad Elkhoury, a resident physician in the department of urology at the Geffen School, is the study's first author. Other authors include Dr. Ely Felker of the department of radiology; Lorna Kwan of the department of urology; Dr. Anthony Sisk of the department of pathology; Merdie Delfin of the department of urology; and Shyam Natarajan of the departments of urology and bioengineering.

In addition to a grant from the National Cancer Institute, funding for the study came from the Jean Perkins Foundation, the Kent Kresa Family Foundation and the Steven C. Gordon Family Foundation. Marks is a co-founder of Avenda Health Inc., a biomedical device company aiming to treat prostate tumors with a laser device.

http://bit.ly/2Req7U0

Oldest evidence of marijuana use discovered in 2500-year-old cemetery in peaks of western China

Physical evidence mourners burned cannabis for its intoxicating fumes in Central Asia some 2500 years ago

By Andrew Lawler

Today, more than 150 million people regularly smoke cannabis, making it one of the world's most popular recreational drugs. But when and where humans began to appreciate the psychoactive properties of weed has been more a matter of speculation than science. Now, a team led by archaeologists Yang Yimin and Ren Meng of the Chinese Academy of Sciences in Beijing reports clear physical evidence that mourners burned cannabis for its intoxicating fumes on a remote mountain plateau in Central Asia some 2500 years ago.

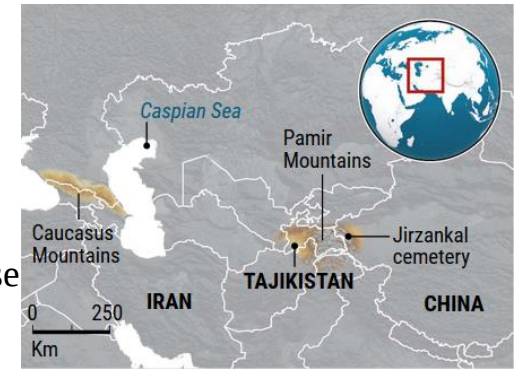
The study, published today in *Science Advances*, relies on new techniques that enable researchers to identify the chemical signature of the plant and even evaluate its potency. "We are in the midst of a really exciting period," says team member Nicole Boivin of the Max Planck Institute for the Science of Human History (MPI-SHH) in Jena, Germany. The paper is part of a wider effort to track how the drug spread along the nascent Silk Road, on its way to becoming the global intoxicant it is today.

Cannabis, also known as hemp or marijuana, evolved about 28 million years ago on the eastern Tibetan Plateau, according to a pollen study published in May. A close relative of the common hop found in beer, the plant still grows wild across Central Asia. More than 4000 years ago, Chinese farmers began to grow it for oil and for fiber to make rope, clothing, and paper.

Ancient people put cannabis leaves and hot stones in this brazier, and likely inhaled the resulting smoke. **Xinhua Wu**

Pinpointing when people began to take advantage of hemp's psychoactive properties has proved tricky. Archaeologists had made claims of ritual cannabis burning in Central Asian sites as far back as 5000 years ago. But new analyses of those plant remains by other teams suggest that early cannabis strains had low levels of tetrahydrocannabinol (THC), the plant's most powerful psychoactive component, and so lacked mind-altering properties. One academic who works in Central Asia said he and colleagues tried to smoke and eat wild varieties—but got no buzz.

The cannabis burned 2500 years ago at the Jirzankal cemetery, 3000 meters high in the Pamir Mountains in far western China, was different. Excavations there have uncovered skeletons and wooden plates, bowls, and Chinese harps, as well as wooden braziers that held burning material.



Archaeologists have spotted signs of ancient cannabis use from western China to the Caucasus. **N. Desai/*Science***

All are typical of the Sogdians, a people of western China and Tajikistan who generally followed the Persian faith of Zoroastrianism, which later celebrated the mind-expanding properties of cannabis in sacred texts. At Jirzankal, glass beads typical of Western Asia and silk from China confirm the long-distance trade for which the Sogdians became famous, and isotopic analysis of 34 skeletons showed that nearly a third were migrants. Radiocarbon analysis put the burials at about 500 B.C.E.

The wooden braziers were concentrated in the more elite tombs. Yang's and Ren's team ground bits of brazier into powder and applied gas chromatography and mass spectrometry to identify chemical compounds left behind. They found unusually high levels of THC compared with typical wild cannabis, although much less than in today's highly bred plants.

The cannabis was apparently burned in an enclosed space, so mourners almost certainly inhaled THC-laced fumes, the authors say, making this the earliest solid evidence of cannabis use for psychoactive purposes.

The region's high altitude could have stressed the cannabis, creating plants naturally high in THC, says co-author Robert Spengler, also of MPI-SHH. "It is quite likely that people came across cannabis plants at higher elevations that were naturally producing higher THC levels," he says. But humans may also have intervened to breed a more wicked weed, he adds.

"The methods are convincing, and the data are unambiguous regarding early use of cannabis as a psychoactive substance," says Tengwen Long, an environmental scientist at the University of Nottingham in the United Kingdom who has researched cannabis origins. But Megan Cifarelli, an art historian at Manhattanville College in Purchase, New York, who has studied ancient drug use, notes the aromatic fumes might also have had another purpose: to mask the smell of a putrefying corpse.

Yang's and Ren's team thinks cannabis use was restricted to elites until potent pot began to spread across Central Asia through the Silk Road linking China with Iran. In 440 B.C.E., the Greek historian Herodotus wrote that the nomadic Scythians, who controlled vast areas from Siberia to Eastern Europe, made tents and heated rocks in order to inhale hemp vapors that made them "shout for joy."

And Andrei Belinski, an archaeologist based at the heritage museum in Stavropol, Russia, in 2013 began to excavate a nearby 2400-year-old Scythian tomb that held gold vessels bearing residues of both opium and cannabis, supporting the idea that elites used the drug first.

Ancient artwork and textual references from Syria to China hint at even earlier cannabis drug use, and the new analytical methods could soon provide concrete evidence of this, says Michael Frachetti, an archaeologist at Washington University in St. Louis, Missouri. But it's already clear that the ancient Silk Road trafficked in more than spices, grains, and ideas. "Crops weren't just about food," he says. "They were also about making contact with another world."

Posted in: Archaeology Asia doi:10.1126/science.aay3693

http://bit.ly/2MPzuLD

Rare 'Ectopic Breast Tissue' Caused a Woman to Lactate from Her Vulva

Rare condition caused her to lactate from her vulva after childbirth

By Rachael Rettner, Senior Writer

Women can experience some odd body changes after pregnancy, but for one mother in Austria, those changes were particularly unusual: A rare condition caused her to lactate from her vulva after childbirth, according to a new report of the case.

The 29-year-old woman had recently given birth to her second child when she developed severe pain on the right side of her vulva. Doctors noticed she had a lot of swelling in an area where she had received sutures, and they thought she had developed an abscess. But it was actually something much rarer.

The woman said that four days after giving birth, she developed swelling on both sides of her vulva and noticed the release of a "milky white" fluid from the area. She said she'd had similar swelling in her vulva after her first pregnancy.

Doctors then suspected that the woman had "ectopic" breast tissue, or breast tissue that's found somewhere in the body outside the breast, and the tissue was lactating.

Indeed, when doctors performed an ultrasound of the area, they could see that the tissue looked just like lactating breast tissue, except that it was on the vulva.

It appeared that the right side was particularly swollen and painful because the sutures were covering an "excretory duct" for the milk. Once these sutures were removed, the woman's pain immediately abated, according to the report, which is published in the July issue of the journal Obstetrics & Gynecology.

Dr. Richard Mayer, of the Department of Gynecology, Obstetrics and Gynecologic Endocrinology at Kepler University Hospital in Austria, who treated the patient, said he had never seen a case like this before.

About 1% to 5% of female infants are born with ectopic or "accessory" breast tissue, but it's very rare to find this tissue in the vulva, the report said. Most commonly, ectopic breast tissue occurs in the armpit area. In some cases, women have additional breast tissue with nipples or areola (the pigmented area surrounding the nipple), but in other cases, the breast tissue alone is present, without nipples or areola.

When women have ectopic breast tissue without nipples or areola, the condition is typically diagnosed in pregnancy, when it's easier to detect, Mayer said. In other cases, women may be diagnosed if the tissue becomes cancerous.

There aren't specific guidelines for treating ectopic breast tissue, the report said, but the tissue can be removed because of how it looks or because it's causing discomfort, according to a 2014 paper on accessory breast tissue in the American Journal of Roentgenology.

In the current case, the woman's pain, swelling and milk secretion in the ectopic tissue decreased over the subsequent two weeks and she was able to continue breast-feeding normally. Since ectopic breast tissue can become cancerous, doctors recommended that women who have it consider having the tissue removed.

Although the condition is rare, doctors should consider it as a possible diagnosis among women who have swelling in the vulva, especially if they are lactating, the authors said.

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Study raises concern for sun 'superflare'

Research finds it's not just young stars that behave explosively.

Richard A Lovett reports.

Astronomers monitoring data from thousands of distant stars have come to an unnerving conclusion: every 2000 to 3000 years, ones

just like the sun can produce superflares 100 or more times larger than anything ever recorded in human history.

Such an event, if it were to occur today, would produce a blast of radiation that would destroy satellites, disrupt electronics, knock out communications, and devastate power grids worldwide.

"Our study shows that superflares are rare events," says Yuta Notsu, a visiting researcher at the University of Colorado, Boulder, US, "but there is some possibility that we could experience such an event in the next 100 years or so."

The disturbing find comes from studying data collected by the Kepler Space Telescope, designed to continuously monitor a field of about 150,000 distant stars.

Its primary mission is to look for brightness changes caused by the silhouettes of planets passing in front of their suns. But the same data also allows scientists to collect enormous amounts of data about these stars' flares.

Flares are sudden releases of energy thought to be caused by releases of magnetic energy stored near starspots — the extrasolar equivalent of sunspots. Superflares are simply big versions.

Conventional wisdom held that superflares are a product of young, fast-rotating stars, unlike the sun, which in middle age has seen its rotation slow to about once every 25 days.

But it turns out that as stars age and slow, they don't quit having flares. They simply have them less often.

"Young stars have superflares every week or so," Notsu says. "For the sun, it's once every few thousand years, on average." Nobody knows when, or if, the next such superflare will hit the Earth.

The largest flare on record is the Carrington Event, a giant flare observed by English astronomer Richard Carrington in 1859, which created northern lights that spread as far south as Hawaii and southern lights that spread as far north as Santiago, Chile – slightly farther north than the Australian city of Sydney.

People in the northeastern US claimed they could read the newspaper just from the light of the aurora, and operators of the then-newfangled telegraph reported sparks leaping off their equipment, melting wires and starting fires.

But by superflare standards, the Carrington Event was just a baby, Notsu said recently at a meeting of the American Astronomical Society (AAS) in St. Louis, Missouri.

Its estimated energy was "merely" 10^{33} ergs — the equivalent of a 100,000,000,000-megaton thermonuclear explosion.

The mammoths observed by Notsu's team are immensely larger, suggesting that stars like the sun are capable of producing flares of 10^{35} ergs every few thousand years — one hundred times larger than the Carrington Event.

"So we have no record of any flare as big as you're describing, which means it's yet to come," Rick Fienberg, AAS's press officer, said, only partially in jest, at Notsu's recent press conference.

That doesn't mean, however, that it's impossible to determine if the sun has ever produced such flares. That's because their radiation would create a spike in carbon-14 levels in the upper atmosphere.

Carbon-14 is a radioactive form of carbon which, like the ordinary form, finds its way into biological tissues. It is formed when highly energetic radiation from outer space produces neutrons in the upper atmosphere. These are captured by nitrogen-14, which then decays into carbon-14.

A 2012 study in *Nature* found a spike in carbon-14 levels in tree rings, suggesting that something, possible a massive solar flare, sent carbon-14-forming radiation sleeting into the Earth's upper atmosphere as recently as AD 775. "Such events can be used to investigate long-term [solar] activity," Notsu says.

Meanwhile, he adds, it might be wise to prepare by protecting electronics on the ground and in orbit from massive radiation surges.

"If a superflare occurred 1000 years ago," he says, "it was probably no big problem. People may [simply] have seen a large aurora. Now it's a much bigger problem because of our electronics."

In addition to being presented at the AAS meeting, Notsu's research was published in *The Astrophysical Journal*.

https://wb.md/2Iqwnrr

Bats Now Pose Greatest Risk for Rabies in the US

Number of rabid bats reported surpassed the number of rabid raccoons

Megan Brooks

Rabies continues to be a threat in the United States — with someone treated every 10 minutes for possible exposure to the virus — and bats are now the major source of human cases in the US, according to a Vital Signs report released today by the Centers for Disease Control and Prevention (CDC).

"Dramatic shifts have occurred in the United States in which animals pose the most risk for human rabies," Anne Schuchat, MD, CDC principal deputy director, said during a press briefing.

Before 1960, bites from rabid dogs caused most human rabies cases in the US. But mass pet vaccination programs and leash laws enacted in the 1950s significantly reduced rabies in dogs.

Currently, the US averages one to three human cases of rabies a year, down from 30 to 50 cases annually in the 1940s, largely due to routine pet vaccination and availability of postexposure prophylaxis (PEP), Schuchat said.

"Starting in 2015, the number of rabid bats reported surpassed the number of rabid raccoons for the first time, and the gap has been widening ever since," Schuchat said.

Bats made up roughly 32% of the 5000 rabid animals tested in 2017 whereas raccoons made up 28%, she noted. "In the United States, while bats make up about a third of all rabid animals reported, they are responsible for more than two thirds of all rabies deaths in people. That is, 7 in 10 Americans who die from rabies in the United States were infected by bats."

Bat Bites "Can Go Unnoticed"

In their Vital Signs report, CDC veterinarian Emily Pieracci, DVM, and colleagues report that from 1960 to 2018, a total of 125 human rabies cases were reported in the United States; 36 (28%) were attributed to dog bites during international travel. Among the 89 infections acquired in the US, 62 (70%) were attributed to bats. In 2018, approximately 55,000 people sought PEP after contact with a potentially rabid animal. "We want this Vital Signs [report] to raise awareness about specific rabies risks," Schuchat said.

"People may not realize that bats carry rabies so they may not see their medical provider after touching or handling a bat. Bat bites are small —smaller than the top of a pencil eraser — and can go unnoticed. This is a problem because rabies is deadly once symptoms start," said Schuchat.

"Bats play a critical role in our ecosystem, and it is important [that] people know that most of the bats in the US are not rabid," Pieracci said in a news release. "The problem comes when people try to handle bats they think are healthy, because you really can't tell if an animal has rabies just by looking at it. The best advice is to avoid contact with bats — and other wildlife — to protect yourself from rabies."

MMWR. Published June 12, 2019. Full text

http://bit.ly/2ZyOaAh

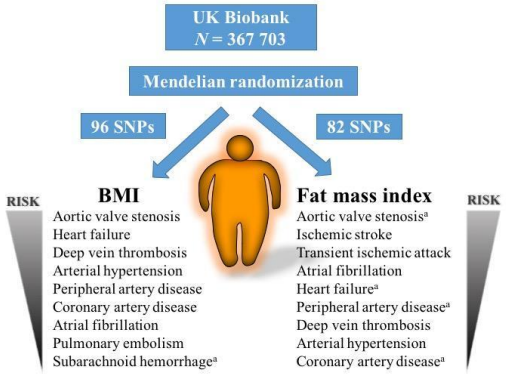
Excess weight and body fat cause cardiovascular disease

Excess weight and body fat cause a range of heart and blood vessel diseases, according to the first study to investigate this using a method called Mendelian randomisation.

In particular, the study published in the European Heart Journal [1] today (Friday), shows that as body mass index (BMI) and fat mass

increase, so does the risk of aortic valve stenosis - a condition in which the valve controlling the flow of blood from the heart to the body's largest blood vessel, the aorta, narrows and fails to open fully.

Mendelian randomisation is a way of showing whether or not individual risk factors actually cause disease, rather than just being associated with it. It uses genetic variants that are already known to be associated with potential risk factors, such as BMI and body fat, as indirect indicators or "proxies" for these risk factors. This enables researchers to discover whether the risk factor is the cause of the disease (rather than the other way around), and reduces bias in results because genetic variants are determined at conception and cannot be affected by subsequent external or environmental factors, or by the development of disease.



Associations of BMI and fat mass index with cardiovascular conditions.
Credit: European Heart Journal and Professor Susanna Larsson

The researchers, led by Susanna Larsson, associate professor and senior researcher at the Karolinska Institute, Stockholm, Sweden, studied 96 genetic variants associated with BMI and body fat mass to estimate their effect on 14 cardiovascular diseases in 367,703 participants of white-British descent in UK Biobank - a UK-based national and international resource containing data on 500,000 people, aged 40-69 years.

She said: "The causal association between BMI and fat mass and several heart and blood vessel diseases, in particular aortic valve stenosis, was unknown. Using Mendelian randomisation we found that higher BMI and fat mass are associated with an increased risk of aortic valve stenosis and most other cardiovascular diseases, suggesting that excess body fat is a cause of cardiovascular disease."

People who had genetic variants that predict higher BMI were at increased risk of aortic valve stenosis, heart failure, deep vein thrombosis, high blood pressure, peripheral artery disease, coronary artery disease, atrial fibrillation and pulmonary embolism. For every genetically-predicted 1kg/m2 increase in BMI, the increased risk ranged from 6% for pulmonary embolism to 13% for aortic valve stenosis. (Above a BMI that is considered 'healthy' (20-25 kg/m2) every 1 kg/m2 increase in BMI for someone who is 1.7 metres tall (5'7") corresponds to a weight gain of nearly 3 kg.)

The researchers also found that risk of cardiovascular diseases increased with the genetic variants predicting increases in fat mass. The greatest increased risk was also for aortic valve stenosis (46% increased risk), followed by ischaemic stroke, transient ischaemic attack, atrial fibrillation, heart failure, peripheral artery disease, deep vein thrombosis, high blood pressure and coronary artery disease.

The researchers stress that although these genetic variants can predispose people to be more likely to gain excess weight, the most important factors implicated in the development of cardiovascular disease are diet and physical activity.

Professor Larsson said: "Our genes can make us somewhat more predisposed to gain body weight but lifestyle factors, such as overeating and lack of physical activity, are the major determinants of overweight. A healthy diet is the cornerstone of cardiovascular disease prevention, and how much we eat should be limited to the amount of energy required to maintain a healthy body weight, which is a BMI of between 20 to 25 kg/m2. People who are predisposed to a higher BMI may need to work a bit harder to maintain a healthy weight."

The strengths of the study include the large numbers of people involved and the fact that they were of European descent, which reduces the potential for bias from different populations. Potential limitations are that some genetic variants may be associated with more than one characteristic, that the number of cases were few for some diseases, and that there was a lack of information on the severity of aortic valve stenosis.

The damaged valve in aortic valve stenosis means that less blood leaves the heart and it has to work harder to pump enough blood out to circulate round the body. Blood can back up in other parts of the heart and sometimes the lungs. This can lead to shortness of breath, tiredness, fainting, chest pain and an irregular heart beat.

[1] *"Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomisation study", by Susanna C. Larsson et al. European Heart Journal. doi:10.1093/eurheartj/ehz388*

http://bit.ly/2WMAIXq

Gut microbes eat our medication

A concrete example of how one species of bacteria consumes levodopa, the primary treatment for Parkinson's disease, could reveal more about how the microbiome impacts our health

The first time Vayu Maini Rekdal manipulated microbes, he made a decent sourdough bread. At the time, young Maini Rekdal, and most people who head to the kitchen to whip up a salad dressing, pop popcorn, ferment vegetables, or caramelize onions, did not consider the crucial chemical reactions behind these concoctions.

Even more crucial are the reactions that happen after the plates are clean. When a slice of sourdough travels through the digestive system, the trillions of microbes that live in our gut help the body break down that bread to absorb the nutrients. Since the human body cannot digest certain substances--all-important fiber, for example--microbes step up to perform chemistry no human can.

"But this kind of microbial metabolism can also be detrimental," said Maini Rekdal, a graduate student in the lab of Professor Emily Balskus and first-author on their new study published in Science. According to Maini Rekdal, gut microbes can chew up medications, too, often with hazardous side effects. "Maybe the drug is not going to reach its target in the body, maybe it's going to be toxic all of a sudden, maybe it's going to be less helpful," Maini Rekdal said.

In their study, Balskus, Maini Rekdal, and their collaborators at the University of California San Francisco, describe one of the first concrete examples of how the microbiome can interfere with a drug's intended path through the body. Focusing on levodopa (L-dopa), the primary treatment for Parkinson's disease, they identified which bacteria out of the trillions of species is responsible for degrading the drug and how to stop this microbial interference.

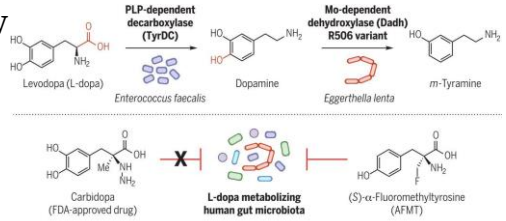
Parkinson's disease attacks nerve cells in the brain that produce dopamine, without which the body can suffer tremors, muscle rigidity, and problems with balance and coordination. L-dopa delivers dopamine to the brain to relieve symptoms. But only about 1 to 5% of the drug actually reaches the brain.

This number--and the drug's efficacy--varies widely from patient to patient. Since the introduction of L-dopa in the late 1960s, researchers have known that the body's enzymes (tools that perform necessary chemistry) can break down L-dopa in the gut, preventing the drug from reaching the brain. So, the pharmaceutical industry introduced a new drug, carbidopa, to block unwanted L-dopa metabolism. Taken together, the treatment seemed to work.

"Even so," Maini Rekdal said, "there's a lot of metabolism that's unexplained, and it's very variable between people." That variance is a problem: Not only is the drug less effective for some patients, but when L-dopa is transformed into dopamine outside the brain, the compound can cause side effects, including severe gastrointestinal distress and cardiac arrhythmias. If less of the drug

reaches the brain, patients are often given more to manage their symptoms, potentially exacerbating these side effects.

Maini Rekdal suspected microbes might be behind the L-dopa disappearance. Since previous research showed that antibiotics improve a patient's response to L-dopa, scientists speculated that bacteria might be to blame. Still, no one identified which bacterial species might be culpable or how and why they eat the drug.



So, the Balskus team launched an investigation. The unusual chemistry--L-dopa to dopamine--was their first clue.

When gut microbes metabolize the Parkinson's drug L-dopa, they produce dopamine; a second microbe then metabolizes dopamine, producing meta-tyramine. While L-dopa metablism likely limits drug availability and contributes to side effects, the potential ramifications of transforming dopamine into meta-tyramine are unknown.

Few bacterial enzymes can perform this conversion. But, a good number bind to tyrosine--an amino acid similar to L-dopa. And one, from a food microbe often found in milk and pickles (Lactobacillus brevis), can accept both tyrosine and L-dopa.

Using the Human Microbiome Project as a reference, Maini Rekdal and his team hunted through bacterial DNA to identify which gut microbes had genes to encode a similar enzyme. Several fit their criteria; but only one strain, Enterococcus faecalis (E. faecalis), ate all the L-dopa, every time.

With this discovery, the team provided the first strong evidence connecting E. faecalis and the bacteria's enzyme (PLP-dependent tyrosine decarboxylase or TyrDC) to L-dopa metabolism.

And yet, a human enzyme can and does convert L-dopa to dopamine in the gut, the same reaction carbidopa is designed to stop. Then why, the team wondered, does the E. faecalis enzyme escape carbidopa's reach?

Even though the human and bacterial enzymes perform the exact same chemical reaction, the bacterial one looks just a little different.

Maini Rekdal speculated that carbidopa may not be able to penetrate the microbial cells or the slight structural variance could prevent the drug from interacting with the bacterial enzyme. If true, other host-targeted treatments may be just as ineffective as carbidopa against similar microbial machinations.

But the cause may not matter. Balskus and her team already discovered a molecule capable of inhibiting the bacterial enzyme.

"The molecule turns off this unwanted bacterial metabolism without killing the bacteria; it's just targeting a non-essential enzyme," Maini Rekdal said. This and similar compounds could provide a starting place for the development of new drugs to improve L-dopa therapy for Parkinson's patients.

The team might have stopped there. But instead, they pushed further to unravel a second step in the microbial metabolism of L-dopa. After E. faecalis converts the drug into dopamine, a second organism converts dopamine into another compound, meta-tyramine.

To find this second organism, Maini Rekdal left behind his mother dough's microbial masses to experiment with a fecal sample. He subjected its diverse microbial community to a Darwinian game, feeding dopamine to hordes of microbes to see which prospered.

Eggerthella lenta won. These bacteria consume dopamine, producing meta-tyramine as a by-product. This kind of reaction is challenging, even for chemists. "There's no way to do it on the bench top," Maini Rekdal said, "and previously no enzymes were known that did this exact reaction."

The meta-tyramine by-product may contribute to some of the noxious L-dopa side effects; more research needs to be done. But, apart from the implications for Parkinson's patients, E. lenta's novel chemistry raises more questions: Why would bacteria adapt to use

dopamine, which is typically associated with the brain? What else can gut microbes do? And does this chemistry impact our health?

"All of this suggests that gut microbes may contribute to the dramatic variability that is observed in side effects and efficacy between different patients taking L-dopa," Balskus said.

But this microbial interference may not be limited to L-dopa and Parkinson's disease. Their study could shepherd additional work to discover exactly who is in our gut, what they can do, and how they can impact our health, for better or worse.

http://bit.ly/2WFk6ks

Man Had a Nearly 5-Foot Wire Left in His Body After Heart Procedure, Lawsuit Claims

A Nevada man is suing his doctor for allegedly leaving several feet of wire in his body for more than a decade, according to news reports.

By Rachael Rettner, Senior Writer

The man, 70-year-old German "OT" Ortiz, of Las Vegas, said the 57-inch (144 centimeters) wire was left in his body in 2005 after he underwent a procedure called an angiogram, according to the Las Vegas Review-Journal. An angiogram allows doctors to take images (X-rays) of blood vessels. The procedure involves threading a catheter through the blood vessels up to the heart with the help of a "guide wire," and injecting a special dye into the catheter. (The dye then shows up on the X-ray, revealing which arteries are narrowed or blocked.)

Ortiz didn't learn that the guide wire was still in his body until 2015, according to the lawsuit. An X-ray taken by a different doctor showed the wire stretching from a blood vessel in his thigh up to his aorta, the main artery in the chest that carries blood away from the heart, Ortiz's lawyer said during the trial's opening statements, according to the Las Vegas Review-Journal.

Ortiz has since undergone an operation to remove most of the wire, although 20 inches (50 cm.) of it still remains in his thigh, the Review-Journal reported.

http://bit.ly/2Riz8vz

'Poop Transplants' Can Transmit Deadly Superbugs, FDA Warns

"Poop transplants" have shown promise in treating severe diarrhea, but now, the Food and Drug Administration (FDA) is warning that these transplants may risk spreading superbugs.

By Rachael Rettner, Senior Writer | June 14, 2019 01:15pm ET

On Thursday (June 13), the FDA announced that two people who underwent this procedure, known medically as fecal microbiota transplantation (FMT), contracted serious drug-resistant infections and one of those patients died.

The two patients, who had weakened immune systems, received fecal transplants from the same donor. Afterward, both patients developed an infection with a strain of Escherichia coli bacteria that's resistant to multiple types of antibiotics. [The Poop on Pooping: 5 Misconceptions Explained]

The donor's stool hadn't been tested for this type of bacteria prior to the transplants. After the two transplant recipients developed infections, the donor stool was tested and found to be positive for the same drug-resistant bacteria seen in the patients.

FMT is considered an experimental treatment for Clostridium difficile, a bacterial infection that causes severe diarrhea and can be life-threatening. The procedure aims to restore a better balance of bacteria within the gut. It involves taking fecal matter from a healthy donor and delivering it into a patient's colon, either directly, through an enema or other infusion of stool, or with the use of "poop pills," capsules containing fecal matter that patients take by mouth.

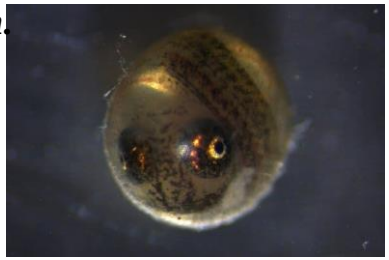
"While we support this area of scientific discovery, it's important to note that FMT does not come without risk," Dr. Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, said in a statement. "We've become aware of infections with multidrug-resistant organisms after patients received investigational FMT, including one patient death. We therefore want to alert all health care professionals who administer FMT about this potential serious risk so they can inform their patients."

The FDA will now require screening of donor stool for multidrug-resistant organisms before the stool's use in any FMT procedure. Potential FMT donors will also be asked questions to determine if they may be at risk for carrying such drug-resistant bacteria, and they will be excluded from donating if they have certain risk factors. The FDA warning "underscores the importance of why new therapies are thoroughly studied to ensure [that] the benefits of taking them outweigh the risks to patients, and we will continue to aggressively monitor clinical trials [of FMT] to ensure patients are protected when safety concerns arise," Marks said.

https://nyti.ms/2RkqGCu

The Fish Egg That Traveled Through a Swan's Gut, Then Hatched

These fish turn up in many surprising location, but this was one place scientists didn't expect to find them.



A killifish egg seven days before hatching. **Lecea-Unisinos**

Killifish manage to endure a variety of environments. The wee freshwater fish survive in isolated desert pools, lakes made by flood water, even seasonal ponds that are little more than puddles.

One place scientists didn't expect to find them was in swan poop. But an international team of researchers reported last week in the journal Ecology that whole killifish eggs make it through the digestive tract of water birds intact, with one egg in the study even hatching more than a month after its transit through a swan. The findings suggest that bird feces may be capable of carrying fish eggs far from their original locations.

Giliandro Silva, a graduate student at Unisinos University in Brazil, and colleagues found last year that small flowering water plants in bird feces were still alive and able to grow. While they were completing that study, they found a killifish egg in a frozen fecal sample from a wild coscoroba swan. They realized that what was true for plants might also be true for fish eggs.

To test this hypothesis, they mixed eggs of two killifish species found in Brazil into the feed of swans living in a zoo. Over the next two days, they collected what the swans excreted and looked for intact eggs. They found five, about one percent of the 650 eggs they'd mixed in.

Then, they kept the eggs in the lab to see if they would continue developing. Of the three that did, two eventually died from an unrelated fungal infection. But one hatched into a young killifish 49 days after its emergence from a swan's gut, apparently none the worse for wear.

When the water they live in dries up, killifish eggs drop into a hibernation-like state, able to revive and hatch months later if water returns. This special ability is often why the fish sometimes seem to appear out of nowhere when a seasonal pool forms.

"They're famous because of their amazing ability to survive in the mud," said Andrew Green, a researcher at Estación Biológica de Doñana in Seville, Spain, and a co-author of the new paper.

But the fact that a small fraction of all killifish eggs consumed can make it through a bird unharmed may explain the appearance of fish in places where no one can imagine a plausible arrival story, he continued. In some cases, the fish may have literally fallen from the sky.

That any survive at all, without the protective casing of a seed or nut, could be because the guts of swans, like the guts of most creatures, are not 100 percent efficient. An animal's digestion extracts the nutrients that are readily available fairly quickly. To be able to eat another meal, the animal must excrete whatever else is left. That includes, in this case, as-yet-undigested killifish eggs.

The researchers are planning a similar experiment now that uses eggs from carp, which hatch much faster than killifish. As killifish and carp can be invasive species outside of their normal range, understanding how they spread can help in containment.

What happened to the sole survivor of the experiment, though, the lone killifish that hatched? Is it swimming in a tank at the lab?

"It's been preserved for scientific posterity," Dr. Green said.

http://bit.ly/2KQXrPS

Humans Are Growing Weird, Bone Spikes on Their Skulls. Smartphones May Be the Culprit.

The younger crowd are developing a weird, bony spike just above their necks

By Laura Geggel, Associate Editor

The hours we spend scrolling through our smartphones appear to be changing our skulls. This may be the reason why some people — especially the younger crowd — are developing a weird, bony spike just above their necks.

The bony skull bump — known as an external occipital protuberance — is sometimes so large, you can feel it by pressing your fingers on the base of your skull.

"I have been a clinician for 20 years, and only in the last decade, increasingly, I have been discovering that my patients have this growth on the skull," David Shahar, a health scientist at the University of The Sunshine Coast, Australia, told the BBC in a fascinating feature about the changing human skeleton.

A cause-and-effect relationship hasn't been identified, but it's possible that the spike comes from constantly bending one's neck at uncomfortable angles to look at smart devices. The human head is heavy, weighing about 10 lbs. (4.5 kilograms), and tilting it forward to look at funny cat photos (or however you spend your smartphone time) can strain the neck — hence the crick people sometimes get, known as "text neck."

Text neck can increase pressure on the juncture where the neck muscles attach to the skull, and the body likely responds by laying down new bone, which leads to that spiky bump, Shahar told the BBC. This spike distributes the weight of the head over a larger area, he said.

In a 2016 study in the Journal of Anatomy, Shahar and a colleague looked at the radiographs of 218 young patients, ages 18 to 30, to determine how many had these bumps. Regular spikes had to measure at least 0.2 inches (5 millimeters), and enlarged spikes measured 0.4 inches (10 mm).

In all, 41% of the group had an enlarged spike and 10% had an especially large spike measuring at least 0.7 inches (20 mm), the doctors found. In general, enlarged spikes were more common in males than in females. The largest spike belonged to a man, sticking out at 1.4 inches (35.7 mm).

Another study of 1,200 individuals, ages 18 to 86, that Shahar and a co-researcher did revealed that these spikes are more prevalent in younger people. Enlarged spikes occurred in 33% of the group, but participants ages 18 to 30 years old were significantly more likely to have these spikes than the older generations, they found.

These bony spikes are likely here to stay, Shahar said. "Imagine if you have stalactites and stalagmites, if no one is bothering them, they will just keep growing," he told the BBC. Luckily, these spikes rarely cause medical issues. If you are experiencing discomfort, however, try improving your posture, he said.

http://bit.ly/2WGJIxm

Vitamin K Involved in Disablement Process in Older Age, Study Suggests

***Reduced levels of circulating vitamin K are linked to an increased risk of mobility limitation and disability in older adults, according to a study published in the* Journals of Gerontology: Series A.**

In humans and other vertebrates, vitamin K is required for blood coagulation and bone and vascular metabolism.

It naturally exists in two forms: vitamin K1 (also known as phylloquinone) and vitamin K2 (a group of compounds called menaquinones). Vitamin K3 (menadione) is a synthetic form of vitamin K.

Phylloquinone, the major dietary form of vitamin K, is widely distributed in green and leafy vegetables such as spinach, kale and broccoli. Menaquinones exist preferentially in meats, eggs, curd, cheese and fermented soyabeans.

For an average adult, one cup of raw spinach provides 145 micrograms (mcg) of vitamin K1, or 181% of the daily value; one cup of raw kale provides 113 mcg, or 141%; and half of a cup of chopped boiled broccoli provides 110 mcg, or 138%.

“Low vitamin K status has been associated with the onset of chronic diseases that lead to disability, but the work to understand this connection is in its infancy,” said Dr. Kyla Shea, a nutrition scientist in the Vitamin K Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University.

“Here, we’re building on previous studies that found that low levels of circulating vitamin K are associated with slower gait speed and a higher risk of osteoarthritis.”

Dr. Shea and colleagues examined two biomarkers: circulating levels of vitamin K and a functional measure of vitamin K (plasma ucMGP).

They used data from 635 men and 688 women ages 70-79 years old, who participated in the Health, Aging, and Body Composition Study (Health ABC).

Mobility was assessed every six months for 6 to 10 years through annual clinic visits and phone interviews in the intervening time.

For the analysis, the researchers defined mobility limitation as two consecutive semi-annual reports of having any amount of difficulty either with walking a quarter of a mile or climbing 10 steps without resting, and mobility disability as two consecutive semi-annual reports of having a lot of difficulty or inability to walk or climb the same amount.

They found that older adults with low levels of circulating vitamin K were more likely to develop mobility limitation and disability.

The other biomarker, plasma ucMGP, did not show clear associations with mobility limitation and disability.

Specifically, older adults with low circulating vitamin K levels were nearly 1.5 times more likely to develop mobility limitation and nearly twice as likely to develop mobility disability compared to those with sufficient levels. This was true for both men and women.

“The connection we saw with low levels of circulating vitamin K further supports vitamin K’s association with mobility disability,” said Dr. Sarah Booth, a nutrition researcher and director of the HNRCA at Tufts University.

“Although the two biomarkers we looked at are known to reflect vitamin K status, biomarker levels can also be affected by additional known or unknown factors. Further experiments to understand the mechanisms of biomarkers and vitamin K and their role in mobility are needed.”

M. Kyla Shea et al. *Vitamin K Status and Mobility Limitation and Disability in Older Adults: The Health, Aging, and Body Composition Study.* Journals of Gerontology: Series A, *published online May 6, 2019; doi: 10.1093/gerona/glz108*

https://bbc.in/2MRCff6

Largest world stock of animal-killing virus destroyed by UK lab

Scientists have destroyed the UK's laboratory stocks of a virus that once caused devastating cattle losses.

These stocks accounted for most of the world's lab samples of rinderpest, which were held at The Pirbright Institute in Surrey.

Rinderpest and the deadly smallpox virus are the only diseases to have been eradicated from the face of the Earth. BBC News had exclusive access to the destruction of the final samples.

Dr Carrie Batten, from The Pirbright Institute, described the moment as "the end of an era". "Rinderpest was devastating and by removing the stocks that are held globally you are essentially reducing the risk dramatically," she said.

Image copyright FAO Image caption Rinderpest devastated cattle in Africa during the 1890s. Millions of people died from starvation.

Dr Michael Baron, honorary fellow at the institute, said the end of rinderpest would mark the beginning of a new war on other diseases.

"The success we have achieved with rinderpest has been one of the main drivers for people saying we can do this with other animal diseases and other human diseases such as polio, mumps and measles. These diseases are eradicable and this should be done," he explained.

Human catastrophe

The rinderpest virus is responsible for one of the worst catastrophes in history. During an outbreak in the 1890s, it killed between 80% and 90% of cattle in eastern and southern Africa. This caused mass starvation in the region.

Millions of people died as a result. In Ethiopia alone, one-third of the human population was wiped out. The toll in lives was on a scale matched only by the Black Death in Europe. A vaccination campaign eventually brought the disease under control until it was declared to have been eradicated in the wild in 2011.

But thousands of samples of the virus remained in 40 laboratories across 36 countries. If there happened to be an accident, the disease could potentially leak out and cause devastation once again.

To prevent this, the UN Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) approved a few highly secure labs and encouraged other institutes to send their rinderpest samples to these facilities.

Among them is the Pirbright Institute in Surrey, which has led efforts to record the genetic information contained in each sample and then destroy it.

Researchers have been reluctant to destroy lab samples of deadly viruses in case they are needed to create a vaccine should the disease ever re-emerge. But a digital record of the virus's genetic code means that this is no longer an issue.

And so Pirbright has been able to destroy all its samples which account for most of the laboratory rinderpest virus in the world.

Dr Samia Metwally, of the FAO, hopes that Pirbright's success will encourage other holding facilities to follow suit so that it is completely eliminated from the face of the Earth. "This is a huge step by Pirbright. It sets a precedent for other countries to do the same."

Dr Monique Eloit, the OIE's director-general, told BBC News that she was "very happy" about the development. "All the work done by farmers, veterinarians and scientists for such a long time is on track to minimise the risk of the re-emergence of rinderpest," she said.

The government's chief vet, Dr Christine Middlemiss, welcomed the news. "It is such a devastating disease. 100% of susceptible animals become infected and die from the virus. So to have that removed as a threat is fantastic," she said.

http://bit.ly/2KQXYBm

Is Consciousness a Fundamental Quality of the Universe?

Scientists have long been trying to understand human consciousness — the subjective 'stuff' of thoughts and sensations inside our minds.

There used to be an assumption that consciousness is produced by our brains, and that in order to understand it, we just need to figure out how the brain works. But this assumption raises questions. Apart from the fact that decades of research and theorizing have not shed any significant light on the issue, there are some strange mismatches between consciousness and brain activity.

As the neuroscientist Giulio Tononi has pointed out, brain cells fire away almost as much in some states of unconsciousness (such as deep sleep) as they do in the wakeful conscious state.

In some parts of the brain, you can identify neurons associated with conscious experience, while other neurons don't seem to have any affect on it.

There are also cases of a very low level of brain activity (such as during some near death experiences and comas) when consciousness may not only continue, but even become more intense.

If you held a human brain in your hand, you would find it to be a soggy clump of gray matter, a bit like putty, weighing about 1.3 kg. How is it possible that this gray soggy stuff can give rise to the richness and depth of your conscious experience? This is known as the 'hard problem' of consciousness.

As a result, many eminent philosophers (such as David Chalmers and Thomas Nagel) and scientists like Christof Koch and Tononi have rejected the idea that consciousness is directly produced by brain processes. They have turned to the alternative view that it is actually a fundamental quality of the Universe.

This might sound far fetched, but think about the other 'fundamentals' in the Universe we take for granted, such as gravity and mass. Consciousness would have the same status as those.

Fundamental explanations

One of the reasons I'm in favor of this approach is that the idea of consciousness as a fundamental quality offers elegant solutions to many problems which are difficult to explain using the standard scientific model.

First, it can explain the relationship between the brain and consciousness. The brain does not produce consciousness, but acts as a kind of receiver which 'picks up' the fundamental consciousness that is all around us, and 'transmits' it into our own being.

Because the human brain is so sophisticated and complex, it is able to receive and transmit consciousness in a very intense and intricate way, so that we are (probably) more intensely and expansively conscious than most other animals.

One of the arguments for assuming that the brain produces consciousness is that, if the brain is damaged, consciousness is impaired or altered. However, this doesn't invalidate the idea that the brain may be a receiver and transmitter of consciousness. A radio doesn't produce the music that comes through it, but if it is damaged, its ability to transmit the music will be impaired.

The puzzle of altruism can also be explained. If, as many scientists believe, human beings are just genetic machines, only concerned with the survival and propagation of our genes, then altruism is difficult to account for.

It makes sense for us to be altruistic to people who are closely related to us genetically, but not so much to strangers, or to members of different species. In the latter cases, from the conventional point of view, there must be some benefit to us, even if we're not aware of it.

Perhaps being kind makes us feel good about ourselves, impresses other people, or encourages people to be kind to us in return.

But these explanations seem unable to explain the full range and depth of human altruism. If we are fundamentally selfish, why should we be willing to risk our own lives for the sake of others? Altruism is often instantaneous and spontaneous, particularly in crisis situations, as if it is deeply instinctive.

From a 'spiritual' perspective (which sees consciousness as fundamental), though, altruism is easy to explain. It is related to empathy.

Human shared fundamental consciousness means that it is possible for us to sense the suffering of others and to respond with altruistic acts. Since we share fundamental consciousness with other species, too, it is possible for us to feel empathy with — and to behave altruistically towards — them as well.

One of my main areas of interest as a psychologist is in what I call 'awakening experiences,' when human awareness intensifies and expands and we experience a sense of oneness with other human beings, nature or the world as a whole.

I see awakening experiences as encounters with fundamental consciousness, in which we sense its presence in everything around us, including our own selves. We experience a sense of oneness because oneness is the fundamental reality of things.

Conventional science also struggles to explain the powerful effect of mental intention and belief on the body (as illustrated by the placebo effect and the pain numbing effects of hypnosis). If the mind is just a byproduct of matter, it should not be able to influence the form and functioning of the body so profoundly.

That would be like saying that images on a computer screen can change the software or hardware inside the computer. But these effects are comprehensible if we presume that mind is more fundamental than the matter of the body, a more subtle and fuller expression of fundamental consciousness. As a result, it has the capacity to alter the functioning of the body.

I believe the idea of consciousness as a fundamental quality of the Universe has a great deal of weight. As I point out in my book *Spiritual Science*, it may be that the best way to understand the world is not through science or spirituality alone — but through an approach which combines them both.

Steve Taylor. 2018. Spiritual Science: Why Science Needs Spirituality to Make Sense of the World. *Watkins Publishing, ISBN: 1786781581*

Author: Steve Taylor, Senior Lecturer in Psychology at Leeds Beckett University.

http://bit.ly/2MSV95l

Harvard chemists' breakthrough in synthesis advances a potent anti-cancer agent

'Unprecedented achievement' provides sufficient quantities of a fully synthetic halichondrin molecule for clinical trials now underway

It's a feat three decades in the making: Harvard University chemists have achieved what a new paper calls a "landmark in drug discovery" with the total synthesis of halichondrin.

Known to be a potent anti-cancer agent in mouse studies, and found naturally in sea sponges -- though only ever in minuscule quantities -- the halichondrin class of molecule is so fiendishly complex that it had never been synthesized on a meaningful scale in the lab.

Researchers led by Yoshito Kishi, Morris Loeb Professor of Chemistry, *Emeritus*, in Harvard's Department of Chemistry and Chemical Biology, have now synthesized sufficient quantities of E7130, a drug candidate from the halichondrin class, to enable for the first time rigorous studies of its biological activity, pharmacological properties, and efficacy, all conducted in collaboration with researchers at Japanese pharmaceutical company Eisai.

The molecule has undergone unusually rapid development and is already being tested in a Phase I clinical trial in Japan, under a license from Harvard's Office of Technology Development (OTD) to Eisai. The company hopes to begin a second clinical trial in the United States in due course.

The Kishi Lab's results, driven to completion through an intense, three-year research collaboration with Eisai, are published today in *Scientific Reports*, an open-access Nature journal. The paper reports the total synthesis of the highly potent halichondrin molecule E7130 -- 11.5 grams of it, with 99.81% purity -- and characterizes its mode of action.

In preclinical studies, the research team has identified it not only as a microtubule dynamics inhibitor, as was previously recognized, but also as a novel agent to target the tumor microenvironment.

"We spent decades on basic research and made very dramatic progress," says Kishi, whose laboratory has, since 1978, received significant and sustaining support from the National Cancer Institute (NCI) of the National Institutes of Health to study the synthesis of natural products.

The structure of the complete E7130 molecule derived by total synthesis is particularly challenging to replicate because it has 31 chiral centers, asymmetrical points that must each be correctly oriented. In other words, there are roughly 4 billion ways to get it wrong.

When the natural product was first identified 33 years ago by Japanese researchers, it sparked immediate interest. "At that time, they realized the halichondrins looked exceedingly potent," recalls Takashi Owa, PhD, Chief Medicine Creation Officer and Chief Discovery Officer for Eisai's oncology business group, and a coauthor of the paper.

Over time, NCI investigators testing tiny amounts of it recognized that it was affecting the formation of microtubules, which are essential to cell division.

"Due to the very unique structure of the natural product, many people were interested in the mode of action, and the investigators wanted to do a clinical study," Owa explains, "but a lack of drug supply prevented them from doing it. So 30 years have passed, very unfortunately, but Prof. Kishi is a pioneer in this field."

Over the years, the Kishi Lab advanced methods of convergent synthesis, which enables complex molecules to be assembled from subunits, rather than constructed linearly.

Another innovation, now known as the Nozaki-Hiyama-Kishi reaction, protected the highly reactive functional groups while they were being assembled. And in 1992, Kishi and colleagues achieved the first total synthesis of a halichondrin molecule (halichondrin B). The process required a sequence of more than 100 chemical reactions and produced less than a 1% overall yield. It was a major achievement, however, and a simplified version of that molecule, eribulin, became a drug to treat metastatic breast cancer and liposarcoma, now marketed by Eisai.

Since then, Kishi's lab has been engaged in basic research on organic synthesis, including discovery and development of new reactions usable at a late stage of synthesis.

"In 1992, it was unthinkable to synthesize a gram-quantity of a halichondrin," Kishi says, "but three years ago we proposed it to Eisai. Organic synthesis has advanced to that level, even with molecular complexity that was untouchable several years ago. We are very delighted to see our basic chemistry discoveries have now made it possible to synthesize this compound at large scale."

"It's a really unprecedented achievement of total synthesis, a special one," says Owa. "No one has been able to produce halichondrins on a 10-gram scale -- one milligram, that's it. They have completed a

remarkable total synthesis, enabling us to initiate a clinical trial of E7130."

The team's *Scientific Reports* paper describes the results of studies conducted in vitro and in vivo, in animal models, that shed light on the molecule's complex mode of action. The team showed that E7130 can increase intratumoral CD31-positive endothelial cells and reduce alpha-SMA-positive cancer-associated fibroblasts, components of the tumor microenvironment that may be involved in the transformation to malignancy.

"Prof. Kishi's expertise provided us with such an exciting and unique opportunity to test the molecule in our systems," says Owa. "I have never experienced this kind of very efficient and rapid, successful collaboration. Just a three-year collaboration took this from the discovery stage to the clinical development of such a complex molecule, having a very unique mechanism and mode of action. To me this is a kind of track record in drug development."

"The collaboration between scientists at Eisai and Harvard is an example of academia and industry working together successfully to accelerate the development of a new class of therapeutics that may address important unmet medical needs," says Vivian Berlin, Managing Director of Strategic Partnerships in Harvard OTD. "The collaborative spirit and transparency of the relationship contributed enormously to the success of the project."

"Without OTD," Owa adds, "this collaboration could never have happened. Harvard OTD has been a core for bridging industry and Harvard researchers, and facilitating discussions about how to build a win-win relationship."

Research for the new publication, titled, "A landmark in drug discovery based on complex natural product synthesis," was conducted jointly by researchers at Harvard and Eisai. Harvard OTD has protected the intellectual property associated with this project, which is now exclusively licensed to Eisai for the commercial development of therapeutics.

https://nyti.ms/2Xkw7jM

The Damage of Dad-Shaming

More than half of the fathers in a national poll reported being criticized about their parenting decisions.

By Perri Klass, M.D. June 16, 2019

Two years ago, a national poll of parents showed that many mothers were very aware of being criticized for the parenting decisions, small and large, that make up daily life with children.

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Now the same poll has turned to fathers, and it turns out that they also frequently feel judged and found wanting. In this national sample of fathers of children up to the age of 13, 52 percent of the fathers surveyed said that they had been criticized for their parenting.

Sarah Clark, the co-director of the C.S. Mott Children's Hospital National Poll on Children's Health at the University of Michigan, said that ever since the poll of mothers, she had been curious about whether the same factors involved in what is known as mom-shaming also play out with fathers.

"I think there was a sense that it was a mom phenomenon," she said. "This poll shows it's really not."

As with the mothers, much of the criticism the fathers recalled was coming from close to home: 44 percent from the child's other parent, 24 percent from grandparents. And both mothers and fathers were most likely to be criticized around discipline (67 percent of the dads), followed by nutrition (43 percent).

People volunteer advice to parents all the time, said Dr. David L. Hill, an adjunct assistant professor of pediatrics at the University of North Carolina School of Medicine, and the author of "Dad to Dad:

Parenting Like a Pro." But unless it's been requested, that advice is rarely welcome.

"If somebody does offer advice, our tendency is to be angry — somebody has taken something very important to us, which is how we raise our children and suggested that we're doing it wrong, and that is immensely inflammatory," he said. And it sometimes makes fathers feel that it's not worth trying.

The report made Dr. Craig Garfield recall a moment when he was a resident, pushing his 1-year-old in a stroller, with the child in his customary preferred position, his leg bent back. One of his professors — an expert who had recently lectured the residents on child abuse — came up to him and said: "Look, your child is uncomfortable in the stroller. Straighten his leg out."

"It was quite a moment for me," said Dr. Garfield, now a professor of pediatrics at Northwestern University and Lurie Children's Hospital, and the co-author of both versions of the American Academy of Pediatrics clinical reports on the role of fathers. "Here was this international expert and I was getting scolded on the street."

Dr. Garfield works with expectant fathers and encourages them to get closely involved with their babies right from the beginning.

Geoffrey Brown, a developmental psychologist in the department of human development and family science at the University of Georgia, who has studied fathers of young children, described the phenomenon of "maternal gatekeeping — mothers play a large role in determining fathers' roles." Mothers can encourage and they can discourage, he said, and sometimes both at once, with mothers asking fathers to do something and then not liking the way it gets done.

In one of his research studies, looking at fathers and 3-year-olds, the effects of the father's involvement on the child's attachment varied depending on whether the involvement was play or caregiving, and whether it happened on workdays or non-workdays.

Research has shown that fathers' involvement has lots of benefits, Dr. Garfield said. "We know that fathers use different words than mothers, and that helps develop the child's expressive vocabulary, they use different language when out and about in the world." Fathers are more likely to engage in "rough and tumble" play, he said, and they often keep changing the rules, which can be very exciting for children and helps them learn.

In the poll, 32 percent of the fathers had been criticized for being too rough, and 32 percent for not paying attention to their children. "Some things are unique to dads," Ms. Clark said. "Being too rough and not paying attention play into some of the gender stereotypes still present in our society."

Fathers tend to engage with their children in more physically active ways, Dr. Brown said, and tend to take more risks and encourage exploration. "They might be engaging with their kids in a way, not just not harmful but actually helpful, but different from mothers."

Mothers sometimes note with irritation that fathers may get a great deal of praise just for showing up or for getting a child dressed. But it's insulting when fathers "face the assumption that we're babysitting rather than parenting," Dr. Hill said. "You wouldn't praise a woman for getting the barrettes in straight." A father might hear something like, "Wow, her hair is combed, congratulations!"

"I think we have to be aware of praising rudimentary success as almost a form of insult," he said. "As a society, we need to have high expectations for dads and help them to meet them."

Sometimes, of course, fathers (like mothers) really do have mistaken ideas about discipline, and fathers may feel their role is to deal out penalties. Dr. Hill said that he often starts conversations about spanking with the question, "What are you trying to do

here?" Sometimes a parent will reflect, he said, and conclude that physical discipline is not, in fact, working very well.

Where there is any chance that a child may be in danger, or any question of abuse, you have to intervene. Dr. Hill suggested that one way to help before things go too far may be to offer a hand: "Hey, looks like you're having a hard time, can I help?"

Criticism, of course, can sometimes have the desired effect. "One of the things I thought was very heartening," Dr. Hill said, was that almost half of the fathers who reported being criticized said that they either changed their behavior in response or sought out more information. "They took this moment to educate themselves."

But being criticized made some fathers want to be less involved, especially when the negative voice was coming from the child's other parent. "I would encourage parents not to feel they have to solve an impasse on their own," Dr. Hill said. "There are all sorts of third parties that can help, counselors, pediatricians and other providers."

There are also lessons in the poll for pediatricians — like me — and for teachers and day care providers. One in 10 fathers reported they had felt that a child's teacher or health care provider assumed they were not very knowledgeable about their child, and about a quarter said they felt excluded from those communications.

"Even pediatricians are often operating from an unconscious bias that dads are going to be less tuned in to their children's behavior," Dr. Hill said. "Even as a dad, I have to make a conscious effort to turn to the dad."

Sending signals that fathers are somehow less qualified in their knowledge and ability to parent "can really undermine both their confidence and their level of engagement," Ms. Clark said.

"The fathers I come across are all problem solvers," Dr. Garfield said. "They see a problem — the child's behavior, or mom's unhappy — and they want to find a way to fix it."