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Are Probiotics Safe? We Really Don't Know

Have you been asked by patients about taking probiotics? What do you base your answer on?

Arefa Cassoobhoy, MD, MPH

Hello. I'm Dr Arefa Cassoobhoy, a practicing internist, Medscape advisor, and senior medical director for WebMD. Welcome to Medscape Morning Report, our 1-minute news story for primary care. Have you been asked by patients about taking probiotics? What do you base your answer on? As supplements, rather than drugs, probiotics aren't subjected to the same degree of scrutiny by regulators.

It turns out that very few probiotic or prebiotic studies report any data at all on specific harms. In a recent meta-analysis of nearly 400 randomized trials, only 6% adequately reported safety data. This includes the number of participant withdrawals related to harms, and the number and type of adverse events.

This leaves clinicians in a difficult position. Although research shows promise for probiotics in preventing and treating some gastrointestinal conditions, it's impossible to tell patients that these products are completely safe.

In fact, from what we know so far, the only answer we can give with confidence is that we really don't know.

http://bit.ly/2vyNLRw

More sensitive blood test diagnoses heart attacks faster

Circulation Journal Report

DALLAS - A new test to assess a whether or not someone is having a heart attack upon arriving in the emergency room was safe and effective, ruling out heart attack in emergency room patients faster than a conventional method, according to new research in the American Heart Association's journal Circulation.

The new high-sensitivity blood test for cardiac troponin, given in a hospital emergency room, was also found to be safe and effective. When patients present to emergency rooms with heart attack symptoms, doctors assess them in part by using a cardiac troponin test to measure a protein released into the blood when the heart is damaged.

"We did not miss any heart attacks using this test in this population," said lead author Rebecca Vigen, M.D., M.S.C.S., a cardiologist at the University of Texas Southwestern Medical Center. "The test also allowed us to determine faster that many patients who had symptoms of a heart attack were not having a heart attack than if we had relied on the traditional test."

Recently the United States Food and Drug Administration approved a high-sensitivity troponin test already used in Europe. The researchers developed a procedure for assessing the results of the new test and compared it to existing practice using a conventional troponin test, which takes three hours to complete. Study participants were 536 patients admitted to an emergency room with heart attack symptoms, including chest pains and shortness of breath.

The new procedure successfully "ruled out" 30 percent of patients immediately and an additional 25 percent at one hour. By three hours, the new procedure ruled out heart attack in 83.8 percent of patients compared with 80.4 percent using the conventional test.

"We anticipate that this procedure will allow many patients with chest pain to be given a 'yes' or 'no' diagnosis of whether they are having a heart attack faster," said Vigen, who hopes clinicians from other institutions will learn from these results.

Co-authors are Patricia Kuscher, M.T., A.S.C.P.; Fernabelle Fernandez, M.L.S., A.S.C.P.; Amy Yu, M.L.S., A.S.C.P.; Bryan Bertulfo, M.L.S., A.S.C.P.; Ibrahim Hashim, M.Sc; Kyle Molberg, M.D.; Deborah Diercks, M.D., M.P.H.; Jeffery Metzger, M.D., M.B.A.; Jose Soto, M.D.; Dergham Alzubaidy, M.D.; Lorie Thibodeaux, M.H.A.; Jose Joglar, M.D.; James de Lemos, M.D.; and Sandeep Das, M.D., M.P.H. Author disclosures are on the manuscript.

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http://bit.ly/2KFnxSa

If you're a woman having a heart attack, insist on a female physician

New study coauthored by Harvard Business School professor Laura Haung says it's a matter of life or death

If you're a woman and having a heart attack (what's called in medical parlance an "acute myocardial infarction" or AMI), do your best to make sure you're treated by a female physician. It's literally a matter of life or death.

That's the takeaway of new research by Harvard Business School associate professor Laura Huang (lhuang@hbs.edu) and her coauthors, Brad Greenwood of the University of Minnesota-Twin Cities (wood@umn.edu) and Seth Carnahan of Washington University in St. Louis (seth.carnahan@wustl.edu), in an article to be published next week online in the Proceedings of the National Academy of Sciences (PNAS).

According to their findings in "Patient-Physician Gender Concordance and Increased Mortality Among Female Heart Attack Patients," of more than 500,000 heart attack patients admitted to hospital emergency departments in Florida between 1991 and 2010, female patients treated by male physicians were less likely to survive than patients of either gender treated by female physicians or male patients treated by male physicians. In addition, they found that survival rates among female patients treated by male physicians improved with an increase in the percentage of female physicians in the emergency department and an increase in the number of female patients previously treated by the physician.

"These results," they write, "suggest a reason why gender inequality in heart attack mortality persists: Most physicians are male, and male physicians appear to have trouble treating female patients. The fact that gender concordance (that is, men treating men or women treating women) correlates with whether a patient survives a heart attack has implications for theory and practice:

Medical practitioners should be aware of the possible challenges male providers face when treating female AMI patients--for example, a propensity among women to delay seeking treatment and the presentation of symptoms that differ from those of men.

Although mortality rates for female patients treated by male physicians decrease as the male physician treats more female patients, this decrease may come at the expense of earlier female patients. Given the cost of male physicians' learning on the job, it may be more effective to increase the presence of female physicians within the emergency department.

All this underscores the need to update the training physicians receive to ensure that heart disease is not simply cast as a "male" condition, which is often taken as conventional wisdom in both the media and the medical community.

Huang and her colleagues conclude that there is still work to be done to understand the precise mechanism as to why gender concordance appears critical, particularly for female patients. "Such research might include experimental interventions, or tests of more targeted training, to examine how exposing male physicians more thoroughly to the presentation of female patients might impact outcomes," they say.

Another variable they cite, omitted in this study, is the previous finding by other researchers that female physicians tend to perform better than male physicians across a wide variety of ailments. "If female patients tend to be more challenging for male and female doctors to diagnose and treat, the patterns we document may reflect the fact that the most skillful physicians (i.e., female physicians) provide the highest return to their skills when treating the most challenging patients (i.e., female patients)."

"Finally," they write, "interesting opportunities for research exist in an examination of the role played by residents, nurses, and other physicians who may be present or provide information to the supervising physician...future work that considers these supporting figures would advance our understanding of how coordination between [all] healthcare providers might influence the relationship between physician-patient gender concordance and patient survival."

http://bit.ly/2KGKPaa

Earth at risk of heading towards 'hothouse Earth' state

Keeping global warming to within 1.5-2°C may be more difficult than previously assessed, according to researchers.

An international team of scientists has published a study in Proceedings of the National Academy of Sciences (PNAS) showing that even if the carbon emission reductions called for in the Paris Agreement are met, there is a risk of Earth entering what the scientists call "Hothouse Earth" conditions. A "Hothouse Earth" climate will in the long-term stabilize at a global average of 4-5°C higher than pre-industrial temperatures with sea level 10-60 m higher than today, the paper says. The authors conclude it is now urgent to greatly accelerate the transition towards an emission-free world economy.

"Human emissions of greenhouse gas are not the sole determinant of temperature on Earth. Our study suggests that human-induced global warming of 2°C may trigger other Earth system processes, often called "feedbacks", that can drive further warming - even if we stop emitting greenhouse gases", says lead author Will Steffen from the Australian National University and Stockholm Resilience Centre. "Avoiding this scenario requires a redirection of human actions from exploitation to stewardship of the Earth system."

Currently, global average temperatures are just over 1°C above pre-industrial and rising at 0.17°C per decade.

The authors of the study consider ten natural feedback processes, some of which are "tipping elements" that lead to abrupt change if a critical threshold is crossed. These feedbacks could turn from being a "friend" that stores carbon to a "foe" that emits it uncontrollably in a warmer world. These feedbacks are: permafrost thaw, loss of methane hydrates from the ocean floor, weakening land and ocean carbon sinks, increasing bacterial respiration in the oceans, Amazon rainforest dieback, boreal forest dieback, reduction of northern hemisphere snow cover, loss of Arctic summer sea ice, and reduction of Antarctic sea ice and polar ice sheets.

"These tipping elements can potentially act like a row of dominoes. Once one is pushed over, it pushes Earth towards another. It may be very difficult or impossible to stop the whole row of dominoes from tumbling over. Places on Earth will become uninhabitable if "Hothouse Earth" becomes the reality," adds co-author Johan Rockström, Executive Director of the Stockholm Resilience Centre and incoming co-Director of the Potsdam Institute for Climate Impact Research.

Hans Joachim Schellnhuber, Director of the Potsdam Institute for Climate Impact Research, says, "We show how industrial-age greenhouse gas emissions force our climate, and ultimately the Earth system, out of balance. In particular, we address tipping elements in the planetary machinery that might, once a certain stress level has been passed, one by one change fundamentally, rapidly, and perhaps irreversibly. This cascade of events may tip the entire Earth system into a new mode of operation."

"What we do not know yet is whether the climate system can be safely 'parked' near 2°C above preindustrial levels, as the Paris Agreement envisages. Or if it will, once pushed so far, slip down the slope towards a hothouse planet. Research must assess this risk as soon as possible."

Cutting greenhouse gases is not enough

Maximizing the chances of avoiding a "Hothouse Earth" requires not only reduction of carbon dioxide and other greenhouse gas emissions but also enhancement and/or creation of new biological carbon stores, for example, through improved forest, agricultural and soil management; biodiversity conservation; and technologies that remove carbon dioxide from the atmosphere and store it underground, the paper says. Critically, the study emphasizes that these measures must be underpinned by fundamental societal changes that are required to maintain a "Stabilized Earth" where temperatures are ~2°C warmer that the pre-industrial.

"Climate and other global changes show us that we humans are impacting the Earth system at the global level. This means that we as a global community can also manage our relationship with the system to influence future planetary conditions. This study identifies some of the levers that can be used to do so," concludes co-author, Katherine Richardson from the University of Copenhagen.

http://bit.ly/2OW2PAY

Comprehensive pediatric CAR T guidelines developed by MD Anderson and PALISI

Treatment guidelines for managing chimeric antigen receptor cell therapy for children with acute lymphoblastic leukemia

Almost one year after the U.S. Food and Drug Administration (FDA) approval of chimeric antigen receptor (CAR) T-cell therapy for children with acute lymphoblastic leukemia (ALL), researchers at The University of Texas MD Anderson Cancer Center and the Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI) today published treatment guidelines for managing the treatment in the online issue of Nature Reviews Clinical Oncology. These guidelines outline lessons learned by leading experts in various fields to identify early signs and symptoms of treatment-related toxicity and detail ways in which to manage it.

CAR T-cell therapy involves removing patient T cells, re-engineering them, and introducing them back into the body, where they attack cancer cells. The FDA approved the first CAR T-cell therapy for children and young adults with ALL last year. Ongoing research aims to expand its use for other cancers.

"CAR T-cell therapy has been associated with remarkable response rates for children and young adults with ALL, yet this innovative form of cellular immunotherapy has resulted in unique and severe toxicities which can lead to rapid cardiorespiratory and/or neurological deterioration," said Kris Mahadeo, M.D., associate professor of Pediatrics and Chief of Stem Cell Transplant and Cellular Therapy at MD Anderson. "This novel therapy requires the medical vigilance of a diverse multi-disciplinary team and associated clinical infrastructure to ensure optimal patient outcomes."

As CAR T-cell therapy becomes more widely used, treatment guidelines, comprehensive training of multi-disciplinary staff, and other measures should facilitate the appropriate management of toxicities that may occur following this new treatment, added Mahadeo.

MD Anderson's CAR T-cell-therapy-associated Toxicity (CARTOX) program collaborated with PALISI and its Hematopoietic Stem Cell Transplantation (HSCT) sub-group in creating the comprehensive guidelines for treating children with cancer receiving CAR T-cell therapy. By bringing together experts from many areas, including pediatric intensivists, pharmacy, neurology, and translational immunotherapy research, the guidelines offer key learnings to providers and aim to help improve the patient experience and outcome.

"CARTOX, which oversees care for MD Anderson CAR T-cell therapy patients, is the first stand-alone immune effector cellular therapy program to earn accreditation from the Foundation for the Accreditation of Cellular Therapy (FACT)," said Elizabeth Shpall,

M.D., professor of Stem Cell Transplantation and Cellular Therapy and one of the senior authors on the Natures Reviews Clinical Oncology paper. "The program provides oversight for more than 20 active immune effector cell research protocols and two approved standard of care therapies at MD Anderson, and it is clear these new guidelines will serve as an important new model for care of CAR T-cell patients."

In 2017, MD Anderson's CARTOX Program published guidelines in Nature Reviews Clinical Oncology on management of adult patients receiving CAR T-cell therapy. However, early signs and symptoms of toxicity in children brought attention to pediatric-specific monitoring including escalation of care based on parent and caregiver concerns.

Some examples of the recommendations include: * Monitoring for cytokine release syndrome (CRS) using pediatric normal ranges for organ function. * Promptly addressing parent and/or caregiver concerns as early signs or symptoms of CRS can be subtle and best recognized by those who know the child best.

MD Anderson team members who collaborated on development of the guidelines included Elizabeth Shpall, M.D.; Katy Rezvani, M.D., Ph.D.; and Partow Kebriaei, M.D.; all of the Department of Stem Cell Transplantation and Cellular Therapy; Sattva Neelapu, M.D., of the Department of Lymphoma and Myeloma; Sajad Khazhal, M.D.; David McCall, M.D.; Demetrios Petrepolous, M.D.; Joan O'Hanlon Curry; Sarah Featherston; Jessica Fogelsong, M.D.; Lisa Hafemeister; Cathy Nguyen; Rodrigo Mejia, M.D.; and John Slopis, M.D.; all of the Division of Pediatrics; and Alison Gulbis; and Maria Mireles, Pharm.D.; of the Department of Pharmacy.

Other participating institutions included the Keck School of Medicine, University of Southern California, Los Angeles; University of Pennsylvania Perelman School of Medicine, Philadelphia; University of Washington Seattle Children's Hospital; George Washington University and Children's National, Washington D.C.; Baylor College of Medicine, Houston; Dana-Farber Cancer Institute, Harvard University, Boston; Weill Cornell Medical College Presbyterian Hospital, New York; University of Minnesota Masonic Children's Hospital, Minneapolis; Duke Children's Hospital, Duke University, Durham, N.C.; Nationwide Children's Hospital, Ohio State University, Columbus; St. Jude's Children's Research Hospital, Memphis, Tenn.; and Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, N.Y.

http://bit.ly/2np1FBv

CAR-T May Be a Silver Bullet Against Cancer—and Here's What Else It Can Do

Can potentially open up the application of this anti-cancer technology to the treatment of a much wider range of diseases, including autoimmunity and transplant rejection

By Shelly Fan

CAR-T is the super-soldier serum of cell therapy: you pluck out an immune cell soldier, inject it with a dose of new genes, and send the enhanced cell back into the host body—bam! Suddenly the host has a slew of Captain America-esque superpowered cells ready to tackle cancer and all sorts of cellular enemies.

Without doubt, CAR-T is set to overhaul cancer therapy. Last year several variants of the immunocellular technique earned the FDA's nod of approval for blood cancers; with big pharma pouring in billions to develop the technology, more are certainly to come.

Yet a small group of ingenious scientists are already thinking ahead: can CAR-T do more?

To Dr. Michael Milone at the University of Pennsylvania, the answer is a clear yes: there's the potential to "open up the application of this anti-cancer technology to the treatment of a much wider range of diseases, including autoimmunity and transplant rejection," he said.

It's likely to trigger "a next wave in cellular immunotherapy," said Dr. Everett Meyer at Stanford Medical Center, who uses the technology to help islet transplants. Islets are clusters of insulin-producing cells that are destroyed by immune cells in Type I diabetes. With CAR-T ready for autoimmune trials by 2019, here's what's in the works.

Civil War

In cancer therapies, a type of immune cell called killer T cells are extracted through a process similar to dialysis and given genes that help them recognize various types of blood cancers.

The overwhelming culprit of these cancers? B cells. Normally these cells are a critical component of the immune system: they make and deploy antibodies, which hunt down invasive bacteria and nip them in the bud.

But when B cells go rogue, they trigger multiple types of deadly blood cancers. What's more, B cells can sometimes pump out antibodies that mistake healthy tissue for infections. In autoimmune diseases, antibodies tag onto normal cells, mislabeling them as dangerous, which in turn provokes a T cell onslaught. These autoimmune attacks lead to Type I diabetes, in which insulin-producing cells are slaughtered by the body's own immune cells, and lupus, where tissues from the lung, heart, brain, and kidneys are caught in friendly fire.

Currently there are no cures for autoimmune disorders. For severe cases, immunosuppressant drugs can help, but they increase the chances of infections and cancer.

Back in 2016, Milone's team had a eureka moment: in traditional CAR-T therapy, T cells are often engineered to target cancerous B cells. What if the same super-soldiers can hunt down autoimmune-causing B cells?

"We thought we could adapt this technology that's really good at killing all B cells in the body to target specifically the B cells that make antibodies that cause autoimmune disease," Milone said at the time.

"Targeting just the cells that cause autoimmunity has been the ultimate goal for therapy in this field," added study author Dr. Aimee Payne.

In a proof-of-concept, the team took on pemphigus vulgaris (PV), an autoimmune condition that causes the skin to gradually peel off and is almost always fatal. The team first figured out which B cells were producing the disease-causing antibodies. Like most cell types, B cells have specific protein "barcodes" on their surface—the PV-causing B cell subtype has a particular protein dubbed Dsg3 (yeah, biologists aren't the best at giving catchy names to proteins).

Bingo, target acquired. Next, the team constructed a protein "claw" that grabs onto Dsg3. This claw is a "chimeric autoantibody receptor"—or the "CAR" in CAR-T. Armed with the claw, the genetically-enhanced T cells were then infused back into the bodies of mice.

The result was shockingly positive. "We were able to show that the treatment killed all the Dsg3-specific B cells, a proof-of-concept that this approach works," without harming other B cells, Payne said.

The best part about the treatment? It's plug-and-play: change the CAR, and it's possible to target any type of B cell—and potentially treat any autoimmune disorder caused by antibodies gone wild.

New T on the Block

So far, the T immune cells used in CAR-T have all been killer T cells. Yet these killers are only a fraction of the immune cell zoo. The new contender? T regulatory cells, or Tregs.

Tregs are the killjoys of the immune system. They shut the party down before it gets too rowdy, thus inhibiting immune attacks from getting out of control. Autoimmune diseases often are caused or exacerbated by ineffective Tregs. The reason is unclear: sometimes they have a genetic deficit, or they might resist activation because of something in their environment. Regardless, Tregs fail in autoimmune disorders—which makes them promising candidates for CAR-T.

At the forerunner of Treg enhancement is Txcell, a startup based in Valbonne, France. Two years ago, the company began experimenting with giving Tregs their own protein claws against inflammation.

It's a big step away from traditional CAR-T. Rather than targeting a specific barcode on a cell, TxCell engineers Tregs that home to a particular type of tissue ravaged by autoimmune attacks.

"For example," explained Stepane Boissel, CEO of TxCell, "if you have multiple sclerosis, the antigen is specifically present in the brain. If you have Crohn's disease, the antigen has to be in the guts. In fact, given the large number of relevant antigens, we believe our technology has possibly a larger potential than CAR-T cell therapy in oncology."

Far along the TxCell pipeline is an engineered Treg that helps treat Type I diabetes, in which immune cells attack insulin-releasing cells in the pancreas. Without insulin, the body struggles to maintain normal blood sugar levels, leading to diabetes.

Dr. Megan Levings, a researcher at the University of British Columbia in Vancouver, collaborates with TxCell on the project. In 2016, Levings and team published a paper showing that Tregs enhanced with CAR "protein claws" could help dampen the immune response to organ transplants.

"This work provides what we believe is the first proof-of-concept that CAR Tregs have the potential to be used therapeutically," Levings' team wrote at the time.

Just last year, Meyers backed up these data with a new study showing that engineered Tregs allow better islet transplantation in mice. We clearly show that CAR-T with Tregs is a "powerful new platform that's very flexible for many immune diseases," said Meyers.

"On paper, that's a very powerful, very directed, very targeted kind of therapy," said Boissels. "Again, we have to be cautious, but if it works, there is a very large panel of diseases we can potentially target. If you combine all autoimmune disorders…the field of autoimmune disease is probably the largest pharmaceutical market in the world."

TxCell is aiming to launch the first CAR-T trial for boosting organ transplants by next year, which will be the first time CAR-Tregs are tested in humans. Although it may not be entirely smooth sailing, previous CAR-T trials for cancer could help pave the way to approval. CAR-T for autoimmune is still at an early stage. And without long-term data, it's hard to say whether suppressing the suppressors could lead to side effects like infections and cancer.

But for those suffering from autoimmune disorders and organ rejection, CAR-Tregs represents an entirely new possibility that could revolutionize treatment as CAR-T is doing for cancer.

That's definitely something to be excited about.

http://bit.ly/2MxN812

This Unusual Meteorite Flew Around in Space Before Earth Was Born

Newly discovered, 4.6-billion-year-old meteorite that formed just before the solar system did is helping scientists learn how it all came together

By Kimberly Hickok, Staff Writer | August 6, 2018 07:23am ET

Approximately 4.5 billion years ago, the catastrophic explosion of a massive star, a supernova, caused an immense cloud of cosmic dust and gas to come together and form our solar system. But exactly how the planets were built remains somewhat of a mystery to scientists.

The NWA 11119 meteorite is about the size of a baseball and is estimated to be 4.6 billion years old. The light color and green crystals make this meteorite particularly extraordinary. **UNM Newsroom**

Now, a newly discovered, 4.6-billion-year-old, sparkly, green meteorite that formed just before that explosion is helping scientists learn more about how the solar system's planets were pieced together. The remarkable, baseball-size space rock, called Northwest Africa (NWA) 11119, was acquired by a meteorite dealer in Africa in 2016. That dealer sent the specimen to Carl Agee, a planetary geologist and

meteorite curator at the University of New Mexico. Agee wasn't sure if the rock was a meteorite (which would mean it came from space), so he asked his doctoral student Poorna Srinivasan to analyze the object.

At first, both Agee and Srinivasan were skeptical that the rock had come from beyond our planet. "We did not think this rock was a meteor at all. We thought it was from Earth," Srinivasan told Live Science. But after closer examination, she said, "we saw that this could, in no way, be from Earth." While the rock closely resembled volcanic rocks on Earth, its chemical composition indicated it was definitely from space, and it wasn't just an ordinary meteorite, the researchers found.

NWA 11119 is an igneous meteorite, which means it was formed by the cooling and solidification of magma or lava (which is what magma is called once it reaches a planet's surface). At 4.6 billion years old, NWA 11119 is the oldest igneous meteorite ever discovered. (Srinivasan explained that several nonigneous meteorites are even older.)

Large silica crystals, called tridymite, account for about 30 percent of NWA 11119. That amount of tridymite is comparable to what's found in volcanic rocks on Earth, but it's unheard of in meteorites, Srinivasan said in a University of New Mexico statement.

Overall, the composition of NWA 11119 is strikingly similar to the material that makes up Earth's crust, the outer layer of rock that forms a solid shell around the planet. That's why the researchers suspect that NWA 11119 is a crustal rock from an asteroid with a crust layer that formed in a way similar to how Earth's crust formed.

Additional chemical analyses revealed that the meteorite closely resembled two other unusual meteorites — NWA 7235 and Almahata Sitta — suggesting that all three space rocks may have come from the same parent body, Srinivasan said.

There is still much scientists don't understand about how planets are built, but a discovery like this one can help researchers understand "what an earlier version of Earth might have looked like," Srinivasan said.

"There's still so much to learn about how Earth's crust could have formed," she said. "We just scraped the surface here."

Srinivasan is the lead author on the study describing NWA 11119, published yesterday (Aug. 2) in the journal Nature Communications.

http://bit.ly/2OZCzW7

The Lancet Child & Adolescent Health: Catch-up HPV vaccine effective for women aged up to 20 years, US study suggests

US study confirms effectiveness of quadrivalent human papillomavirus (HPV) vaccine in women aged up to 20 years who receive all three doses, but more research is needed in women aged 21-26 years.

For women aged 14-20 years, catch-up HPV vaccination - offered if American women miss the recommended vaccination series at 11-12 years - is effective against the risk of important cervical precancers if women receive all three doses, according to a population case-control study of over 25000 people published in The Lancet Child & Adolescent Health journal.

The study analysed cases of CIN2+ or CIN3+ (cervical intraepithelial neoplasia - abnormal growth of cells on the surface of the cervix that could potentially lead to cervical cancer) in a population of women and girls in California (USA).

In the USA, HPV vaccination is recommended for girls aged 11-12. For those who did not receive the vaccine at this age, catch-up vaccination is recommended for girls and women aged 13-26 years. The vaccine is approved as a three-dose series, and the US Centers

for Disease Control and Prevention also allows for a two-dose series for girls aged 9-14.

However, rates of adolescent HPV vaccination are relatively low in the USA, with less than half of girls aged 13-17 years up to date with the HPV vaccine series. [1]

The findings of the new study suggest catch-up with the full three-dose series for girls and women who receive the first dose at age 14-20 years will offer significant protection. However, they find that more research is needed to confirm the effectiveness of catch-up vaccination in older women aged 21-26 years.

Importantly, the study looked at the effectiveness of the quadrivalent HPV vaccine, and not of the more recently introduced nonavalent HPV vaccine, which is anticipated to prevent more CIN2+ cases than the quadrivalent HPV vaccine. Therefore, further research, including in women aged over 21 years, will be important as new vaccines become more widely used.

The study included 4357 women with CIN2+ or CIN3+ who were aged 26 or younger when the quadrivalent HPV vaccine was introduced in 2006. For each case, five age-matched controls without CIN2+ or CIN3+ were randomly selected (21773). All women were enrolled at Kaiser Permanente North California. A total of 2837 women enrolled in the study had received at least one dose of the vaccine between 2006 and 2014.

The strongest protection against CIN2+ and CIN3+ was identified for women who had received at least three vaccine doses and had received their first dose aged 14-17 years, or aged 18-20 years. No significant protection was found in women who received their first dose aged 21 years or older, or who received fewer than the full three dose in the series.

"In comparison to other countries, HPV vaccine uptake in the US has been relatively low. Our findings show that girls and women who did not receive the full vaccine series at age 11-12 can still benefit from significant protection if they receive the full three doses of vaccine by the age of 20. The evidence suggests that protection is strongest the earlier the vaccine is initiated, and after the age of 21, the evidence of effectiveness is unclear. Further research in other settings, and using the recently introduced nonavalent vaccine, will now be needed to assess the effectiveness of vaccinating women aged 21-26 years," says lead author Michael J. Silverberg, a research scientist with Kaiser Permanente Northern California's Division of Research, Oakland (USA). [2]

The authors note that only 23 women were diagnosed with cervical cancer in the study, of which only 3 had had prior HPV vaccination. All three women had received at least three doses, and all were 21 or older at the age of the first dose. However, the small numbers limit the researchers' ability to quantify the effect of the HPV vaccine on cervical cancer incidence, rather than the composite outcomes of CIN2+ and CIN3+, which includes both cancer and precancerous lesions.

Additionally, the authors note that the study was conducted in a single health-care setting, meaning that it may only be generalizable to other integrated health care settings and insured women in the area, which may not represent the most at-risk populations. The study did not look at the effect of the HPV vaccine on other clinically important outcomes such as low-grade dysplasia (i.e., CIN1), persistent HPV infection, or genital warts.

Writing in a linked Comment, Sarah Dilley and Warner Huh, Division of Gynecologic Oncology, University of Alabama, Birmingham (USA) advise caution before abandoning the practice of catch-up vaccination in women aged over 21 years: "The results of this study confirm existing research which showed that the HPV vaccine is most effective when given at younger ages, but no benefit was found in patients older than 21 years. Efforts towards increasing HPV vaccine uptake should be focused on younger adolescents--with

a priority on vaccinating children aged 11-12 years - and providing catch-up dosing for older adolescents. However, in the setting of low rates of HPV vaccination in the USA, the importance of catch-up dosing in young women should not be ignored. Given that prospective efficacy studies have shown benefits for catch-up vaccination up to at least age 26 years, more data is needed before abandoning this practice."

Peer-reviewed / Observational study / People

NOTES TO EDITORS

The study was funded by the US National Cancer Institute

The labels have been added to this press release as part of a project run by the Academy of Medical Sciences seeking to improve the communication of evidence. For more information, please see: http://www.sciencemediacentre.org/wp-content/uploads/2018/01/AMS-press-release-labelling-system-GUIDANCE.pdf if you have any questions or feedback, please contact The Lancet press office pressoffice@lancet.com

[1] CDC data (2016) https://www.cdc.gov/mmwr/volumes/66/wr/mm6633a2.htm

[2] Quote direct from author and cannot be found in the text of the Article.

http://bit.ly/2AYNZ9J

The sun should not set twice before hip fracture repair

Optimal window of 24 hours to reduce mortality after hip surgery in medically stable older patients

Optimal timing to reduce mortality after hip surgery in medically stable older patients is on the day of admission or the following day, according to a large study published in CMAJ (Canadian Medical Association Journal).

In Canada, about 30 000 older adults are admitted to hospital each year with hip fracture. They are at increased risk of death, with about 5% of women and 10% of men dying within 30 days. Canadian Health Ministers have set 48 hours from admission as a standard for 90% of hip fracture surgeries. However, the appropriate timing of hip fracture surgery remains a matter of debate, with some research indicating an optimal window of 24 hours.

"Our study was concerned with effects of possible changes in policy for the timing of surgery on mortality in the population of patients with hip fracture in Canada," says lead author, Prof. Boris Sobolev, School of Population and Public Health, the University of British Columbia, Vancouver, BC.

Researchers from Canada, the United Kingdom and the United States analyzed data from the Canadian Institute for Health Information on nearly 140 000 patients aged 65 years or older who had surgery for a first-time hip fracture at 144 hospitals in Canada (38 teaching and 106 community hospitals). The majority (74%) were women and almost half were older than 85 years.

The authors asked how postoperative mortality would change if the same patient population were to undergo surgery on the day of admission, on inpatient day 2, day 3, or after day 3, as would be done in a randomized trial. Previous studies had, in contrast, compared mortality among patients with various observed times to surgery.

The authors project an additional 11 deaths for every 1000 hip fracture surgeries if all surgeries in medically stable patients were done after inpatient day 3 instead of on admission day.

"Our findings allow us to infer a critical point for the timing of hip fracture repair. We suggest that clinicians, administrators, and policy-makers 'not let the sun set twice' on medically stable older adults before their hip fracture repair," says Dr. Pierre Guy, an orthopedic surgeon and a principal investigator in this study.

"We estimate that 16.5% of in-hospital deaths currently occurring in patients delayed for more than two days are avoidable by adopting the 'don't let the sun set twice' policy for hip fracture patients," he says.

The "two sunsets" recommendation is stricter than the current 48-hour standard and places the emphasis of managerial efforts on ensuring timely access to the operating room for patients whose surgery might be delayed due to late admission or hospital transfer.

Visual abstract: http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.171512/-/DC2

The study was conducted by researchers from University of British Columbia, University of Manitoba, Winnipeg, Manitoba; McGill University, Montreal, Quebec; University of

Alberta, Edmonton, Alberta; University of Toronto, Toronto, Ontario; Dalhousie University, Halifax, Nova Scotia; Vancouver Coastal Health Research Institute; King's College London, London, United Kingdom; and William Beaumont Army Medical Center, El Paso, Texas, United States.

It was funded by the Canadian Institutes of Health Research (CIHR).

"Mortality effects of timing alternatives for hip fracture surgery" is published August 7, 2018.

http://bit.ly/2M5yWQK

Largest haul of extrasolar planets for Japan

Confirmation of exoplanets and solar systems may shed light on our place in the cosmos

Forty-four planets in solar systems beyond our own have been unveiled in one go, dwarfing the usual number of confirmations from extrasolar surveys, which is typically a dozen or less. The findings will *improve* our models of solar systems and may help researchers investigate exoplanet atmospheres. Novel techniques developed to validate the find could hugely accelerate the confirmation of more extrasolar planet candidates.

An international team of astronomers pooled data from U.S. space agency NASA's Kepler and the European Space Agency (ESA)'s Gaia space telescopes, as well as ground-based telescopes in the U.S. Alongside John Livingston, lead author of the study and a graduate student at the University of Tokyo, the team's combined resources led to the confirmed existence of these 44 exoplanets and described various details about them.

A portion of the findings yield some surprising characteristics: "For example, four of the planets orbit their host stars in less than 24 hours," says Livingston. "In other words, a year on each of those planets is shorter than a day here on Earth." These contribute to a small but growing list of "ultrashort-period" planets, so it could turn out they're not as unusual as they might seem.

"It was also gratifying to verify so many small planets," continues Livingston. "Sixteen were in the same size class as Earth, one in particular turning out to be extremely small -- about the size of Venus -- which was a nice affirmation as it's close to the limit of what is possible to detect."

The source observations for this study were made by Kepler, and they would not have happened were it not for a fault in 2013, which prevented accurate control of the space telescope. "Two out of the four control-reaction wheels failed, which meant Kepler couldn't perform its original mission to stare at one specific patch of the sky," explains Professor Motohide Tamura of the University of Tokyo. "This led to its contingent mission, 'K2' -- our observations came from campaign 10 of this mission. We're lucky Kepler continues to function as well as it does."

The planets observed by K2 are known as transiting planets because their orbits bring them in front of their host stars, slightly reducing their brightness. However, other astrophysical phenomena can cause similar signals, so follow-up observations and detailed statistical analyses were performed to confirm the planetary nature of these signals.

As part of his doctoral work, Livingston traveled to Kitt Peak observatory in the U.S. state of Arizona to obtain data from a special type of camera, known as a speckle interferometer installed on a large telescope there. These observations, along with follow-up observations from a telescope in the state of Texas, were necessary to characterize the host stars and rule out false positives. The combination of detailed analyses of data from these ground-based telescopes, K2 and Gaia enabled the precise determination of the planets' sizes and temperatures. The team's findings include 27 additional candidates that are likely to be real planets, which will be the subject of future research.

Scientists hope to understand what kinds of planets might be out there, but can only draw valid conclusions if there are enough planets for robust statistical analysis. The addition of a large number of new

planets, therefore, leads directly to a better theoretical understanding of solar-system formation. The planets also provide good targets for detailed individual studies to yield measurements of planetary composition, interior structure and atmospheres -- in particular, the 18 planets in several multiplanet systems. "The investigation of other solar systems can help us understand how planets and even our own solar system formed," says Livingston. "The study of other worlds has much to teach us about our own."

Journal article

John H. Livingston, Michael Endl, Fei Dai, William D. Cochran, Oscar Barragan, Davide Gandolfi, Teruyuki Hirano, Sascha Grziwa, Alexis M. S. Smith, Simon Albrecht, Juan Cabrera, Szilard Csizmadia, Jerome P. de Leon, Hans Deeg, Philipp Eigmueller, Anders Erikson, Mark Everett, Malcolm Fridlund, Akihiko Fukui, Eike W. Guenther, Artie P. Hatzes, Steve Howell, Judith Korth, Norio Narita, David Nespral, Grzegorz Nowak, Enric Palle, Martin Patzold, Carina M. Persson, Jorge Prieto-Arranz, Heike Rauer, Motohide Tamura, Vincent Van Eylen, and Joshua N. Winn

"44 validated planets from K2 campaign 10," The Astronomical Journal

http://bit.ly/2AWNNrN

US invaded by savage tick that sucks animals dry, spawns without mating

Eight states reporting the little suckers. No evidence they're carrying disease—yet.

Beth Mole - 8/9/2018, 5:00 AM

A vicious species of tick originating from Eastern Asia has invaded the US and is rapidly sweeping the Eastern Seaboard, state and federal officials warn.

The tick, the Asian longhorned tick (or *Haemaphysalis longicornis*), has the potential to transmit an assortment of nasty diseases to humans, including an emerging virus that kills up to 30 percent of victims. So far, the tick hasn't been found carrying any diseases in the US. It currently poses the largest threat to livestock, pets, and wild animals; the ticks can attack en masse and drain young animals of blood so quickly that they die—an execution method called exsanguination.

Key to the tick's explosive spread and bloody blitzes is that its invasive populations tend to reproduce asexually—that is, without mating. Females drop up to 2,000 eggs over the course of two or three weeks, quickly giving rise to a ravenous army of clones. In one US population studied so far, experts encountered a massive swarm of the ticks in a single paddock, totaling well into the thousands. They speculated that the population might have a ratio of about one male to 400 females.

***Two* Haemaphysalis longicornis *on a US dime.* CDC / James Gathany**

Yesterday, August 7, Maryland became the eighth state to report the presence of the tick. It followed a similar announcement last Friday, August 3, from Pennsylvania. Other affected states include New York, Arkansas, North Carolina, Virginia, and West Virginia.

Plagued paddock

It all started last August in New Jersey, the first state to identify the bloodsuckers. In a case report recently published in the *Journal of Medical Entomology*, infectious disease and tick experts reported the sad state of a 12-year-old Icelandic sheep housed alone in a paddock amid manicured lawns and large houses in the state's wealthy Hunterdon County. No other animals were located on the property, and the sheep had never traveled outside of the country. Yet the beast was besieged, covered by hundreds of feasting ticks of all life-stages. Just stepping foot in the paddock, the owner and health investigators were inundated with thirsty ticks that instantly began clawing up their pant legs. DNA analysis ultimately determined that the ticks were *H. longicornis*. Investigators found only one male out of 1,058 ticks collected.

To fight back the swarms, the owner doused the sheep in a wash of the insecticide permethrin. By November, it was cleared of ticks, and population levels in the vegetation around the paddock seemed to be

dying down, although that was likely due to several nights of below-freezing temperatures.

In April, New Jersey's Department of Agriculture confirmed that the population had successfully overwintered in the state, suggesting that it has now become established there.

Spreading scourge

So far, it's unclear how, when, or where *H. longicornis* first arrived in the country. According to a regional consortium of vector-borne disease experts, archived tick samples suggest the species arrived several years prior to 2017. In the past, researchers have occasionally intercepted the ticks in US quarantine stations, including finding a tick on a quarantined horse at a station in New Jersey in 1969.

H. longicornis is native to parts of East Asia, namely China, Japan, the former USSR, and Korea, living in meadows and grassy areas near forests. They're also an established invasive pest of cattle in New Zealand, parts of Australia, and several Pacific islands. They've been known to feed on livestock like sheep, goats, cattle, and horses as well humans, dogs, cats, birds, and a range of wild animals, including bears, foxes, raccoons, rabbits, deer, and opossum.

In Asia, the longhorned tick is known to carry a variety of pathogens, including *Rickettsia japonica*, the bacteria behind Oriental spotted fever, and *Theileria orientalis*, a parasite that causes cattle theileriosis. It has also been found harboring relatives to pathogens present in the US, including bacteria that cause anaplasmosis and ehrlichiosis, the parasite that causes babesiosis, and the Powassan virus.

Additionally, *H. longicornis* may harbor a newly emerging virus that causes SFTS, which is short for severe fever with thrombocytopenia syndrome. SFTS was first identified in China in 2009 and is marked by fever, vomiting, hemorrhaging, and organ failure. Reported fatality rates fall between 6 percent and 30 percent. Several studies have pointed to the longhorned tick as being a reservoir and source for the virus.

Journal of Medical Entomology, 2018. DOI: 10.1093/jme/tjy006 (About DOIs).

http://bit.ly/2nqNzPR

When did Aboriginal people first arrive in Australia?

Many Aboriginal Australians would say with conviction that they have always been here. Their ancestors and traditional learnings tell them of this history, and their precise place within it.

August 7, 2018 by Alan Cooper, Alan N Williams, Nigel Spooner

Our review of the scientific evidence, published today in *Proceedings of the National Academy of Sciences*, suggests that for all practical purposes, this is indeed the case.

Their ancestors arrived shortly after 50,000 years ago – effectively forever, given that modern human populations only moved out of Africa 50,000-55,000 years ago.

Long connection to country

Earlier genetic analysis of historic Aboriginal hair samples confirmed the incredibly long and deep relationships between individual Aboriginal groups and their particular country. The small locks of hair were collected during anthropological expeditions across Australia from the 1920s to the 1960s.

Analysis of maternal genetic lineages revealed that Aboriginal populations moved into Australia around 50,000 years ago. They rapidly swept around the west and east coasts in parallel movements—meeting around the Nullarbor just west of modern-day Adelaide.

Archaeological sites and dates (shown above) closely match the genetic estimates. This indicates a very rapid movement throughout Australia 48,000-50,000 years ago.

Out of Africa

It was only a few thousand years earlier that a small population of modern humans moved out of Africa. As they did, they met and

briefly hybridised with Neandertals before rapidly spreading around the world. They became the genetic ancestors of all surviving modern human populations outside of Africa, who are all characterised by a distinctive small subset of Neandertal DNA – around 2.5% – preserved in their genomes.

This distinctive marker is found in Aboriginal populations, indicating they are part of this original diaspora, but one that must have moved to Australia almost immediately after leaving Africa.

How to get to Australia 50,000 years ago

The movement from Africa to Australia culminated in a series of hazardous sea voyages across island southeast Asia.

Recent studies suggest the last voyage, potentially between Timor/Roti and the northern Kimberley coast, would have involved advanced planning skills, four to seven days paddling on a raft, and a total group of more than 100 to 400 people. The possibility that earlier waves of modern human populations might have moved out of Africa before 50,000 years has also been raised. But in our review of these events, we point out that there is no convincing fossil evidence to support this idea beyond the Middle East.

One of the most important claimed potential early sites is in northern Australia, at Madjedbebe, a rock shelter in Arnhem Land. Human presence here was recently declared at more than 65,000 years ago.

This 65,000-year date has rapidly become accepted as the age for colonisation of Australia. It has appeared widely in the media and elsewhere, in political statements and comments by the Prime Minister.

But there is good reason to question a 65,000-year date, and the extent to which this contrasts with the sudden wave of archaeological sites that sweep across Australia shortly after 50,000 years ago.

These sites include Barrow Island and Carpenters Gap in the Kimberley, Devils Lair south of Perth, Willandra Lakes in NSW, and Warratyi rockshelter in the Flinders Ranges.

This rapid archaeological manifestation at 50,000 years is a perfect match for the genetic evidence from Aboriginal maternal, paternal, and genomic lineages, and a far better fit with the extinction of Australia's megafauna around 42,000 years ago.

An age limit for human migration

One of the most interesting ways we can date the dispersal of modern humans around the globe, including Australia, is through that original interbreeding event with Neandertals as we left Africa.

About a decade ago, an ancient human leg bone was found on the banks of a Siberian river by an ivory hunter. Radiocarbon-dated at 43,000-45,000 years ago, the entire genome of this individual, named Ust'-Ishim after the site, was sequenced using the latest ancient DNA technology.

The genomic sequence revealed the bone contained the standard 2.5% Neandertal DNA signal carried by all non-Africans. But it was still present in large continuous blocks and had yet not been dispersed into fragments around the genome as we see in more recent ancestors and ourselves.

In fact, the size of the blocks showed that the 43,000-45,000-year-old Ust'-Ishim specimen could only be a maximum of 230-430 generations after that initial Neandertal liaison, dating our movement out of Africa to no more than 50,000-55,000 years ago.

50,000 years, or more than 65,000 years?

Given the evidence is so strong that the ancestors of modern human populations only started moving around the world 50,000-55,000 years ago, could the human activity at Madjedbebe really be more than 65,000 years old?

One of the major limitations of the Madjedbebe study is that the stone artefacts themselves weren't dated, just the surrounding sand layers.

As a result, over time, even the slightest downward movement of the artefacts within the unconsolidated sand layers at Madjedbebe would make them appear too old.

We identify a range of factors which are common around the site, such as termite burrowing and heavy rainfall, that could cause stone artefacts to sink. Many archaeological signs suggest activity at Madjedbebe is actually much younger than 65,000 years, and overall, the extent to which the site is an outlier to the rest of the Australian record should raise a red flag.

Connection to country

Either way, Aboriginal Australians have effectively been on their country as long as modern human populations have been outside of Africa.

How does this help us better understand Aboriginal history? By appreciating the enormous depth of time that Aboriginal groups have been on their own particular country, and the extent to which all their history, knowledge, and ancestors form part of that country.

It is this gulf between a European history of constant migration and global dispersal, and the profoundly deep Aboriginal connection to one particular part of the world, that leads to failures to comprehend why being on country is not simply "a lifestyle choice", but a fundamental part of their identity.

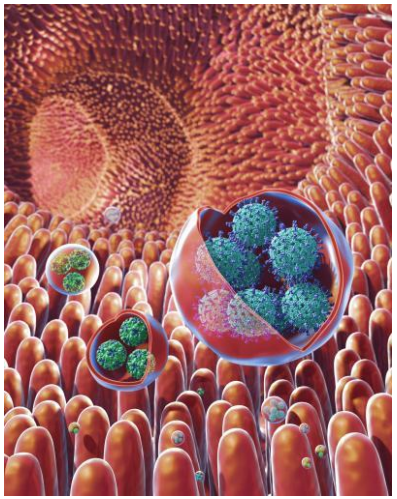
More information: *James F. O'Connell et al. When didHomo sapiensfirst reach Southeast Asia and Sahul?, Proceedings of the National Academy of Sciences (2018). DOI: 10.1073/pnas.1808385115*

http://bit.ly/2nvmdIr

NIH researchers discover highly infectious vehicle for virus transmission among humans

Membrane-bound virus clusters provide promising target for the treatment of gastroenteritis, other diseases

Researchers have found that a group of viruses that cause severe stomach illness--including the one famous for widespread outbreaks on cruise ships-- get transmitted to humans through membrane-cloaked "virus clusters" that exacerbate the spread and severity of disease. Previously, it was believed that these viruses only spread through individual virus particles. The discovery of these clusters, the scientists say, marks a turning point in the understanding of how these viruses spread and why they are so infectious. This preliminary work could lead to the development of more effective antiviral agents than existing treatments that mainly target individual particles. The researchers studied norovirus and rotavirus--hard-to-treat viruses that are the most common cause of stomach illness, or gastroenteritis, and that afflicts millions of people each year.



This is an illustration of membrane-bound vesicles containing clusters of viruses, including rotavirus and norovirus, within the gut. Rotaviruses are shown in the large vesicles, while noroviruses are shown in the smaller vesicles. **NIH**

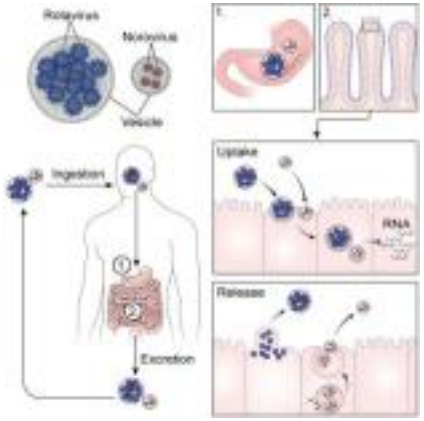
The viruses cause symptoms ranging from diarrhea to abdominal pain and can sometimes result in death, particularly among young children and the elderly. Their highly contagious nature has led to serious outbreaks in crowded spaces throughout many communities; most notably in cruise ships, daycare centers, classrooms, and nursing homes. Fortunately, vaccines against rotavirus are now available and are routinely given to babies in the United States.

"This is a really exciting finding in the field of virology because it reveals a mode of virus spread that has not been observed among humans and animals," said study leader Nihal Altan-Bonnet, Ph.D., senior investigator and head of the Laboratory of Host-Pathogen Dynamics at the National Heart, Lung, and Blood Institute (NHLBI). "We hope that it will provide new clues to fighting a wide range of diseases involving many types of viruses, including those that cause

gastrointestinal illnesses, heart inflammation, certain respiratory illnesses, and even the common cold."

The study was supported in part by the Intramural Research programs of the NHLBI and the National Institute of Allergy and Infectious Diseases (NIAID), both part of the National Institutes of Health. It is featured as the cover story of *Cell Host & Microbe* and is scheduled for online publication on August 8.

Until a few years ago, most scientists believed that viruses, particularly those responsible for stomach illnesses, could only behave as independent infectious agents. However, in 2015 Altan-Bonnet and her colleagues showed that polioviruses could transmit themselves in packets, or membrane-bound vesicles containing multiple virus particles. The scientists compared this new model of viral transmission to a Trojan horse: A group of membrane-bound viruses arrives at a host cell and deposits viruses in the cell while dodging detection by the immune system. The scientists did not know whether this system applied to animals and humans, or how effective these packets were in infecting host cells.



This is an illustration showing fecal-oral transmission of membrane-bound vesicles containing clusters of rotavirus and norovirus. Vesicles produced in the gut of infected individual are shed into stool before being spread to other individuals, where they can cause severe gastrointestinal illnesses. **NIH**

To find out, they focused on rotaviruses and noroviruses, which mainly get spread by accidentally ingesting tiny particles of an infected person's stool--through, for example, contaminated food or liquids. The researchers obtained fecal samples of humans and animals (pigs and mice) and found that the viruses are shed in the stool as virus clusters inside membrane-bound packets. In addition, they found that these virus-containing vesicles were significantly more infectious than the free, unbound viruses within the samples.

The researchers determined that the high level of infectiousness was likely due to the vesicles delivering many viruses at once to the target tissues; protecting their viral cargo from being destroyed by prolonged exposure to enzymes; and possibly by making their viral cargo invisible to the antibodies that are in the stool or gut of the host.

More studies are needed, but the extreme potency of the virus packets, they said, has a clear consequence: it not only enhances the virus' ability to spread more aggressively; it also increases the severity of the disease it causes.

"Our findings indicate that vesicle-cloaked viruses are highly virulent units of fecal-oral transmission and highlight a need for antivirals targeting vesicles and virus clustering," Altan-Bonnet noted. Handwashing with soap and water helps prevent the spread of viruses.

NIH support also includes the following grant from the NIAID: RO1-AI091985.

http://bit.ly/2M9r5lk

Inducing labor at 39 weeks decreases need for cesarean section

Inducing labor in healthy women at 39 weeks into their pregnancy reduces the need for cesarean section and is at least as safe for mother and baby as waiting for spontaneous labor.

Choosing to induce could also reduce the risk that mothers will develop preeclampsia and that newborns will need respiratory support after delivery, according to a study publishing online in the *New England Journal of Medicine* on August 8.

"This doesn't mean that everyone should be induced at 39 weeks," says the study's co-author Robert Silver, M.D., chair of Obstetrics & Gynecology at University of Utah Health and a Maternal-Fetal Medicine physician at Intermountain Healthcare in Salt Lake City.

Kim Hall, R.N., B.S.N., a research nurse coordinator at U of U Health and Intermountain Healthcare is also co-author on the study.

"Electing to induce labor is a reasonable option that may give the best chance for vaginal delivery and improve outcomes," says Silver.

Results were from 6,106 first-time mothers enrolled into the randomized ARRIVE clinical trial carried out at 41 hospitals participating in the National Institutes of Health-supported Maternal Fetal Medicine Units Network. More than 1,200 women were at the Utah MFMUN, consisting of University Hospital and Intermountain Medical Center, the largest enrolling site in the trial.

A Rising C-Section Rate

Driving the study is a steadily increasing rate of babies being delivered by C-section in the U.S., a number that has been holding at 32 percent since 2016. Medically unnecessary cesarean deliveries in healthy first-time mothers account for 80 percent of those deliveries, a point of concern.

Although the procedure is generally safe, the major surgery increases risk for complications to both mother and baby, and to future pregnancies. Women who deliver by C-section once are more likely to continue delivering that way, increasing the likelihood of high-risk complications such as placenta accreta.

For years, health care providers had been taught to avoid inducing labor in healthy, first-time mothers based on the belief that inducing increases the chance for C-section births. However, recent results from small, observational studies indicated that this may not necessarily be the case.

ARRIVE was a prospective trial designed to test this premise by examining outcomes from two groups of healthy, first-time mothers. One group elected to induce labor at 39 weeks, when the baby is full term and it is considered safe for mothers to give birth. The other group took part in expectant management or "watchful waiting," the routine practice of waiting for spontaneous labor but undergoing active intervention should a medical need arise.

Inducing Labor vs. Waiting

On average, women who chose to induce at 39 weeks delivered nearly one week earlier than women who waited for spontaneous labor. C-section delivery was significantly less likely after elective induction than after expectant management (18.6 vs. 22.2 percent).

Based on these data, the researchers estimate that inducing labor at 39 weeks could eliminate the need for 1 C-section for every 28 deliveries.

"We're always trying to find the safest way to deliver babies and take care of our patients," says M. Sean Esplin, M.D., an associate professor of Obstetrics and Gynecology at U of U Health and chief of Maternal-Fetal Medicine at Intermountain Healthcare. "If the primary goal is to keep rates of C-sections down, then elective induction is an option."

Choosing to induce labor at 39 weeks is at least as safe as spontaneous labor, according to results from the study. A composite score measuring several health indicators in newborns -- including death, seizures, hemorrhage and trauma -- was not significantly different between the two groups.

Inducing labor was linked to significant improvement in two specific outcomes: women were less likely to develop preeclampsia (9 vs. 14 percent), and rates of respiratory distress decreased in newborns. Silver says that the placenta tends not to function as well later in pregnancy, possibly explaining why mothers and babies who deliver earlier may fare better.

The study's findings held true regardless of the woman's age, ethnicity and BMI. Currently, researchers are evaluating whether inducing delivery at 39 weeks is cost effective.

"These results open the door for pregnant women and their health care providers to talk about what the woman wants to do," says

Michael Varner, M.D., vice chair for research in Obstetrics and Gynecology at U of U Health and primary investigator of the Utah MFMUN. "The opinions that matter most comes from the women we serve," says Varner.

This research was supported by the National Institutes of Health and publishes online as "Labor Induction versus Expectant Management in Low-Risk Nulliparous Women" in the New England Journal of Medicine *on August 8, 2018.*

http://bit.ly/2w0ZEiE

A diverse diet may not be the healthiest one

American Heart Association Scientific Statement

DALLAS - Encouraging people to eat a wide variety of foods to ensure they meet all their dietary needs may backfire, according to a new scientific statement from the American Heart Association that provides an overview of recent scientific studies.

"Eating a more diverse diet might be associated with eating a greater variety of both healthy and unhealthy foods" said Marcia C. de Oliveira Otto, Ph.D., lead author of the statement published in the American Heart Association journal Circulation. "Combined, such an eating pattern may lead to increased food consumption and obesity.

"Eating a variety of foods" has been a public health recommendation in the United States and worldwide for decades. While some dietary guidelines highlight greater diversity of recommended foods, there is little consensus about what so-called dietary diversity is, how it is measured and whether it is a healthy dietary goal. The statement authors conducted a thorough scientific literature review of articles published between January 2000 and December 2017. They concluded:

- ***There is no evidence that greater overall dietary diversity promotes healthy weight or optimal eating.***
- ***There is some evidence that a wider variety of food options in a meal may delay people's feeling of satiation (fullness), increasing the amount of food they eat.***
- ***Limited evidence suggests that greater dietary diversity is associated with eating more calories, poor eating patterns and weight gain in adults.***

Instead of telling people to eat a variety of foods, the statement authors conclude that dietary recommendations should emphasize adequate consumption of plant foods, such as fruit, vegetables, beans and whole grains, low-fat dairy products, non-tropical vegetable oils, nuts, poultry and fish, and limit consumption of red meat, sweets and sugary drinks. The American Heart Association Dietary Recommendations and the DASH Diet (Dietary Approaches to Stop Hypertension) are both examples of healthy eating patterns.

"Selecting a range of healthy foods, which fits one's budget or taste, and sticking with them, is potentially better at helping people maintain a healthy weight than choosing a greater range of foods that may include less healthy items such as donuts, chips, fries and cheeseburgers, even in moderation," said Otto, who is also assistant professor of epidemiology, human genetics and environmental science at The University of Texas Health Science Center at Houston, Texas.

Co-authors are Cheryl A.M. Anderson, Ph.D., M.P.H., M.S.; Jennifer L. Dearborn, M.D., M.P.H.; Erin P. Ferranti, Ph.D., M.P.H., R.N.; Dariush Mozaffarian, M.D., D.P.H.; Goutham Rao, M.D., Judith Wylie-Rosett, Ed.D., R.D. and Alice H. Lichtenstein, D.Sc. Author disclosures are on the manuscript.

http://bit.ly/2vHAk1K

Forget Doorframes: Expert Advice on Earthquake Survival Strategies

Indonesia's Lombok quake revives the question of taking cover versus running outside

By Robin George Andrews on August 9, 2018

A magnitude 6.9 earthquake struck the Indonesian island of Lombok and the adjacent Gili Islands this week, and was felt on the nearby tourist island of Bali. Leaving more than 300 dead and around 84,000 others displaced, the event is yet another chapter in the age-old

seismic story of humans trying to cope with an unpredictably rattling planet. But even though quakes have always been with us, something about them tends to leave us stunned and caught off guard. A lot of people start running for the exits the moment the shaking starts.

Many recommended earthquake preparedness strategies have multiple steps, and experts' guides to best practices get tweaked and refined over the years as experience accumulates, scientific knowledge expands and construction techniques evolve. Situational awareness and having a plan (pdf) in mind remain key. But if a quake strikes when one is inside a building, many experts' core mantra remains surprisingly simple and unchanging: Drop, cover and hold on.

This method is promoted by the U.S. Department of Homeland Security, American Red Cross (pdf), Federal Emergency Management Agency, the U.S. Geological Survey (USGS), the New Zealand Ministry of Civil Defense and Emergency Management (pdf) and the Japanese government, to name but a few. None of these recommend going outside if one is already in a building.

As soon as you feel any shaking, the guidelines advise, do not wait to see if it gets stronger. Drop to your hands and knees, cover your head, locate a sturdy table or desk and crawl under it. Then hold onto one of its legs and do not come out until at least a minute after the shaking stops. No sturdy desk? Stay on your knees in the corner of a room. If you are in bed, lie face down and cover your head (pdf) with a pillow. Stay away from windows and unfixed objects.

As for standing in a doorway, the USGS and some other agencies say this is outdated advice—based largely on old photographs of doorframes still standing in otherwise collapsed unreinforced masonry or adobe buildings. Today doorframes are often no stronger than the rest of a house and do not offer much protection from falling debris.

Make sure you stay put until the shaking has clearly stopped. It is not easy to know what part of an earthquake cycle one is experiencing; it could be a foreshock to something larger or perhaps a strong aftershock is on its way. An end to lighter, initial shaking can give people an erroneous sense of control and safety, and the subsequent violence can take them by surprise. "That's why, when we recommend drop, cover and hold on, we say, 'Drop before the earthquake drops you,'" says Jason Ballmann, communications manager for the Southern California Earthquake Center.

The idea of staying inside a swaying building can seem counterintuitive, to say the least. The horrific images of collapsed buildings that emerge after major quakes understandably imprint themselves onto the public consciousness. This may make it seem like running for the exit is a good idea—but such photographs can sometimes give a false impression of the primary hazards associated with earthquakes.

Ballmann says rescue teams retrieving people from collapsed structures around the world can attest to the effectiveness of the drop, cover and hold on strategy. Thanks to increasingly strict building codes in a rising (pdf) number of countries, modern buildings are becoming less likely to collapse. A greater danger often comes from falling and flying objects—which is precisely why getting under a table is a highly recommended course of action.

Ken Hudnut, a California Institute of Technology geophysicist who has studied earthquakes worldwide with the USGS, points out there can be an interesting caveat to drop, cover and hold on. A few cities including San Francisco and Los Angeles have required seismic retrofits for older building types, meaning one is generally safer inside them, Hudnut says. However, a broader lack of such ordinances—along with uneven enforcement of building codes all over the world, including within the U.S.—do make it harder know if a structure will withstand a major quake. This can endanger those

outside a building as well. “If you are in an older structure and you do try to run outside, you are putting yourself at risk of the building falling on you,” Hudnut says. “That’s a really bad idea.”

Caltech seismologist Lucy Jones, author of *The Big Ones: How Natural Disasters Have Shaped Us* and scientist emerita at the USGS, says “collapsing buildings are rare—extremely so in places like Chile, California or Japan”—and even in places with the worst construction. “In the rare situation that your building does collapse, drop, cover and hold on can be the best choice. It likely gives you some defensible air space to wait for rescue.”

Jones notes one relatively improbable situation in which it may be advisable to make a run for it: if a person is at the entrance of a poorly built structure, far from any tables, and can get to a clear outside space and away from the building extremely quickly. Still, she adds experts endorse drop, cover and hold on because it is “the best answer for most situations.” Hudnut says this “universal advice” has “a really great basic sensibility to it.”

Nearly half the U.S. population is exposed to potential damaging earthquakes, which is why drills are held regularly in some regions. A wide range of groups—including national, state and local governments—hold such dry runs during Great ShakeOut Earthquake Drills, a global initiative Ballmann helps coordinate.

International ShakeOut Day is held annually on the third Thursday of October. Countries from Japan to New Zealand take part, hoping repetitive practice will simply become instinct. Many earthquake-riddled nations, however, remain conspicuously absent from the list of participants.

The recent deaths in Indonesia are likely attributable to a range of complex, interrelated factors, including poor building quality (pdf). But it is clear that the more people practice proper safety measures—no matter where they are—the more likely they will be to survive a major quake.

http://bit.ly/2MDy6ak

The physician's white coat: Iconic and comforting or likely covered in germs?

Physicians' white coats are one of the most iconic symbols of medicine, wearing one doesn't impact patients' satisfaction

GALVESTON, Texas - A new study from The University of Texas Medical Branch at Galveston department of Obstetrics and Gynecology has found that although the physicians' white coat is one of the most iconic symbols of the trade, whether or not they wear it, doesn't impact patients' satisfaction. The findings are available in the *American Journal of Perinatology*.

Past studies have shown that a physician's attire affects patients' trust and confidence in them. Patient satisfaction and quality of communication between patient and physician are linked with better patient care and outcomes.

However, coats worn throughout a day filled with treating patients - some of whom have contagious illnesses - has been shown to carry infectious agents that can be spread around.

The researchers conducted the study to find out if or how the white coat affects physician-patient communication and satisfaction among new mothers in the postpartum unit at the hospital.

All of the women were randomly assigned to teams of rounding physicians who either wore a white coat or not but beyond this, their care was the same. Shortly before discharge from the hospital, the patients completed a modified Hospital Consumer Assessment of Healthcare Providers and Systems survey. The survey is the only national, standardized survey used to assess patient satisfaction.

"Our study showed that not wearing a white coat by the physicians team, didn't impact the communication between patients and physicians nor patients' satisfaction," said Dr. Mauricio La Rosa, principal investigator of the study. "Actually, 40 percent of the

patients couldn't remember if their physicians were wearing white coats or not."

In a prior study that was not conducted at UTMB, 18 percent of the physicians' white coats were colonized with antibiotic-resistant staphylococcus aureus.

Twenty five percent of all hospital admission in the U.S. are related to pregnancy, so any intervention that improves pregnant or postpartum women's satisfaction may have a great impact on health care. Moreover, health care professionals must determine the benefits of any interventions whether old or new before widespread utilizations.

Other authors include Nicholas Spencer, Mahmoud Abdelwahab, Gabriela Zambrano, Fawzi Saoud, Katherine Jelliffe, Gayle Olson, Mary Munn, George Saade and Maged Costantine.

http://bit.ly/2MnPe6Q

Evolutionary changes in the human brain may have led to bipolar disorder and schizophrenia

Evolutionary changes that make us prone to bad backs and impacted molars may have generated long, stretches of DNA that predispose individuals neuropsychiatric diseases

The same aspects of relatively recent evolutionary changes that make us prone to bad backs and impacted third molars may have generated long, noncoding stretches of DNA that predispose individuals to schizophrenia, bipolar disorder, and other neuropsychiatric diseases.

A study publishing August 9 in the American Journal of Human Genetics identifies an unusually lengthy array of tandem repeats found only within the human version of a gene governing calcium transport in the brain.

"Changes in the structure and sequence of these nucleotide arrays likely contributed to changes in CACNA1C function during human evolution and may modulate neuropsychiatric disease risk in modern human populations," says senior author David Kingsley, professor of developmental biology at Stanford University.

Common ailments such as lower back, knee, and foot problems are likely due to the transition to walking upright; impacted wisdom teeth may be tied to humans' smaller jaws and recent changes in diet.

Kingsley hypothesizes that the prevalence of neurological diseases in modern humans may stem from recent evolutionary changes in genes controlling brain size, connectivity, and function.

Bipolar disorder and schizophrenia affect more than 3 percent of the population worldwide.

Missing data

Tandem repeats are repeated lengths of DNA occurring either inside or outside a gene's coding sequence. They have been hypothesized to explain individual-to-individual variations in complex neurological functions and may act as "tuning knobs" for modulating gene expression.

The tandem repeats may affect CACNA1C function--even when the coding region of the gene itself is free of mutations.

Most genetic studies focus on how simple letter substitutions in the DNA code cause disease. Yet 15 years after the human genome was mapped, regions of the human genome are still largely unexplored, missing, or understudied, Kingsley says.

In particular, large regions of repeated sequence can be difficult to propagate in bacteria and to assemble correctly. Many of these regions also vary substantially between individuals and may contribute to key phenotypic traits and disease susceptibilities in humans and other organisms.

After identifying a large discrepancy between the standard human reference genome and levels of DNA sequence reads coming from a key calcium channel gene previously linked to psychiatric disease, Kingsley and Stanford colleagues Janet Song and Craig Lowe carried out further studies of 181 human cell lines and postmortem brain

tissue samples. They found lengthy stretches of DNA--ten to a hundred times longer and more complex than expected--containing many variant nucleotide base pairs embedded in a noncoding region of the CACNA1C gene.

Different versions of the highly repeated sequences showed different abilities to activate gene expression and were tightly linked to genetic markers of bipolar disease and schizophrenia disease susceptibility in humans. Such "hidden variants" may illuminate the risk of psychiatric disease among patients whose DNA profile is otherwise unremarkable, he says.

Kingsley, a Howard Hughes Medical Institute investigator, says classifying patients based on their repeat arrays may help identify those most likely to respond to existing calcium channel drugs.

These medications have produced mixed results to date, he notes, and further study is needed to clarify whether patients with a genetic variation of CACNA1C have too much or too little calcium channel activity. "We hope genotype-based drug targeting will lead to improved future treatments," he says.

Evolutionary byproducts

Kingsley says the large structural arrays found in the CACNA1C gene are unique to humans, raising the question of whether we derived an evolutionary advantage from this expanded genetic sequence--even though it apparently increased our susceptibility to neuropsychiatric disease.

His team plans to study the effects on neural differentiation, cell excitability, and brain circuit formation of adding and removing entire repeat arrays from CACNA1C in animal models and cultured cells.

This work is supported by the National Institutes of Health.

American Journal of Human Genetics, Song and Lowe et al.: "Characterization of a Human-Specific Tandem Repeat Associated with Bipolar Disorder and Schizophrenia" *https://www.cell.com/ajhg/fulltext/S0002-9297(18)30238-6*

http://bit.ly/2w7QaCu

The Lancet: Sodium reduction programmes may only be appropriate for communities with very high salt intake

Sodium consumption not associated with increase in health risks except for those whose average consumption exceeds 5g/day

A new study shows that for the vast majority of communities, sodium consumption is not associated with an increase in health risks except for those whose average consumption exceeds 5g/day (equivalent to 12.5g of salt, or 2½ teaspoons). Communities with high average levels of sodium intake (above 5g/day) were mostly seen in China, with only about 15% of communities outside China exceeding this level of consumption.

WHO guidelines recommend a global approach to reducing sodium intake in all populations to below 2g/day, but this has not been achieved in any country. The authors say that sodium reduction strategies should instead target communities with high average levels of sodium consumption (above 5g/day).

The findings come from a new observational study of over 90000 people in more than 300 communities in 18 countries, published in *The Lancet*.

"No country has managed to reduce levels of sodium consumption from moderate to very low (below 2g/day), and our study shows we should be far more concerned about targeting communities and countries with high average sodium intake (above 5g/day, such as China) and bringing them down to the moderate range (3 to 5g/day)," says Professor Andrew Mente, Population Health Research Institute (PHRI) of Hamilton Health Sciences and McMaster University (Canada). [1]

Data from the ongoing Prospective Urban Rural Epidemiology (PURE) study was used in the analysis, and 95,767 participants aged

35-70 years in 369 communities in 18 countries [2] were included in the study. A morning fasting midstream urine sample was collected from every participant and was used to estimate 24h urinary sodium and potassium intake. Information about demographic factors, lifestyle, health history, and medication use were recorded and height, weight and blood pressure were measured.

Average follow-up was 8.1 years, during which time 3695 people died, 3543 had major cardiovascular events (1372 myocardial infarctions; 1965 strokes; 343 heart failures; 914 cardiovascular deaths). The analysis was based on the number of people who suffered a cardiovascular event or death (6281).

The analysis was done at a community level: 255 communities (all with over 100 participants) for cardiovascular disease and mortality, and 369 (all with over 50 participants) for blood pressure.

80% (82/103) of the communities in China has a mean sodium intake greater than 5g/day, whereas in other countries, 84% (224/266) communities had a mean intake of 3-5g/day. No communities in the study had a mean sodium intake below 3 g/day.

Higher sodium intake was associated with increased blood pressure and increased incidence of stroke, but the association was found in communities with very high sodium intake (mostly in China) and not others. Higher sodium intake was associated with lower rates of myocardial infarction and total mortality.

"Our study adds to growing evidence to suggest that, at moderate intake, sodium may have a beneficial role in cardiovascular health, but a potentially more harmful role when intake is very high or very low.

This is the relationship we would expect for any essential nutrient and health. Our bodies need essential nutrients like sodium, but the question is how much. The recommendation to lower sodium consumption to 2g/day is based on short-term trials of sodium intake and blood pressure, and the assumption that any approach to reduce blood pressure will necessarily translate into a lower risk of cardiovascular disease with no unintended consequences. While low sodium intake does reduce blood pressure, at very low levels it may also have other effects, including adverse elevations of certain hormones associated with an increase in risk of death and cardiovascular diseases," adds Professor Mente. [1]

Furthermore, rates of stroke, cardiovascular death, and total mortality decreased with increasing potassium intake in these communities. Diets rich in fruit and vegetables are high in potassium. However, it is not known whether potassium itself is protective, or whether it might simply be a marker of a healthy diet.

Professor Martin O'Donnell, McMaster University, co-author on the study, adds: "Our findings support other research recommending an all-round healthy diet with an emphasis fruit and vegetables, dairy foods, potatoes, nuts and beans. Very high sodium consumption (above 5g/day) is harmful, but the amount that is consumed by the majority of people does not appear to be linked to an increased risk of cardiovascular disease or death." [1]

The study published today follows a paper published in *The Lancet* in 2016 [3], which used the same cohort but the analyses were performed at an individual level, rather than community.

Compared with moderate sodium intake, the study found that high sodium intake (above 7g/day) was associated with an increased risk of cardiovascular events and mortality in hypertensive populations, and low sodium (below 3g/day) intake was associated with an increased risk of cardiovascular events and mortality in people with or without hypertension.

By including the community level analyses, and additional years' follow-up, the new study adds additional evidence and approaches to prevention for communities and countries.

Writing in a linked Comment, Franz H Messerli and Louis Hofstetter, University Hospital, Bern (Switzerland) and Sripal Bangalore, New

York University School of Medicine (USA), note: *"A cursory look at 24h urinary sodium excretion in 2010 and the 2012 UN healthy life expectancy at birth in 182 countries, ignoring potential confounders, such as gross domestic product, does not seem to indicate that salt intake, except possibly when very high, curtails life span...*

Before we change recommendations, let us remember, that Mente and colleagues' findings are observational data in a predominately Asian population, and base 24 h sodium excretion calculations on overnight fasting urine measurements. It does not necessarily follow that active intervention, such as decreasing salt intake in patients at risk of stroke or increasing salt intake in patients at risk of myocardial infarction, will turn out to be beneficial.

Nevertheless, the findings are exceedingly interesting and should be tested in a randomised controlled trial. Indeed, such a trial has been proposed in a closely controlled environment, the federal prison population in the USA...

The simple fact that a trial looking at salt restriction has to be done in the federal prison population indicates that curtailing salt intake is notoriously difficult. Incentivising people to enrich their diets with potassium through eating more fruit and vegetables is likely to need less persuasion."

NOTES TO EDITORS

The study was funded by the Population Health Research Institute, Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, and European

[1] Quote direct from author and cannot be found in the text of the Article.

[2] The PURE study includes data from three high-income countries (Canada, Sweden, and United Arab Emirates), 11 middle-income (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, occupied Palestinian territory, Poland, South Africa, and Turkey) and four low-income countries (Bangladesh, India, Pakistan, and Zimbabwe).

[3] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30467-6/fulltext

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31376-X/fulltext

http://bit.ly/2MidIhU

Loss of a gene long ago puts marine mammals at risk today, as environments change

Ancient loss of gene function across ancestral marine mammal lineages may now be putting modern marine mammals at risk, leaving them defenseless against toxic organophosphates.

According to new research, the shared, or convergent, genetic loss of Paraoxonase 1 (PON1) has left many marine mammal species without a mechanism to break down these neurotoxic chemicals, which are increasingly finding their way into their marine habitats. When land mammals returned to the sea, millions of years of adaptive changes allowed them to colonize the planet's oceans. Some physiological and morphological changes occurred similarly across multiple distinct lineages of marine mammals, like the development of flippers in whales, seals and sea cows.

As part of such processes, associated changes at the gene level, however, can influence more than one potentially unrelated trait, leading to unforeseen outcomes in changing environments. Wynn Meyer et al. conducted a genome-wide scan for shared losses of gene function across marine mammal species, related to their ancestral transition to aquatic environments. The authors revealed a striking pattern of convergent loss at the gene PON1, mammals' lone defense against the highly toxic organophosphate compounds found in the heavily used pesticide chlorpyrifos. The gene lost function independently in all three marine mammal lineages (cetacean, pinniped and sirenian) the authors evaluated, but remained intact in terrestrial mammal genomes.

According to Meyer et al., the loss of PON1 may be related to its role in fatty acid oxidation. The results underscore the potential health risks for marine mammals that live close to agricultural runoff containing organophosphorus pesticides, like manatees and dugongs.

http://bit.ly/2nvsdAO

Why hospital architects need to talk to nurses

Ensuring that these projects not only deliver economic value for the private companies building the hospital – but also social value for the doctors, nurses and patients

Jens Roehrich Professor of Supply Chain Innovation, University of Bath

Many of us pay close attention to how our taxes are spent, and how well governments invest in infrastructure projects such as roads, schools and hospitals. Value for money is key. Yet horror stories of waste, lateness and poor quality are common.

To develop and finance public services and infrastructure, governments around the world (but especially in Europe) have become increasingly keen on private sector involvement. These cross-sector collaborations can help provide value for money for taxpayers – but they are also at risk of wasting it.

In health care, collaborations between public and private partners have a direct impact on society. This is why it is important for health care professionals like doctors and nurses to talk directly to the designers and builders of a new hospital. It ensures that these projects not only deliver economic value for the private companies building the hospital – but also social value for the doctors, nurses and patients who will use the hospital for decades to come.

For instance, in one recently built British hospital, medical staff were able to bring valuable insight to the design process. A visit by some of the hospital's senior nurses to a children's hospital in the US led to the replication of a lighting design on the ceiling of a children's ward so that it mimicked a starry night sky. As one of the nurses explained to me afterwards:

It might sound like a small change, but it provides a much more homely surrounding than the normal NHS lighting. This is important for our young patients [providing a] less scary, hospital experience which positively impacts on the healing process. […] It creates a much nicer environment in which our little patients can recover.

In another hospital, input from senior nurses helped to establish a ward design that most suited their professional needs – right down to the placement of plumbing. This saved large amounts of money that might have been spent on undoing unnecessary building work had the nurses not been consulted.

As one project manager of the construction company told me: "Thanks to [the senior nurses'] input and telling us how they intend to use wards, we changed the ward layout, such as the position of sinks. This may seem to be a minor issue, but may have a huge impact when caring for a patient."

To see how social value can be best achieved through cross-sector collaborations we looked into the key building blocks that go beyond a mere focus on contracts.

An organisations' prior experience of cross sector collaboration and a supportive climate is vital in creating social value. It also helps to have had some exposure to previous projects (good and bad). But a major ingredient is the individual employees in both public and private sector organisations.

Building mutual knowledge and aligning goals between doctors, nurses and design and construction professionals is key, as public and private sector employees often have different objectives for projects (making a profit vs healing patients). A shared understanding can come through listening to and appreciating the other parties' professional language and the expertise that language expresses.

Joint expertise

Beyond an understanding of the other parties' expertise, practical matters of shared goals and jointly developed timelines are necessary. Coordinating efforts between the two sectors needs to take priority at the outset – rather than emphasising project speed and completion.

To encourage these positive outcomes, the key people need to meet frequently to exchange information, address problems and discuss plans. Without this kind of coordination and collaboration, it will be impossible to make the most of both sides' specialist knowledge.

So when it comes to hospitals and clinics, the private company needs to actively seek the involvement of doctors and nurses in the design and construction phases. Similarly, doctors and nurses should not be threatened by private companies, but instead seek to become actively engaged. This will help drive creative design innovations such as the "night sky" ceiling in the children's ward.

It takes time and resources, but this kind of collaboration and coordination between public and private sectors provides an opportunity to increase value – both economic and social. And that's something that not only benefits construction companies and health care professionals – but patients and taxpayers, too.

Disclosure statement

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http://bit.ly/2w7nidi

Worms may age because they cannibalize their own intestines

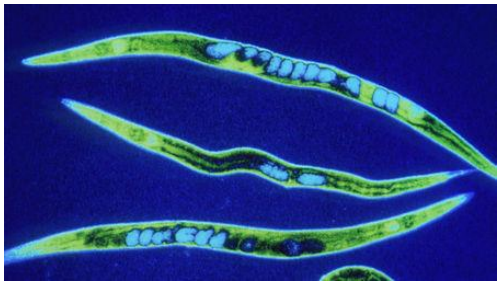
The microscopic nematode worms that squirm around in soil and researchers' labs have a taste for tripe—their own.

By Mitch LeslieAug. 9, 2018 , 11:45 AM

Their habit of digesting their own intestines helps them reproduce, but it also accelerates their aging, a new study suggests. Those results support an unorthodox hypothesis: Humans and other organisms break down as they get older because traits that benefited them when they are young become harmful.

"It's a very provocative paper," says geneticist Keith Blackwell of Harvard Medical School in Boston. "This is telling us that we really need to be paying attention to this idea" about why aging occurs.

Time takes a toll on nematodes. Like many people, the worms, which live about 3 weeks, become obese as they get older. The bodies of elderly worms are jam-packed with fat, which they store in the form of egg yolk. The worms are also prone to uterine tumors, and their intestines wither.



These nematodes need yolk to make their eggs (the blue orbs). **James King-Holmes/Science Source**

What drives the deterioration of the worms and other organisms? One idea is that aging occurs because molecules such as DNA and proteins accrue damage and start to malfunction. Another possible explanation, known as the run-on hypothesis, holds that organisms break down over time because abilities that help them survive and reproduce early in life continue to "run on" and become a problem later. Certain genes that orchestrate growth and development, for instance, are advantageous for a young animal. But if they continue operating in an older animal, they can promote cancer.

Geneticist David Gems of University College London and colleagues may have discovered a prime example of the run-on hypothesis in action. The team found that nematodes consume their own intestines so they can synthesize yolk for their eggs. The ability to convert the organ into yolk may enable young worms to produce eggs even when food is scarce. But the nematodes keep digesting their intestine even after they stop laying eggs.

This continued self-cannibalization fosters the animals' aging, Gems and colleagues report today in *Current Biology*. When the scientists curtailed yolk synthesis by altering certain genes, the animals' intestines didn't disintegrate, and the worms didn't pack on fat. The

researchers also found that preventing intestinal breakdown allowed some of the animals to live longer.

Evidence from male nematodes also supports the idea. Male worms are scarce—more than 99% of the animals are hermaphrodites that pump out eggs and sperm. Males don't normally produce yolk, and as Gems and his team noted, their intestine does not degenerate. But when the researchers genetically modified male worms to manufacture a key yolk protein, the animals began to show two signs of aging they hadn't shown before: Their intestines deteriorated and they amassed fat.

"When we age, it's not that we wear out. Our own genes are destroying us," Gems says. Humans don't digest their own intestines to make yolk. But run-on processes could also be abetting our aging. One example is the mTOR protein, a master controller of cell metabolism and growth that is necessary during our embryonic development. It remains active in older animals and promotes cancer, neurodegenerative diseases, and other age-related infirmities.

The study "may make people take the [run-on] hypothesis more seriously," says biogerontologist Steven Austad of the University of Alabama in Birmingham. However, he adds, the findings may only apply to nematodes. "I don't see the link to mammalian aging."

https://bbc.in/2Othnqy

The unpleasant reason men navigate better than women

Men are better at navigating than women, but they shouldn't be proud about.

By James Gallagher Health and science correspondent, BBC News

Men are better at navigating than women, according to a massive study, but there's not much for men to be proud about.

Scientists at University College London say the difference has more to do with discrimination and unequal opportunities than any innate ability. The findings come from research into a test for dementia.

But it has also given an unprecedented insight into people's navigational ability all around the world.

The experiment is actually a computer game, Sea Hero Quest, that has had more than four million players. It's a nautical adventure to save an old sailor's lost memories and with a touch of a smartphone screen, you chart a course round desert islands and icy oceans.

The game anonymously records the player's sense of direction and navigational ability. One clear picture, published in the journal Current Biology, was that men were better at navigating than women. But why?

Prof Hugo Spiers thinks he has found the answer by looking at data from the World Economic Forum's Gender Gap Index - which studies equality in areas from education to health and jobs to politics. He told the BBC: "We don't think the effects we see are innate.

"So countries where there is high equality between men and women, the difference between men and women is very small on our spatial navigation test.

"But when there's high inequality the difference between men and women is much bigger. And that suggests the culture people are living in has an effect on their cognitive abilities."

The deeper the colour, the stronger the country's navigational ability **UCL**

Sea Hero Quest has produced a raft of other findings.

- ***Denmark, Finland and Norway have the world's best navigational skills - possibly down to their "Viking blood"***
- ***Sense of direction is in constant decline after you emerge from your teenage years***
- ***People in wealthier countries also tend to be the best navigators***

The popularity of the game has turned it into the world's biggest dementia research experiment. Being lost or disoriented is one of the first signs of the disease.

The next step in the research is to see if catching sudden declines in navigational ability could be used to test for dementia.

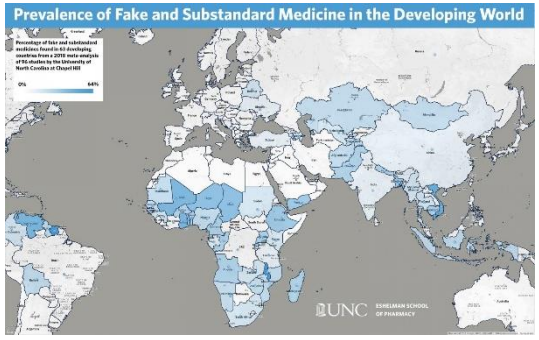
Tim Parry, the director of Alzheimer's Research UK, said: "The data from Sea Hero Quest is providing an unparalleled benchmark for how human navigation varies and changes across age, location and other factors. "This really is only the beginning of what we might learn about navigation from this powerful analysis."

This project was funded by Deutsche Telekom and the game was designed by Glitchers.

http://bit.ly/2MEeoel

New study finds fake, low-quality medicines prevalent in the developing world

The color-coded map shows the percentage of fake and substandard medicines found in 63 developing countries. UNC Eshelman School of Pharmacy



A new study from the University of North Carolina at Chapel Hill found that substandard and falsified medicines, including medicines to treat malaria, are a serious problem in much of the world. In low- and middle-income countries, more than 13 percent of the essential medicines that satisfy the priority health care needs of the population fall in this category. When looking specifically at African countries, the portion of substandard and falsified medicines rises to almost 19 percent.

Falsified medicines are medical products that deliberately and fraudulently misrepresent their identity, composition or source. Substandard medicines are real medical products that fail to meet quality standards or specifications for a variety of reasons, including poor manufacturing, shipping or storage conditions, or because the drug is sold beyond its expiration date.

Researchers analyzed 96 previous studies of falsified and substandard medicines and each of the studies tested more than 50 medications. The team found that antimalarials and antibiotics were the medicines most commonly sold in substandard or falsified conditions. In low- and middle-income countries, 19 percent of antimalarials and 12 percent of antibiotics are substandard or falsified.

Sachiko Ozawa, an associate professor at the UNC Eshelman School of Pharmacy, led the research along with collaborators. The paper published in the journal JAMA Network Open on August 10.

"The prevalence of substandard and falsified medicines is a substantial public health problem because these medicines can be ineffective or harmful and can prolong illnesses, cause poisoning or lead to dangerous drug interactions," said Ozawa. "Our study shows that a concerted global effort is needed to improve supply chain management for medicines and to identify solutions to this understudied issue."

The researchers searched five databases for studies related to substandard and falsified medicines. They reviewed 256 studies and included 96 studies in their analysis.

"We need more global collaboration to implement laws on drug quality, increase quality control capacity, and improve surveillance and data sharing," said James Herrington, a professor in the UNC Gillings School of Global Public Health and a co-author of the study. "This can strengthen the global supply chain against poor quality medicines, improve health outcomes by reducing

antimicrobial and anti-parasitic resistance and, ultimately, help governments, businesses and patients save money."

The team's analysis found limited information on the economic impact of poor quality medicines, with the estimates of market size ranging widely from $10 billion to $200 billion. Substandard and falsified medicines can burden health systems by diverting resources to ineffective or harmful therapies and cause additional treatment costs and reduced worker productivity due to treatable illnesses, but these effects have not been measured.

Ozawa's research collaborators included Daniel Evans, Tatenda Yemeke and Sarah Laing of the UNC Eshelman School of Pharmacy; James Herrington of UNC Gillings School of Global Public Health; Sophia Bessias of Enterprise Analytics and Data Sciences with University of North Carolina Health Care; and Deson Haynie of the University of Virginia School of Medicine.

http://bit.ly/2B7BsB0

Early type 1 diabetes shortens women's lives by 18 years

Women who developed type 1 diabetes before the age of ten years die an nearly 18 years earlier than women without it

Women who developed type 1 diabetes before the age of ten years die an average of nearly 18 years earlier than women who do not have diabetes. Men in the corresponding situation lose almost 14 years of life. The lives of patients diagnosed at age 26-30 years are shortened by an average of ten years, according to research published in the British medical journal the Lancet.

"These are disappointing and previously unknown figures. The study suggests that we must make an even greater effort to aggressively treat patients diagnosed at an early age to reduce the risk of complications and premature death," says Araz Rawshani, researcher at the Department of Internal Medicine, Sahlgrenska Academy, and the Swedish National Diabetes Registry.

The research is based on extensive material from the registry which has monitored 27,195 individuals with type 1 diabetes for an average of ten years. The group was compared with 135,178 controls from the general population who did not have diabetes, maintaining the same distribution regarding gender, age and county of residence.

While researchers already knew that type 1 diabetes is associated with a lower life expectancy, until now it was unclear whether and how much gender and age at onset of illness affect both life expectancy and the risk of cardiovascular disease.

The probability of severe cardiovascular disease generally proved to be 30 times higher for those who developed type 1 diabetes before the age of ten years than for controls. With a diagnosis of diabetes at the age of 26-30 years, the corresponding risk increased by a factor of six.

One of the highest increases in risk noted in the study involved heart attacks in women who developed type 1 diabetes before the age of ten years. The risk for these women is 90 times higher than for controls without diabetes.

"The study opens up the potential for individualized care. We know with certainty that if we maintain good blood sugar control in these patients, we can lower the risk of cardiovascular damage. This makes it important to carefully consider both evidence-based medications and modern technological aids for blood sugar measurements and insulin administration in patients diagnosed with type 1 diabetes at an early age," says Araz Rawshani.

"At the same time the study must also be viewed in the light of the tremendous progress that has been made in the past few decades. Management of type 1 diabetes is nowadays highly sophisticated, with modern tools for glucose monitoring, delivery of insulin and management of cardiovascular risk factors. Those who live with diabetes today, and those who will acquire the disease, will enjoy longer and healthier lives in the years to come", says Araz Rawshani.

Type 1 diabetes is one of the most common chronic diseases that affect children in Sweden. The majority are diagnosed between the

ages of 10 and 14 years. The number of diagnoses among children is increasing and the percentage is among the highest in the world; Sweden is second after Finland. Between 50,000 and 60,000 people in Sweden suffer from the disease.

"From the patient perspective this study is tremendously important. Suddenly we can answer questions about complications and life expectancy that we were previously unable to answer. Now there is robust evidence that survival largely depends on the age at which the patient develops the disease, and that there is a difference between men and women," says Araz Rawshani.

Title: Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study;
https://qubox.box.com/s/v2h3dxeupwpbox3l5eiklwq93lvq6l2q

http://bit.ly/2MCJ2ou

Laziness helped lead to extinction of Homo erectus

Homo erectus *went extinct in part because they were 'lazy'*

New archaeological research from The Australian National University (ANU) has found that *Homo erectus*, an extinct species of primitive humans, went extinct in part because they were 'lazy'.

An archaeological excavation of ancient human populations in the Arabian Peninsula during the Early Stone Age, found that *Homo erectus* used 'least-effort strategies' for tool making and collecting resources.

This 'laziness' paired with an inability to adapt to a changing climate likely played a role in the species going extinct, according to lead researcher Dr Ceri Shipton of the ANU School of Culture, History and Language.

"They really don't seem to have been pushing themselves," Dr Shipton said.

"I don't get the sense they were explorers looking over the horizon. They didn't have that same sense of wonder that we have."

Dr Shipton said this was evident in the way the species made their stone tools and collected resources.

"To make their stone tools they would use whatever rocks they could find lying around their camp, which were mostly of comparatively low quality to what later stone tool makers used," he said.

"At the site we looked at there was a big rocky outcrop of quality stone just a short distance away up a small hill.

"But rather than walk up the hill they would just use whatever bits had rolled down and were lying at the bottom.

"When we looked at the rocky outcrop there were no signs of any activity, no artefacts and no quarrying of the stone.

"They knew it was there, but because they had enough adequate resources they seem to have thought, 'why bother?'".

This is in contrast to the stone tool makers of later periods, including early *Homo sapiens* and Neanderthals, who were climbing mountains to find good quality stone and transporting it over long distances.

Dr Shipton said a failure to progress technologically, as their environment dried out into a desert, also contributed to the population's demise.

"Not only were they lazy, but they were also very conservative," Dr Shipton said.

"The sediment samples showed the environment around them was changing, but they were doing the exact same things with their tools.

"There was no progression at all, and their tools are never very far from these now dry river beds. I think in the end the environment just got too dry for them."

The excavation and survey work was undertaken in 2014 at the site of Saffaqah near Dawadmi in central Saudi Arabia.

The research has been published in a paper for the *PLoS One* scientific journal.

http://bit.ly/2MGsrjK

Study suggests glaucoma may be an autoimmune disease

Unexpected findings show that the body's own immune system destroys retinal cells

CAMBRIDGE, MA -- Glaucoma, a disease that afflicts nearly 70 million people worldwide, is something of a mystery despite its prevalence. Little is known about the origins of the disease, which damages the retina and optic nerve and can lead to blindness.

A new study from MIT and Massachusetts Eye and Ear has found that glaucoma may in fact be an autoimmune disorder. In a study of mice, the researchers showed that the body's own T cells are responsible for the progressive retinal degeneration seen in glaucoma. Furthermore, these T cells appear to be primed to attack retinal neurons as the result of previous interactions with bacteria that normally live in our body.

The discovery suggests that it could be possible to develop new treatments for glaucoma by blocking this autoimmune activity, the researchers say.

"This opens a new approach to prevent and treat glaucoma," says Jianzhu Chen, an MIT professor of biology, a member of MIT's Koch Institute for Integrative Cancer Research, and one of the senior authors of the study, which appears in *Nature Communications* on Aug. 10.

Dong Feng Chen, an associate professor of ophthalmology at Harvard Medical School and the Schepens Eye Research Institute of Massachusetts Eye and Ear, is also a senior author of the study. The paper's lead authors are Massachusetts Eye and Ear researchers Huihui Chen, Kin-Sang Cho, and T.H. Khanh Vu.

Genesis of glaucoma

One of the biggest risk factors for glaucoma is elevated pressure in the eye, which often occurs as people age and the ducts that allow fluid to drain from the eye become blocked. The disease often goes undetected at first; patients may not realize they have the disease until half of their retinal ganglion cells have been lost.

Most treatments focus on lowering pressure in the eye (also known as intraocular pressure). However, in many patients, the disease worsens even after intraocular pressure returns to normal. In studies in mice, Dong Feng Chen found the same effect.

"That led us to the thought that this pressure change must be triggering something progressive, and the first thing that came to mind is that it has to be an immune response," she says.

To test that hypothesis, the researchers looked for immune cells in the retinas of these mice and found that indeed, T cells were there. This is unusual because T cells are normally blocked from entering the retina, by a tight layer of cells called the blood-retina barrier, to suppress inflammation of the eye. The researchers found that when intraocular pressure goes up, T cells are somehow able to get through this barrier and into the retina.

The Mass Eye and Ear team then enlisted Jianzhu Chen, an immunologist, to further investigate what role these T cells might be playing in glaucoma. The researchers generated high intraocular pressure in mice that lack T cells and found that while this pressure induced only a small amount of damage to the retina, the disease did not progress any further after eye pressure returned to normal.

Further studies revealed that the glaucoma-linked T cells target proteins called heat shock proteins, which help cells respond to stress or injury. Normally, T cells should not target proteins produced by the host, but the researchers suspected that these T cells had been previously exposed to bacterial heat shock proteins. Because heat shock proteins from different species are very similar, the resulting T cells can cross-react with mouse and human heat shock proteins.

To test this hypothesis, the team brought in James Fox, a professor in MIT's Department of Biological Engineering and Division of

Comparative Medicine, whose team maintains mice with no bacteria. The researchers found that when they tried to induce glaucoma in these germ-free mice, the mice did not develop the disease.

Human connection

The researchers then turned to human patients with glaucoma and found that these patients had five times the normal level of T cells specific to heat shock proteins, suggesting that the same phenomenon may also contribute to the disease in humans. The researchers' studies thus far suggest that the effect is not specific to a particular strain of bacteria; rather, exposure to a combination of bacteria can generate T cells that target heat shock proteins.

One question the researchers plan to study further is whether other components of the immune system may be involved in the autoimmune process that gives rise to glaucoma. They are also investigating the possibility that this phenomenon may underlie other neurodegenerative disorders, and looking for ways to treat such disorders by blocking the autoimmune response.

"What we learn from the eye can be applied to the brain diseases, and may eventually help develop new methods of treatment and diagnosis," Dong Feng Chen says.

The research was funded by the National Institutes of Health, the Lion's Foundation, the Miriam and Sheldon Adelson Medical Research Foundation, the National Nature Science Foundation of China, the Ivan R. Cottrell Professorship and Research Fund, the Koch Institute Support (core) Grant from the National Cancer Institute, and the National Eye Institute Core Grant for Vision Research.

http://bit.ly/2vHZDke

Novel approach keeps liquids from freezing at very low temperatures for extended periods

Simple method to maintain water and water-based solutions in a liquid state far below the usual "freezing point"

Investigators from the Massachusetts General Hospital Center for Engineering in Medicine (MGH-CEM) have developed a simple method to maintain water and water-based solutions in a liquid state at temperatures far below the usual "freezing point" for greatly extended periods of time. While they currently have accomplished this for volumes of only a few ounces, their approach—described in the journal *Nature Communications* - may someday enable safe, extended preservation of blood cells, tissues and organs, along with improved food preservation.

"Water and other aqueous solutions in the sorts of volumes we deal with every day normally freeze when cooled below the freezing point of 0° C or 32° F," says O. Berk Usta, Ph.D., of the MGH-CEM, co-corresponding author of the report. "Our approach, which we dubbed 'deep supercooling,' is simply to cover the surface of such a liquid with a solution that does not mix with water, like mineral oil, to block the interface between water and air, which is the major site of crystallization. This surprisingly simple, practical and low-cost approach to supercooling solutions for extended periods can enable many medical and food preservation methods, as well as fundamental experiments that were not previously possible."

In most real-world environments, water and water-based solutions begin to freeze when the temperature reaches below 0° C/32° F, with ice crystals randomly forming where the liquids contact air or various impurities in the solution. Supercooling—reducing a liquid below its usual freezing point without crystallization—has been achieved for very small volumes and brief periods of time or by using high pressure equipment that is both costly and possibly damaging to tissues or other biological materials.

Reducing the temperature of any biological material—such as cold storage of perishable foods and organs for transplantation—slows down metabolic and other reactions. Supercooling extends this metabolic deceleration further without the damage caused by ice crystallization.

Following upon observations by lead author Haishui Huang, Ph.D., the team first found that sealing the surface of a small (1 ml) water

sample with a hydrocarbon-based oil—such as mineral oil, olive oil or paraffin oil—could suppress ice formation at temperatures as low as -13° C (around 9° F) for up to a week.

Through a series of experiments both with more complex oils and with pure simple hydrocarbons, such as alcohols and alkanes, they succeeded in keeping 1 ml samples of water and cell suspensions supercooled at -20° C (-4° F) for 100 days and 100 ml (3.2 oz) samples for a week.

The team also demonstrated application of their deep supercooling method to the extended preservation of red blood cells.

While red blood cells are usually stored at 4° C (39° F) for as long as 42 days, recent reports have suggested that cell quality at that temperature begins to decline after around 14 days, and irreversible cellular injury sets in after 28 days, challenging current blood banking practice.

The MGH-CEM team's preliminary experiments indicated that their deep supercooling approach could safely preserve red-blood-cell suspensions of up to 100 ml at -13° C for as long as 100 days, more than doubling the current storage time.

"We currently are conducting experiments to increase the volume of red blood cell storage samples up to the more clinically relevant 300 to 500 ml range," says Usta, who is an assistant professor of Surgery at Harvard Medical School.

"We also are working on applying this method to other cells and on translating it to large tissues and whole organs like the liver. Along with potential applications in medicine and food preservation, we also believe this invention could be used to study chemical reactions in the liquid state at low temperatures without the usual costly and complicated high-pressure equipment."

More information: *Haishui Huang et al, Long-term deep-supercooling of large-volume water and red cell suspensions via surface sealing with immiscible liquids, Nature Communications (2018).* *DOI: 10.1038/s41467-018-05636-0*

http://bit.ly/2nyLPEr

Bacteria spread through dog saliva linked to death of South Milwaukee woman

A bacteria spread through animal saliva, has been linked to two other Wisconsin cases in recent years, including the death of a Milwaukee County woman

Samantha West, Milwaukee Journal Sentinel Published 2:10 p.m. CT Aug. 11, 2018 | Updated 11:55 p.m. CT Aug. 11, 2018

A bacteria spread through animal saliva, which forced the amputation of a West Bend man's hands and legs in June, has been linked to two other Wisconsin cases in recent years, including the death of a Milwaukee County woman. Sharon Larson, 58, of South Milwaukee, died June 23, not long after being nipped by her new dog, Bo, according to a report by WISN-TV.

(Photo: Courtesy of sepsis.org)

And a then-3-year-old Grant County boy, Liam Young, had his fingers and toes amputated in 2015 after he developed the same infection, his father said Saturday.

Both had tested positive for capnocytophaga canimorsus, a bacteria often found in the saliva of dogs and cats.

In June, Greg Manteufel of West Bend lost both hands and his lower legs because of the same bacteria, which entered his bloodstream, causing sepsis. Although he had contact with a few dogs just before he'd gotten the infection, none had bitten him.

The mystery surrounding the condition drew national attention from news outlets across the country, including The Washington Post and Newsweek.

The stories had the same pattern – flu-like symptoms that rapidly grew more serious, sometimes to the point of death.

"She just kept getting worse," Larson's husband, Daniel, told the TV station of his wife. "Now I feel like I lost my right arm, my best friend, my wife. It's tore me apart."

Hearing Larson's and Manteufel's stories caused memories to flood back to Chris Young, Liam's father, who remembers all too well when his son's seemingly minor flu symptoms grew so serious he was put into a medically induced coma and lost his fingers and toes.

Doctors still aren't sure what caused the infection in Liam, now 5.

After a full genetic analysis of Liam and his parents, Chris Young said they discovered less than a month ago that capnocytophaga may have played a role.

"This was the first time I'd seen a story similar with that bacteria involved," Young said. "It was just kind of insane. It feels like it's starting to happen more, or people are just starting to discover what it actually is."

Liam Young of Louisburg suffered from an infection that was likely caused by a bacteria often found in dogs and cats called Capnocytophaga canimorsus. **(Photo: Family photo)**

Although the bacteria is common and not harmful to pets, it can in rare cases make humans sick, according to the Centers for Disease Control and Prevention. About 30% of people who are infected die as a result, it said. The agency does not track it because it is considered so rare.

People who abuse alcohol, don't have a spleen, have weak immune systems, or have cancer, diabetes or HIV are at more of a risk to be affected by the bacteria, according to the CDC.

Neither Manteufel nor Larson reported any of these risk factors before the infection set in, according to NBC News. Both their illnesses began with flu-like symptoms that grew more serious within days of making contact with a dog.

"My mother was amazingly kind; she would do anything for others," Stacy Larson-Hruzek told NBC News. "Her smile will live on through her five grandkids, and a sixth on the way."

http://bit.ly/2McozL3

From folklore to pharmacy

It's used to treat gout or in most common use is in dressings.

By Hayley Bennett13 August 2018

A dark red resin oozes from the trunk of *Croton lechleri,* giving the tree its Peruvian name, *Sangre de grado*: 'dragon's blood'. The people of the western Amazonian rainforest prize this tree for its medicinal properties, and they use it to treat everything from haemorrhoids to haemorrhaging.

The dragon's blood tree grows in South America and has been used by indigenous people to cure a range of problems **Source: © Blend Images/Alamy Stock Photo**

Bernabé Cobo, a Spanish missionary and naturalist who was posted to missions across Bolivia and Peru during the 17th century, was among the first to document its use. 'This brew helps stop all kinds of incontinence and washing the haemorrhoids with it stops the bleeding common on them ,' he wrote in his *History of the New World*. 'The brew of its leaves and bark, when drunk daily, stops the flow of blood in the chest and stomach, and blood in urine.' *Sangre de grado* can also be found in traditional remedies for gastrointestinal and circulation problems, staph, cancer and rheumatism. Cobo even described how, in a salty brew with

Peruvian peppertree and wine, it's used to treat gout. As for the sap, one of its most common uses is in dressings. The resin is daubed on open wounds, where it dries to form a blood-coloured latex seal that prevents infection.

Think some of this sounds like an old wives' tale? Dragon's blood is now a *bone fide* medicine.

Six years ago, crofelemer, an extract from *Sangre de grado* sap, was approved by the Food and Drug Administration (FDA) in the US as a prescription drug for treating chronic diarrhoea in people with HIV. It's the only antidiarrheal available that doesn't interfere with antiretroviral medication and, apparently, it works – in clinical trials, 89% of patients on the two-pill-a-day regimen had a reduction in symptoms and over half had no diarrhoea at all after 20 weeks.

Napo Pharmaceuticals, who market crofelemer as Mytesi, just signed a deal in the US with the Aids Drug Assistance Programs, which means people on low incomes in every state will be able to get it on the cheap.

Because it's not a single molecule, crofelemer went via a slightly different route to get FDA approval compared to most drugs.

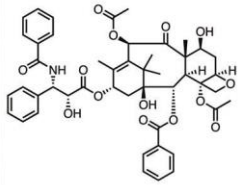
Another anticancer drug, vincristine (right), is isolated from the periwinkle, as is vinblastine (not shown) **Source: Periwinkle flowers © iStock/Getty Images**

The 'botanicals' pipeline allows drug makers to market mixtures of compounds from natural sources and takes into account any history of use in traditional medicine. Crofelemer is one of only two drugs to get approval via the botanicals route since the FDA first released its guidance for the process in 2004. So how does folklore become an FDA-approved treatment and why aren't more traditional plant-based remedies making it?

The plants behind the pills

The fact that plants have a long history in modern medicine has not escaped today's pharmaceutical chemists.

Let's return to Peru briefly for an example: quinine. Long before the advent of modern medicine, the Peruvians were fending off malaria with bark from the 'quina-quina' tree (now known as cinchona). According to legend, it was given as a cure to a Spanish countess who fell ill with the disease in Lima in around 1630.[1] And it was Cobo again who was first to bring the bark to Europe. Quinine was eventually purified from the bark by French pharmacists and is still the next best option in areas of the world where other antimalarial drugs aren't available.



Yew tree bark (left) and Taxol structure (right) **Source: Yew tree image © Alan Sirulnikoff/Science Photo Library**

There are contemporary examples too, as Satyajit Sarker, director of the school of pharmacy at Liverpool John Moores University, points out. Several prominent cancer drugs come from plants, including paclitaxel (Taxol) from yew trees, and vincristine and vinblastine from periwinkle flowering plants. 'They are a great success,' he says. Despite this, only around 15% of plant species have ever been investigated and, according to Sarker, some that have already been dismissed could still yield interesting compounds with the help of modern separation and identification techniques.

Microbes tend to be more popular sources, though most chemists who work on microbes could probably work on plants. 'Once you have the extract, whether it is from microbes or plants, you have to test that extract in the same ways,' he says.

With a quarter of a million plants to get through, working with those from traditional medicine at least provides a starting point, but even that's a broad spectrum. For Sarker, the most reliable selection approach is a thorough search of the literature, which might include phytochemical databases and books on Chinese traditional medicines, as well as what we think of as ordinary scientific journals. Others favour field work. This was the ethnobotanical approach that led Steven King – today executive vice-president at Napo Pharmaceuticals – to pursue the promise of dragon's blood for three decades. He is reported to have applied the sap to his savaged feet whilst working with Amazonian tribes in the 1970s.

Someone else who's more comfortable in the field is Cassandra Quave, an ethnobotanist based at Emory University in Atlanta, US. She describes her approach as 'using human knowledge of the environment' to guide the search for medicine, though admits it may all seem a little 'out there' for some people's tastes. 'This whole thing where I go out and hike, talk to people in different languages and collect plants – I mean, that's kind of weird for a lot of people,' she says. But it's led her to make some interesting selections.

Her current project is one that she's now considering taking down the botanicals route. It began with a trip to southern Italy more than a decade ago, when she heard from locals about how they use sweet chestnut leaves in a rinse to treat inflamed skin.

Sweet chestnut trees, the source of the chestnuts we roast and eat out of paper cones at Christmas markets, are found all over Europe. Their leaves are a little toothier and less broad than those of a horse chestnut.

The Italian skin rinse piqued Quave's interest because she knew that, in eczema, the sore patches of skin are a breeding ground for the bacterium *Staphylococcus aureus*. If extracts from this very common tree could take out staph, they might even offer a new strategy for tackling MRSA – the drug-resistant form. So she collected some leaves, dried them, and sent them home to the US in a vacuum-sealed bag for later analysis.

Fruity fractions

However you get your hands on the plants, it's at this point that the serious business of phytochemistry begins. 'It's a long process,' Sarker explains, and a repetitive one involving extraction, fractionation and testing of the various fractions for activities that could be important in disease. In traditional remedies, crude extracts or infusions might work wonders, but for chemists, it's all about refining down the extract to the smallest possible number of compounds that have an effect and trying to work out exactly how those compounds interact with cells. The bioactive ones will often be plant secondary metabolites; molecules with some non-essential role in the plant.

The first principle of any anticancer drug is that it will have to kill cells

Generally, the process starts with grinding the plant material into a fine powder to increase the surface area, then extraction using solvents of increasing polarity.

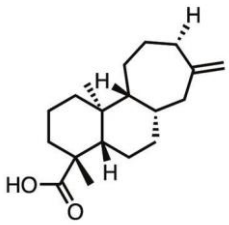
The initial extractions get rid of the oily and fat-linked compounds, leaving polar compounds like the flavonoids, tannins and lignins to the methanol extract, usually the most active portion. However, each has to be tested.

As one of Sarker's main focuses is anticancer compounds, his starting point is often a cytoxicity – cell-killing – assay. 'The first principle of any anticancer drug is that it will have to kill cells,' he says. 'So we do the assay to find out which one of these extracts is active.'

By now, the number of different molecules has shrunk significantly but it's still too many to deal with. 'You have one total methanol extract, which contains maybe 100 to 200 compounds,' says Sarker. 'So now we have to fractionate them according to the various

chemical groups.' They do this using solid phase extraction, working from low concentrations to high concentrations of methanol in water, to produce different fractions that are again dried and tested to find out which is active. Then it's down to high-performance liquid chromatography (HPLC) to separate the compounds from the active portion.

Finally, when they've narrowed down their candidate compounds to around 10–15, they start using spectroscopic techniques like nuclear magnetic resonance (NMR) and mass spectroscopy to identify them, confirming which ones are responsible for the plant's medicinal properties with yet more activity tests.



Kaurenoic acid

Sarker's team recently went through a version of this process with some small reddish-orange fruits picked up in a market in Dschang, Cameroon.[2] The dried fruits of 'sand knobwood' (*Zanthoxylum leprieurii*) are made into infusions for treating sickle cell anaemia but are also notable in the scientific literature for containing compounds with anticancer and antimicrobial activities. The fruit extracts yielded five diterpene compounds, one of which wiped out 92% of human prostate cancer cells in a cytotoxicity assay. Spectroscopic data confirmed it was kaurenoic acid, a molecule with known painkilling, anti-inflammatory and antioxidant activities, but it was the first time the compound had been isolated from the tree or any of its relatives in the genus *Zanthoxylum*. What's satisfying about this work is that it can validate the medicinal benefits of plants that are already widely used in traditional treatments. From here, Sarker hands over any potential lead compounds to other groups or companies that carry out animal testing, where the task of developing an anticancer drug based on a single molecule can begin in a fairly typical way.

In the mix

However, it's not always possible to nail a single molecule that's responsible for a plant's beneficial effects. At the time of writing, Quave is still working on isolating active compounds from sweet chestnut. After the vacuum-sealed leaves arrived from Italy, the Emory team worked hard on making its extracts and separating them into various fractions, but soon discovered that they were useless at killing staph.

For Quave, this was just an incentive to start thinking further outside the box. Eventually, in a 2015 paper in *PLoS ONE*,[3] she and her team showed the surprising way in which a plant that has no power to kill MRSA could stop it causing harm. Instead of destroying the bugs, like conventional antibiotics, sweet chestnut stops them communicating.

Although they couldn't pinpoint the exact mechanism, or compound, Quave's team showed that something in the most potent portion of their extract (labelled 224C-F2) was inhibiting staph signalling molecules involved in triggering bacterial toxin production.

This same portion also reduced the size of skin ulcers in mice infected with MRSA. Ironically, the fact that 224C-F2 doesn't actually kill staph is what makes it such an exciting prospect, because it may exert less pressure on the bug to adapt and develop resistance.

After hearing that Italians use sweet chestnut leaves to treat inflamed skin, Cassandra Quave hopes that compounds from them may be able to treat staph infections **Source: © Colin Varndell/Science Photo Library**

The implication is that Quave may have found a whole new way to treat staph infections, but because she's still working with a mixture of plant molecules she's going to have some tricky decisions to make; whether to go down the botanical route to getting a treatment approved, or the ordinary one. 'I'm torn in two directions here,' she says. 'On the one hand, we can create an enriched extract that works really well in vitro and also in animals, and there is a drug development pathway for that. On the other hand, to make this really amenable for, perhaps, joint therapy with antibiotics in the future, the best scenario would be to isolate a single compound.'

With botanicals, it's most likely that it's a group contribution

If she did go down the botanicals route, 224C-F2 would be thrown into a pipeline with at least 600 other botanicals registered as investigational new drugs since its inception – with only crofelemer and a genital warts product, sinecatechins, having seen the light of day so far. According to the FDA, only 2% (so roughly 12) of these potential products have made it to phase III clinical trials thus far. The proportion of ordinary investigational new drugs that make it is 23%, although it's difficult to make comparisons given that so few botanical drugs have gone through the whole process.

There is an argument for going down the botanical route in cases where an extract is safe and does a decent job, especially if it appears the composition or mixture works better than any single compound that it contains. 'With botanicals, it's most likely that it's a group contribution; that individual isolates may not work,' explains Laird Forrest, a pharmaceutical chemist at the University of Kansas in the US. 'It's more a synergy between all of them together.' Which brings us back to dragon's blood.

While some of the early studies on crofelemer put its antidiarrheal activity down to a molecule called SP-303, a precursor to the drug,[4] Forrest's recent work for the FDA shows there are many different chemical structures that have a similar effect.[5] The crofelemer molecule itself is a type of polyphenol called a proanthocyanidin that is made up of catechin (a type of flavonoid) subunits linked together in a polymer chain. In the extract made from the Amazonian tree sap, however, the number of catechin units in each chain varies wildly, depending on aspects such as the particular grove of tree that the sap was sourced from, how it was harvested and even what season it was harvested in. There could be anywhere between one and 28 catechin units per chain and, according to Forrest, they all work. 'We found, actually, anything works – even the monomers,' he says. 'We analysed several available batches of crofelemer and they were very, very different on the basis of chemistry and size, but they all appeared to work the same by our *in vitro* assays.'

No one knows why these random mixtures of crofelemer chains work, because no one really knows exactly how crofelemer works. The same is true of the other approved botanical, sinecatechins, which is also catechin-based. Crofelemer apparently reduces diarrhoea by targeting chloride channels in gut cells that are involved in triggering the passage of water through the bowel,[6] but the exact nature of its interactions with chloride channels remains unclear.

Weighing it up

It's because of the problems with variability that Sarker remains unenthused about pursuing extracts as medicine. Crofelemer is considered a relatively safe drug because it passes through the intestines without being absorbed, but Sarker says some potential botanical products could do great harm. 'There are so many variables,' he says. 'Unless they are controlled properly, it is really dangerous, because some plants growing in different places may have different compositions of compounds. The balance between toxicity and efficacy may shift and that may produce unnecessary side effects, or even kill patients.' Unfortunately, it may be the only

cost-effective option for drug development in countries with limited resources for R&D.

For a scientist in a rich country, it's more about weighing up the best way to get your treatment to market when it's more complex than a single molecule. Mixtures, in particular, are a headache. As Quave explains, doing all the pharmacology on one compound is hard enough; add in one more, plus the pharmacology on both together, and things are already very complicated, never mind if you want to mix up, say, five. And that's if you know what all the important compounds are.

Crofelemer is isolated from dragon's blood tree sap, whose appearance may give you a clue where it gets its name from… **Source: © Morley Read/Science Photo Library**

For those who do end up going down the botanicals route, it's not much different to the regular one. According to the FDA, botanicals are given some 'flexibilities' in the early phase trials given previous use in humans but the process is otherwise the same as it is for all drugs. As Jeremy Kahn, a spokesperson for the Center for Drug Evaluation & Research at the FDA, points out, botanicals do have some additional issues that can frustrate the process. 'Botanical mixtures often contain small and large molecules, and there are often challenging issues surrounding analytical method and reference standard development.' He lists raw material and manufacturing process control, and batch-to-batch consistency, as additional challenges. How can you tell, for example, if the correct plants have been harvested, or if they're suddenly being imported from a completely different country?

The FDA is trying to address these problems. When it commissioned Forrest's crofelemer studies, it was trying to learn something more general about how to test batch quality in botanicals. The trouble with modern analytical techniques is that there are a lot to choose from, so the FDA wanted ways to establish the fewest possible number of tests that could determine quality. Forrest's approach was interesting because he uses machine learning. Put simply, he uses computers to look at large amounts of data and pick out what's critical; in this case, the tests that are going to determine quality. '[The FDA] told us that they do plan to incorporate this type of machine learning into development programmes in the future,' says Forrest.

Time is a healer

If crofelemer is anything to go by, getting a botanical through the FDA is not exactly a breeze. The normal approval process is said to take an average of 12 years. After being granted 'fast-track' designation in 1998, crofelemer suffered issues of 'identity and potency' (in Forrest's words) before eventually being approved 14 years later, by which time its original backers, Shaman Pharmaceuticals, had filed for bankruptcy.

The plants that had some effect became traditions that were passed down and refined over the centuries

For now, Quave is continuing the hunt for a single active molecule in sweet chestnut, though she's bearing in mind 'what's really feasible for getting these drugs out to people through frameworks that currently exist for approval and manufacturing'. Getting to the root of how some of these traditional medicines work can be a trial, even with all the tools of modern medicine. Yet, for hundreds of years, communities developed practical treatments based on the only thing they had at their disposal: nature. As Quave points out, they were immersed in it 'on a daily basis'; they tasted the plants, smelled them and saw how animals interacted with them. Aside from that, there's no underestimating the importance of time. 'For those [plants] that had some effect, over the centuries, they became

traditions that were passed down and refined,' says Quave. 'Knowledge was spread, just like in the western medical systems that we have today.'

Hayley Bennett is a science writer based in Bristol, UK. Spanish translation by Adriana Castro

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