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Scientists triple storage time of human donor livers

NIH-funded research project develops new method to preserve human livers for transplantation

Scientists have greatly extended the amount of time human livers can be stored for transplantation by modifying a previous protocol to extend the viability of rat livers. Previously, human livers were only viable for an average of nine hours, but the new method of preservation maintains liver tissue for up to 27 hours, giving transplant doctors and patients a much longer timeframe to work with.

The research is supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), both part of the National Institutes of Health.

Like a glass container broken by frozen water, when cells freeze, they often experience irreparable damage. Since human cells are especially sensitive, donor livers are stored above freezing at 4 degrees Celsius. As a result, doctors can typically only preserve human livers for nine hours before the chances of a successful transplantation drastically decrease. This short time frame makes it more difficult, and sometimes impossible, to get the organs to compatible patients who are located farther away.

"Delivering viable organs to matching recipients within the window of viability can often be the most challenging aspect of organ transplantation," said Seila Selimovic, Ph.D., director of NIBIB's Engineered Tissues program. "By giving doctors and patients more time, this research could someday affect thousands of patients who are waiting for liver transplants."

In previous studies funded by NIH, Martin Yarmush, Ph.D., director of the Center for Engineering in Medicine, Korkut Uygun, Ph.D., associate professor of surgery, and their collaborators at Massachusetts General Hospital (MGH), Boston, had developed new techniques that extended the time that rat liver (hepatic) tissue can be stored at subzero temperatures without damage. They were able to do this by adding a modified glucose compound, 3-OMG, and PEG-35kD--an ingredient in antifreeze--to the protective solution that they use to cool the livers. The PEG compound lowers the temperature at which the cells freeze and 3-OMG acts as a protectant against the cold. With these additions, they were able to cool the rat livers to -6 degrees Celsius without freezing them--a process called supercooling.

However, while the techniques worked with the rat livers in those earlier studies, it was unsuccessful when applied to human livers, which are 200 times larger. The size difference significantly increased the risk that ice crystals would start to spontaneously form (heterogenous ice nucleation), making the organ unusable for transplantation. In a paper published in Nature Biotechnology on Sept. 9, Reinier de Vries, M.D., a research fellow in surgery, Shannon Tessier, Ph.D., instructor in surgery at MGH and Harvard Medical School, Boston, and Uygun, and their collaborators at MGH detail three new steps to the protocol to avoid ice nucleation and preserve human livers for up to 27 hours.

"With supercooling, as the volume increases it becomes exponentially more difficult to prevent ice formation at sub-zero temperatures," said de Vries. "Before, there were a lot of experts who said, 'well this is amazing in small rats, but it will not work in human organs,' and now we have successfully scaled it up 200 times from rat to human livers using a combination of technologies."

The first step was to limit the contact of the storage liquid to air. When supercooled, the livers are submerged in the supercooling protective solution. The researchers found that the risk of ice crystals forming greatly increased in areas where the solution was

in contact with air. To eliminate this risk, the scientists removed the air from the storage solution bag prior to supercooling, effectively eliminating the chance of spontaneous ice nucleation on the surface of the organ.

Next, the researchers included two additional ingredients to the protective solution to help protect the hepatocytes. The first additive, trehalose, helps to protect the cell as well as stabilize the cell membranes. The second, glycerol, supports the protective properties of the 3-OMG glucose compound added in the previous experiments. Both additives have been used in the cryogenic preservation of cells in the laboratory but had not been used in the preservation of organs for transplantation.

Finally, they developed a new method of delivering the preservation solution to the liver. The traditional method of delivery of the protective solution used in previous studies is to manually flush the preservation solution through the tissue. However, the new protective solution is thicker than the traditional solutions and can cause damage to the cell lining the inside of the blood vessels. In addition, the higher viscosity means that the solution is often not uniformly distributed throughout the organ, increasing the chance of ice nucleation spreading and freezing the liver. To combat this problem, the researchers used machine perfusion--a way of delivering oxygen and nutrients to capillaries in biological tissues while outside the body--at 4 degrees Celsius with the traditional protective solution. They then slowly lowered the temperature while increasing the concentration of the new protective additives. The staggered approach allowed the hepatic tissue time to adjust and the solution was able to spread throughout the organ more uniformly.

While the researchers have yet to implant a liver preserved using this new method into a human subject, traditional standards of assessing liver viability indicate that this process will not negatively affect the organ.

"This new liver preservation method exemplifies NIH's goal to foster the discovery and translation of innovative ideas," said Averell H. Sherker, M.D, NIDDK program director for liver diseases. "With further research, organs will be able to travel greater distances and benefit the most critically ill patients requiring liver transplantation."

This work was supported by NIH's National Institute of Biomedical Imaging and Bioengineering and the National Institute of Diabetes and Digestive and Kidney Diseases under award numbers R21EB023031, R01DK096075, R01DK107875, R01DK114506.

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Are the History and Physical Coming to an End?

As far back as the 1970s, doctors have pondered whether one day, as medical technology barrels ahead, the patient history and physical examination (H&P) would eventually become obsolete.

David M. Warmflash, MD

And yet, we were all told in medical school that a proper history is enough to make X percent of diagnoses, which increases further when you work in physical findings. But today we are on the brink of the era of multiomics, a term encompassing the numerous data available for patients, from genomics, epigenomics, proteomics, microbiomics, metabolomics, and an array of other omics.

These days, a health dataset from a single patient can be immense, to be sure. Advances in artificial intelligence and machine learning, however, are making it possible to organize and filter multiomic data from a patient in ways that make them useful to physicians—ways that can personalize diagnosis and care, and bypass the often imperfect recollections of patients and patients' families obtained during a history.

"We are entering an age when medicine can become truly personalized, as we learn to interpret multiomics data and integrate them with data from other sources, such as sensors, scanners,

wearables, and other devices," notes Shane McKee, MD, consultant in genetic and genomic medicine at Northern Ireland Regional Genetics Centre, Belfast City Hospital.

Arguably, today many entrepreneurs aren't merely asking whether new technology can replace the H&P but whether it can do even better. "The patient is telling us what they can via patient history, physical examination, and family history, but emerging tests are letting us in on unrecognized disease states, inherited risk, and physical circumstances," says Howard McLeod, MD, medical director of the DeBartolo Family Personalized Medicine Institute at the Moffitt Cancer Center in Tampa, Florida. "This goes beyond what a patient 'knows' and leads us toward a level of forecasting that has previously been impossible."

The relevance of obtaining a history or performing a physical has been questioned in the past, particularly with the emergence of clinical genomics and increasingly automated laboratory testing.

In 1975, the *British Medical Journal* published a paper by Hampton and colleagues exploring the relative contribution of the H&P compared with laboratory testing in the diagnosis of outpatients. Of 80 outpatients assessed, 66 (approximately 83%) could be diagnosed on the basis of only a referral letter and a medical history. A physical examination proved useful in seven of the remaining patients, making the combined H&P adequate for diagnosis of 91% of patients in the study. This was only one study, of course, but it was a watershed that has since been cited more than 700 times in the literature. The findings perhaps played a role in medical education's emphasis on the H&P.

A 2008 study published in the *British Journal of General Practice* asked essentially the same question specifically in migraine and supported the earlier findings. The authors found that when a primary care physician conducts a history revealing a new-onset unilateral headache with nausea, there is an 80% chance that the diagnosis is migraine. They felt that their data countered the idea that expanded use of MRI is useful in headache screening.

A new inquiry into the utility of multiomics in diagnosis, published this past May in *Nature Medicine*, assessed the diagnosis of type 2 diabetes mellitus. The researchers developed models for predicting insulin resistance using a combination of clinical measures along with patient data gleaned from a parade of "omes": The genome, immunome, transcriptome, proteome, metabolome, and microbiome were all assessed in the study.

The authors concluded that these omics measurements could replace traditional tests, which the paper deems burdensome.

Given the different possible manifestations of the condition, however, one of the authors of the paper, Michael Snyder, PhD, of Stanford University, was asked about the differential utility of multiomics. "Multiomics and big data will be powerful for diagnosing and subtyping complex diseases," says Snyder, who is Stanford W. Ascherman professor and chair of the Department of Genetics, and director of the Center for Genomics and Personalized Medicine. "For example, diabetes is a highly heterogenous disease, and making many measurements will likely distinguish its different subtypes."

[P]lenty of clinicians still believe in the value of simply talking to their patients...

Geneticist Angus John Clarke, a professor at Cardiff University in Wales, has argued that environmental and epigenomic factors render genomic data of minimal use without also considering family history data. Yet with multiomics now accounting for epigenomic and environmental factors, these concerns eventually may be overcome.

Adding another perspective, McKee, the Belfast genomics consultant, suggests that the new technology has set the stage for medicine to finally back away from a reliance on large devices and

suites of laboratory equipment. "Paradoxically, as medicine becomes more data oriented and technology driven—by orders of magnitude—its intrusion into our everyday lives as patients will become less, and we'll hardly even recognize it as medicine," suggests McKee. "That sounds like a very attractive goal."

Plenty of clinicians still believe in the value of simply talking to their patients, however, even if not for the explicit purpose of obtaining data relevant to a diagnosis.

PhenoMx, a biotechnology company based in New York City, is commercializing what it calls a personalized digital physical examination. The idea is to make MRI more accessible to the public and use full-body scanning as a preventive tool, as opposed to its typical use in diagnosis. Despite the company's mission, COO Mark Luhovy, MD, isn't suggesting that physicians abandon the tried-and-true patient encounter.

"Integrated multiomics, next-generation imaging, and wearables' data will reduce physician diagnostic speculation and enhance prognostic modeling capabilities," he says. "But the patient story must remain preserved to ensure an authentic connection. Not all of the information exchanged during a physician-patient interaction is quantifiable."

Stanford Medical School's Stanford Medicine 25 program is one of the leading programs intent on fostering bedside medicine. Through various in-person and online courses, it trains young physician on the importance of observing and connecting with their patients, which typically includes a thorough physical exam and patient history.

In a recent video published on Medscape, program director Dr Abraham Verghese commented, "...the more things that we can do at the bedside and interpret for the patient, the better. The key element is that we should still be there; it would be a mistake to do those things and disappear ourselves."

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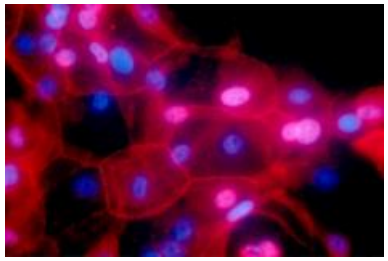
Who's Missing From Breast Cancer Trials? Men, Says the F.D.A.

Men do get breast cancer, but they account for fewer than 1 percent of patients and often receive inadequate care.

By Roni Caryn Rabin

In recent years, health officials have pushed aggressively to include more women in clinical trials of new drugs. Gone is the ban that once excluded women of childbearing age from participating in studies. Even scientists who work with animals are now encouraged to include mice and rats of both sexes.



A culture of human breast cancer cells. In the majority of men with breast cancer, tumors are fueled by the hormone estrogen. **Ewa Krawczyk/NCI/Georgetown Lombardi CCC, NIH, via Associated Press**

But when it comes to breast cancer, it is men who get short shrift. They are often excluded from clinical trials of new treatments. When new breast cancer drugs come to market, there is little data to indicate whether they are safe or effective in men. Some new drugs are approved only for women.

The disease is extremely rare in men, who account for fewer than 1 percent of breast cancer cases. Nonetheless, the Food and Drug Administration is calling on researchers to include male patients in clinical trials of breast cancer treatments, even if the studies are unlikely to enroll more than a handful of male patients.

The guidance is a draft recommendation now open to public comment. Some breast cancer specialists called it a long overdue step.

"It's so frustrating in clinic to see patients and say, 'Well, we don't really know — the drugs have been tested in women. We think it

should work in men, but there's no real evidence to back that up,'" said Dr. Sharon Giordano, a professor of breast medical oncology at M.D. Anderson Cancer Center in Houston who treats many male patients.

Even if only a few men participate in each trial, data on them could be pooled. Coupled with real-world experience using the medications, that data could shed light on treatment of men, she said.

The proposed guideline comes amid growing concerns that men with breast cancer — whose disease tends to be diagnosed in more advanced stages — are often not getting optimal care and may be missing out on lifesaving therapies.

One of the largest analyses of these patients, published in Annals of Oncology in 2017, reported what the authors called "troublesome findings." The study, carried out by the International Male Breast Cancer Program, analyzed 1,500 men with breast cancer in Canada, the United States and seven European countries.

The vast majority of men with breast cancer have tumors that are fueled by estrogen. (Men produce the hormone, too.) In the study, virtually all men whose cancer had not spread had estrogen-receptor-positive tumors, which should be treated with therapy to reduce estrogen levels in the body or to block the hormone from attaching to breast cancer cells.

But only 77 percent of these patients received anti-estrogen therapy, the study found. That means that nearly one in five men who should have received a potentially lifesaving therapy did not get it, said Dr. Fatima Cardoso, the lead author of the study and director of the breast unit at Champalimaud Clinical Center in Lisbon. "We don't know why," she said.

The most common treatment for men was surgery: a mastectomy to remove the breast, or a lumpectomy to remove the tumor. But the men had low rates of radiation treatment, which is standard care after a lumpectomy and often recommended after a mastectomy if, for example, the tumor is very large, said Dr. Marisa C. Weiss, founder of Breastcancer.org. The study called the low rates a "major concern."

Poor care is all too common when patients suffer from rare diseases, and for men, breast cancer is a rare disease, Dr. Cardoso noted.

"Many, many oncologists have never seen a case of breast cancer in a male patient," she said. For these patients, she added, it's particularly important to find experienced doctors.

Men with breast cancer are often older. They may have very large tumors by the time they seek care, because they were not on the lookout for the disease.

"Some men are not even aware they have breasts and not aware they can have breast cancer," Dr. Cardoso said. "Even health professionals often don't think about it. General practitioners who see male patients don't pay attention to the breast."

"We need a lot of education to remind men they have breasts, too, and should check them," she said. "And if they find something, go to the oncologist fast."

Dr. Cardoso and other experts welcomed the proposed new guidelines, but said researchers should collaborate on large international trials focused on men with breast cancer. When the patient population is small, large trials are needed to make significant findings.

"Some data is better than no data, but it's not the ultimate solution," said Dr. Larry Norton, chairman of clinical oncology at Memorial Sloan Kettering Cancer Center in New York.

But pharmaceutical companies are not very interested in funding such trials. "No one wants to invest in a disease that is only 1 percent of all breast cancers," Dr. Cardoso said.

As with women, one of the first warning signs of breast cancer in men can be a lump in the breast. Other possible early symptoms

include nipple pain, discharge from the nipple, a sore on the nipple or areola, an inverted nipple, or swollen lymph glands under the arm.

The risk of breast cancer in men increases with age, and is higher in men who have high estrogen levels or genetic mutations, or who have been exposed to radiation. Men with Klinefelter syndrome — who carry an extra X chromosome — are also at increased risk.

Family history is important: Doctors recommend all men with breast cancer be tested for mutations in the BRCA1 or BRCA2 genes, which are linked to both breast and ovarian cancer in women. Men who have mutations in these genes are 80 times as likely to develop breast cancer as men without these mutations. A positive result alerts female relatives that they may need to be tested, as well.

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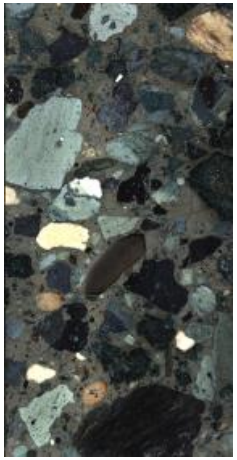
The rocks below a famous crater

Geologists examine what unfolded after that asteroid hit.

Richard A Lovett reports.

Scientists drilling into the heart of the Chicxulub impact crater in the Gulf of Mexico have discovered 130 metres of sediments laid down within hours after the site was struck by the asteroid widely believed to have killed off the dinosaurs.



In part, it's exciting because of the link to the dinosaurs. But it also gives geologists a chance to watch how events unfolded on a time scale of minutes to hours, says Sean Gulick, a geophysicist at the University of Texas, Austin, as opposed to thousands or millions of years, "which is what normal geology would look like".

A portion of the drilled cores from the rocks that filled the crater. International Ocean Discovery Program

The Chicxulub crater was formed 66 million years ago when a 10-kilometre-wide asteroid or comet ploughed into the ocean near what is now Mexico's Yucatan Peninsula.

In 2016, Gulick co-led a team from the International Ocean Discovery Program (IODP) that drilled into the 200-kilometre wide crater in an effort to better understand its history.

The site they chose was a portion of the now-buried crater's peak ring, formed when the impact caused rock from deep beneath the surface to splash upward, forming a plateau near the crater's centre. However, because the ocean at that time was hundreds of metres deep, the peak ring never rose above sea level.

Not that the impact zone was immediately submerged. Initially, the blast drove the water away, leaving a zone of molten rock known as impact melt – now solidified into lava.

But soon, the water came rushing back. At first, Gulick says, it hit the impact melt and exploded into steam, creating about 10 metres of shattered rock, just above the now-solidified impact melt.

That was followed by 80 to 90 metres of gravel-like sediments, with the larger gravel at the bottom and the smaller at the top. The only way that could have happened, he says, is if the waters rushed back so quickly that they were still full of rocks from the blast – rocks that then settled to the bottom: big ones first, smaller ones later.

There are also signs, he says, that the water sloshed around within the crater, like bathwater in a tub. Then came a 10-centimetre layer of gravel-sized material that appears to have been created by the disturbance of the sea floor by a fast-moving wave: i.e., a tsunami.

Gulick thinks it was created when the outrushing waters from the impact reflected off the nearest landmass – which at the time would have been mountains in central Mexico, 800 kilometres away – then came back to deposit sediments on top of the 130 metres of rocks already deposited in the aftermath of the impact.

Support from this, he says, comes from the fact that these deposits contain perylene, a chemical made only in soils. That, he says, "would require land, somewhere, to have been touched by water that then came rushing back".

None of this means the Chicxulub impact killed the dinosaurs. Others have argued that climate-changing volcanism in India may instead have been the culprit. But Gulick's samples also contain charcoal in the layers directly above the tsunami deposits, suggesting that the impact may have set off massive wildfires. "We knew impacts can make wildfires," he says. "But this is direct evidence that this happened at ground zero."

In addition, the rocks returning to the crater after the impact were low in sulfur, even though geologists knew that about one-third of the ones in the impact area initially contained sulfur-rich minerals like gypsum or anhydrite. The sulfur from these rocks must therefore have been vaporised by the impact, Gulick says.

And when it mixed with vaporised ocean water, it would have filled the upper atmosphere with hundreds of gigatons of sulfate aerosols, creating a bright haze that would have dropped global temperatures by more than 25 degrees Celsius, "putting most of the world below freeing for most of the year" – and possibly lasting for "a decade or two".

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New flying reptile species was one of largest ever flying animals

A newly identified species of pterosaur is among the largest ever flying animals, according to a new study from Queen Mary University of London.

Cryodrakon boreas, from the Azhdarchid group of pterosaurs (often incorrectly called 'pterodactyls'), was a flying reptile with a wingspan of up to 10 metres which lived during the Cretaceous period around 77 million years ago.

Its remains were discovered 30 years ago in Alberta, Canada, but palaeontologists had assumed they belonged to an already known species of pterosaur discovered in Texas, USA, named Quetzalcoatlus.

Cryodrakon boreas. **David Maas**

The study, published in the *Journal of Vertebrate Paleontology*, reveals it is actually a new species and the first pterosaur to be discovered in Canada.

Dr. David Hone, lead author of the study from Queen Mary University of London, said: "This is a cool discovery, we knew this animal was here but now we can show it is different to other azhdarchids and so it gets a name."

Although the remains—consisting of a skeleton that has part of the wings, legs, neck and a rib—were originally assigned to Quetzalcoatlus, study of this and additional material uncovered over the years shows it is a different species in light of the growing understanding of azhdarchid diversity.

The main skeleton is from a young animal with a wingspan of about 5 metres but one giant neck bone from another specimen suggests an adult animal would have a wingspan of around 10 metres.

This makes *Cryodrakon boreas* comparable in size to other giant azhdarchids including the Texan Quetzalcoatlus which could reach 10.5 m in wingspan and weighed around 250 kg.

Like other azhdarchids these animals were carnivorous and predominantly predated on small animals which would likely include lizards, mammals and even baby dinosaurs.

Dr. Hone added: "It is great that we can identify Cryodrakon as being distinct to Quetzalcoatlus as it means we have a better picture

of the diversity and evolution of predatory pterosaurs in North America."

Unlike most pterosaur groups, azhdarchids are known primarily from terrestrial settings and, despite their likely capacity to cross oceanic distances in flight, they are broadly considered to be animals that were adapted for, and lived in, inland environments.

Despite their large size and a distribution across North and South America, Asia, Africa and Europe, few azhdarchids are known from more than fragmentary remains. This makes Cryodrakon an important animal since it has very well preserved bones and includes multiple individuals of different sizes.

More information: *'Cryodrakon boreas gen. et sp. nov. a Late Cretaceous Canadian azhdarchid pterosaur'. Hone, David; Habib, Michael; Therrien, Francois. Journal of Vertebrate Paleontology. DOI: 10.1080/02724634.2019.1649681*

Journal information: Journal of Vertebrate Paleontology

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Scientists find biology's optimal 'molecular alphabet' may be preordained

The amino acids, a fundamental set of life's building blocks, may have been adaptive throughout their evolution, suggesting a possible universal biological language.

An international and interdisciplinary team working at the Earth-Life Science Institute (ELSI) at the Tokyo Institute of Technology has modeled the evolution of one of biology's most fundamental sets of building blocks and found that it may have special properties that helped bootstrap itself into its modern form.

All life, from bacteria to blue whales to human beings, uses an almost universal set of 20 coded amino acids (CAAs) to construct proteins. This set was likely "canonicalized" or standardized during early evolution; before this, smaller amino acid sets were gradually expanded as organisms developed new synthetic proofreading and coding abilities. The new study, led by Melissa Ilardo, now at the University of Utah, explored how this set evolution might have occurred.

There are millions of possible types of amino acids that could be found on Earth or elsewhere in the Universe, each with its own distinctive chemical properties. Indeed, scientists have found these unique chemical properties are what give biological proteins, the large molecules that do much of life's catalysis, their own unique capabilities. The team had previously measured how the CAA set compares to random sets of amino acids and found that only about 1 in a billion random sets had chemical properties as unusually distributed as those of the CAAs.

The team thus set out to ask the question of what earlier, smaller coded sets might have been like in terms of their chemical properties. There are many possible subsets of the modern CAAs or other presently uncoded amino acids that could have comprised the earlier sets. The team calculated the possible ways of making a set of 3-20 amino acids using a special library of 1913 structurally diverse "virtual" amino acids they computed and found there are 10^{48} ways of making sets of 20 amino acids. In contrast, there are only ~ 10^{19} grains of sand on Earth, and only ~ 10^{24} stars in the entire Universe. "There are just so many possible amino acids, and so many ways to make combinations of them, a computational approach was the only comprehensive way to address this question," says team member Jim Cleaves of ELSI. "Efficient implementations of algorithms based on appropriate mathematical models allow us to handle even astronomically huge combinatorial spaces," adds co-author Markus Meringer of the Deutsches Zentrum für Luft- und Raumfahrt.

As this number is so large, they used statistical methods to compare the adaptive value of the combined physicochemical properties of the modern CAA set with those of billions of random sets of 3-20 amino acids. What they found was that the CAAs may have been

selectively kept during evolution due to their unique adaptive chemical properties, which help them to make optimal proteins, in turn helping organisms that could produce those proteins become more fit.

They found that even hypothetical sets containing only one or a few modern CAAs were especially adaptive. It was difficult to find sets even among a multitude of alternatives that have the unique chemical properties of the modern CAA set. These results suggest that each time a modern CAA was discovered and embedded in biology's toolkit during evolution, it provided an adaptive value unusual among a huge number of alternatives, and each selective step may have helped bootstrap the developing set to include still more CAAs, ultimately leading to the modern set.

If true, the researchers speculate, it might mean that even given a large variety of starting points for developing coded amino acid sets, biology might end up converging on a similar set. As this model was based on the invariant physical and chemical properties of the amino acids themselves, this could mean that even Life beyond Earth might be very similar to modern Earth life. Co-author Rudrarup Bose, now of the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, further hypothesizes that "Life may not be just a set of accidental events. Rather, there may be some universal laws governing the evolution of life."

Reference:

Melissa Ilardo[1], Rudrarup Bose[2], Markus Meringer[3], Bakhtiyor Rasulev[4], Natalie Grefenstette[5], James Stephenson[6,7], Stephen Freeland[8], Richard J. Gillams[9,10], Christopher J. Butch[9,11,12] & H. James Cleaves II[9,12,13]*

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The Lancet Infectious Diseases: New strain of strep a is causing scarlet fever and invasive infections in England and Wales

Scientists warn vigilance is needed to monitor impact of new bacterial strain on public health

Scientists studying scarlet fever have identified a new strain of disease-causing bacteria, which may explain a rise in more serious Strep A infections in England and Wales, according to results from cases in London and across England and Wales from 2014-16 published in The Lancet Infectious Diseases journal.

In 2014, England experienced the biggest surge in scarlet fever cases since the 1960s. Numbers continued to increase, with 15,000 cases in 2014, 17,000 in 2015 and over 19,000 in 2016. Symptoms, which affect young children, include a high temperature, sore throat, and a pink-red rash that feels like sandpaper [1]. Scarlet fever is caused by toxins released by the bacterium Streptococcus pyogenes, also known as Strep A, and cases follow a seasonal pattern peaking between March and May. Scarlet fever is easily treated with antibiotics. Cases of invasive infections caused by the same bacterium also increased in 2016 compared to the previous five years.

In this new study, the authors provide an explanation for the association between increased incidence of scarlet fever and increased incidence of more serious invasive infections such as

bloodstream infections. They uncovered a new strain of Streptococcus pyogenes with increased capacity to produce scarlet fever toxin.

"Given that this strain has an apparently enhanced ability to cause all types of Strep A infection, it is important to monitor the bacterium both here and globally," says joint first author, Dr Nicola Lynskey from Imperial College London, UK. [2]

The researchers set out to identify the Strep A strains causing infections in London and more widely in England and Wales, as defined by the type of emm gene present. They found that the initial upsurge of scarlet fever in 2014 in London was associated with Strep A strain types emm3 and emm4. However, during the spring of 2015 and 2016, emm1 strains became dominant among throat infections.

In Spring 2014, only 5% (five of 96) of isolates of the bacterium collected in northwest London were emm1 strains, but by 2015, this had increased to 19% (28 of 147). In 2016, emm1 became the single most frequent strain at 33% (47 of 144 isolates).

Analysis confirmed that emm1 strains also became increasingly dominant among strains causing severe invasive infections more widely within England and Wales. By Spring 2016, 42% (267 of 637) of invasive strains collected in England and Wales were emm1 isolates, up from 31% (183 of 587) in Spring 2015.

To investigate the emm1 isolates further, researchers sequenced the genomes of all 135 non-invasive emm1 isolates of the bacterium, collected in northwest London between 2009 and 2016, and all 552 invasive emm1 isolates collected in England and Wales during the seasonal disease spikes between 2013 and 2016, and compared them with one another. They assessed how much toxin was produced by different emm1 strains.

The researchers found that the majority of emm1 strains from 2015 and 2016 were a distinct, breakaway emm1 clone which they refer to as M1UK. The clone had 27 unique mutations, and was associated with significantly increased production of the toxin streptococcal pyrogenic exotoxin A (SpeA). This toxin triggers scarlet fever and may contribute to Strep A pharyngitis and some invasive infections. Analysis confirmed that M1UK produces nine times more toxin than other emm1 strains (190 nanograms per millilitre (ng/mL) compared to 21 ng/mL). It was present in England as early as 2010 and by 2016, M1UK represented 84% of all emm1 genomes analysed in England and Wales.

"The new, more toxigenic strain that we have identified has become the dominant cause of more serious emm1 Strep A infections," says joint first author Dr Elita Jauneikaite from Imperial College London, UK. [2]

The authors speculate that the recent increase in activity of the Streptococcus pyogenes bacterium, which coincided with upsurges of scarlet fever, might have provided the conditions required for it to adapt genetically and spread within the UK.

The researchers compared the M1UK strains with 2,800 emm1 genomes from around the world. The M1UK strains were found to be unique and distinct. However, genetic analysis of strains collected in Denmark and the US also revealed single isolates of M1UK. The authors cannot confirm whether the new strain will be suited to environments in other countries, where factors such as climate and management of streptococcal sore throat vary. However, as SpeA toxin was implicated in the global re-emergence of severe invasive infections in the 1980s, they indicate that wider surveillance will be important.

"The distinct bacterial clone we have discovered appears so far to be largely limited to the UK, but the fact that we have identified two examples of it elsewhere suggests it has the potential to spread internationally and may already be present in other countries. However, it's also possible that the lineage will not last. In the past,

some lineages have appeared and then disappeared quickly. Only further research on recent strains will provide more insights." says senior author Professor Shiranee Sriskandan from Imperial College London, UK. [2]

Writing in a linked Comment, Professor Mark Walker from the University of Queensland, Australia, says: "The continuing increase in scarlet fever and invasive disease notifications in the UK exemplifies the essential need to install global surveillance systems and address the increased GAS disease activity as a public-health priority. We believe that the report by Lynskey and colleagues sends out an important warning for the global public health community - recently emerging scarlet fever GAS strains have enhanced invasive potential which may have profound implications for the future global health burden."

NOTES TO EDITORS

This study was funded by the UK Medical Research Council, the UK National Institute for Health Research (NIHR), the Wellcome Trust, and the Rosetrees and Stoneygates Trusts. It was conducted by researchers from Imperial College London, the University of Sheffield, Public Health England and the Wellcome Sanger Institute.

[1] See NHS information: https://www.nhs.uk/conditions/scarlet-fever/

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

http://bit.ly/2lNYPs4

Commonly used antibiotics may lead to heart problems

Scientists have shown for the first time a link between two types of heart problems and one of the most commonly prescribed classes of antibiotics.

In a study published today in the *Journal of the American College of Cardiology*, researchers at the University of British Columbia (UBC) in partnership with the Provincial Health Services Authority's (PHSA) Therapeutic Evaluation Unit found that current users of fluoroquinolone antibiotics, such as Ciprofloxacin or Cipro, face a 2.4 times greater risk of developing aortic and mitral regurgitation, where the blood backflows into the heart, compared to patients who take amoxicillin, a different type of antibiotic. The greatest risk is within 30 days of use.

Recent studies have also linked the same class of antibiotics to other heart problems.

Some physicians favour fluoroquinolones over other antibiotics for their broad spectrum of antibacterial activity and high oral absorption, which is as effective as intravenous, or IV, treatment.

"You can send patients home with a once-a-day pill," said Mahyar Etminan, lead author and associate professor of ophthalmology and visual sciences in the faculty of medicine at UBC. "This class of antibiotics is very convenient, but for the majority of cases, especially community-related infections, they're not really needed. The inappropriate prescribing may cause both antibiotic resistance as well as serious heart problems."

The researchers hope their study helps inform the public and physicians that if patients present with cardiac issues, where no other cause has been discovered, fluoroquinolone antibiotics could potentially be a cause.

"One of the key objectives of the Therapeutic Evaluation Unit is to evaluate different drugs and health technologies to determine whether they enhance the quality of care delivered by our programs or improve patient outcomes," said Dr. Bruce Carleton, director of the unit and research investigator at BC Children's Hospital, a program of PHSA. "This study highlights the need to be thoughtful when prescribing antibiotics, which can sometimes cause harm. As a result of this work, we will continue working with the BC Antimicrobial Stewardship Committee to ensure the appropriate prescribing of this class of antibiotics to patients across British Columbia, and reduce inappropriate prescribing."

For the study, scientists analyzed data from the U.S. Food and Drug Administration's adverse reporting system. They also analyzed a massive private insurance health claims database in the U.S. that

captures demographics, drug identification, dose prescribed and treatment duration. Researchers identified 12,505 cases of valvular regurgitation with 125,020 case-control subjects in a random sample of more than nine million patients. They defined current fluoroquinolone exposure as an active prescription or 30 days prior to the adverse event, recent exposure as within days 31 to 60, and past exposure as within 61 to 365 days prior to an incident. Scientists compared fluoroquinolone use with amoxicillin and azithromycin.

The results showed that the risk of aortic and mitral regurgitation, blood backflow into the heart, is highest with current use, followed by recent use. They saw no increased risk aortic and mitral regurgitation with past use.

Etminan hopes that if other studies confirm these findings, regulatory agencies would add the risk of aortic and mitral regurgitation to their alerts as potential side effects and that the results would prompt physicians to use other classes of antibiotics as the first line of defense for uncomplicated infections.

This study was funded and conducted by the department of ophthalmology and the Therapeutic Evaluation Unit at the Provincial Health Services Authority.

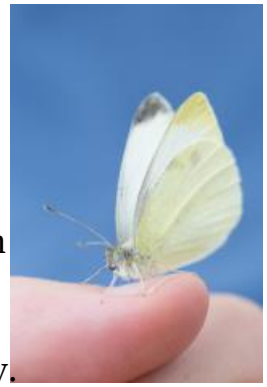
http://bit.ly/2lP3qu2

Every time the small cabbage white butterfly flaps its wings it has us to thank

With the help of citizen scientists researchers document invasive history of agricultural pest

KNOXVILLE, Tenn. -- The caterpillar form of an unassuming, small, white butterfly is among the world's most invasive pests affecting agricultural crops, and a newly published paper by a consortium of scientists documents how humans have helped it spread for thousands of years.

Through close examination of genetic variation and similarities between existing populations, and comparisons of historical data regarding infestations of Pieris rapae in Brassicaceae crops--like cabbage, canola, bok choy and turnips--the researchers document how humans helped the small cabbage white butterfly spread from Europe across the world.



An unassuming, small, white butterfly is among the world's most invasive pests affecting crops like cabbage, kale and broccoli. A newly published study in the Proceedings of the National Academy of Sciences (PNAS) documents how humans have helped Pieris rapae, the small cabbage white butterfly, spread across the globe for thousands of years. **Lauren Nichols, Department of Applied Ecology, North Carolina State University. Used by permission.**

Led by Sean Ryan, formerly a postdoctoral researcher in the Department of Entomology and Plant Pathology at the University of Tennessee Institute of Agriculture, the team of scientists from eight institutions partnered with more than 150 volunteer citizen scientists from 32 countries to detail the pest's range and current genetic diversity.

Published online on September 10, 2019, in the *Proceedings of the National Academy of Sciences (PNAS)*, the paper correlates the pest's invasive spread across the world through human travel and trade beginning with the overland ancient Silk Road routes from Europe to Asia, followed by the tall ships that traveled the more modern Silk Trade Routes, to the "iron horses" that traversed North America beginning in the second half of the19th century.

"The success of the small cabbage white butterfly is the consequences of human activities. Through trade and migration humans humans helped to inadvertently spread the pest beyond its natural range, and through the domestication and diversification of mustard crops, like cabbage, kale and broccoli, humans provided it with the food its caterpillars would need to flourish," says Ryan.

Prior to the study, historical records provided some indication of when this agricultural pest arrived in each new continent it invaded.

However, the timing, sources, and routes remained unsolved. What's more, such detailed knowledge is crucial in developing an effective biological control program as well as for answering basic questions associated with the invasion process, such as genetic changes and how species adapt to new environments.

The research team took to social media to ask the public for help. The approach was similar to how researchers have been expanding our understanding of human ancestry through in-home DNA sampling kits. Instead of asking people to swab their cheek, the butterfly research team asked citizen scientists to grab a butterfly net, then catch and send small cabbage white butterflies to the team for genetic testing. Ryan, currently with Exponent, Inc., in Menlo Park, California, then used the DNA from the submitted specimens to analyze genetic data and determine how the small cabbage white spread across the world. More than 3,000 butterflies were submitted. The samples cover nearly the entire native and invaded ranges of the butterfly and comprise 293 localities.

The researchers found that the small cabbage white butterfly likely originated in eastern Europe and then spread into Asia and Siberia when trade was increasing along the Silk Road. The researchers also found that, as expected, Europe was responsible for the introduction of the small cabbage white to North America. Surprisingly, the introduction into New Zealand came from San Francisco, California. Also, the butterflies living in central California and the surrounding area are genetically distinct from all other butterflies in North America and appear to be the consequence of a few butterflies hitching a train ride from the eastern U.S. to San Francisco. Although each invasion into a new area or country led to significant loss of genetic diversity, the invasions were successful, hence the abundance of small cabbage white butterflies today.

Citizen science--research in which members of the public play a role in project development, data collection or discovery--is subject to the same system of peer review as conventional science. Its power lies in its ability to help conventional studies overcome challenges involving large spatial and temporal scales. Social media and the internet are key tools that allow citizen scientists, who are often share similar interests through memberships in nature-based groups or professional societies, enhance the scale and scope of a particular project and its impact on society.

"Citizen science projects have been growing exponentially over the last decade, opening doors to new scientific frontiers and expanding the limits of what was once feasible," says DeWayne Shoemaker, professor and head of the UT Department of Entomology and Plant Pathology, and one of the paper's co-authors. "The relatively unique approach we took was asking the public to help collect--not just observe--these agricultural pests, and in so doing we were able to extract information recorded within the DNA of each individual butterfly. That information, when aggregated, told a story about the collective past of the small cabbage white butterfly."

"The international success of our citizen science project--the Pieris Project--demonstrates the power of the public to aid scientists in collections-based research addressing important questions in invasion biology, and ecology and evolutionary biology more broadly," says Ryan. He believes the use of collection-based citizen science projects will help society more accurately document ecological and evolutionary changes, which can lead to improvements in crop management and success as well as better environmental controls for invasive species.

Ryan's efforts were funded by a USDA National Institute of Food and Agriculture postdoctoral fellowship grant.

https://wb.md/2lPj9tf

Nearly 1 in 6 Docs Say They Make Diagnostic Errors Every Day

One in six physicians estimated in a Medscape poll that they make diagnostic errors every day.

Marcia Frellick

That number varied by specialty. Pediatricians were less likely to say they made diagnostic errors every day (11%) and emergency medicine (EM) doctors were more likely, at 26%. In between were physicians in family medicine (18%), general practice (22%), and internal medicine (15%).

Nurses, advanced practice registered nurses, and physician assistants (PAs) answered similarly: in all three categories, 17% said they estimated they made diagnostic errors daily.

Poll questions, posted June 26, were posed after Medscape reported results from a study in the *Journal of General Internal Medicine* that suggested that physicians tend to underestimate how often they make diagnostic errors.

Responders included 633 physicians and 118 nurse practitioners (NPs)/PAs, for a total of 751.

Researchers at the Johns Hopkins University School of Medicine in Baltimore, Maryland, conducted a survey of physicians at nine Connecticut internal medicine training programs to assess thoughts about diagnostic uncertainty and error.

Most believed diagnostic errors to be uncommon (once a month or less), despite half of them reporting that they felt diagnostic uncertainty every day. Previously published figures estimate that diagnostic errors occur in 10% to 15% of all patient encounters.

A registered nurse wrote in the Medscape poll comments that it's important to make a distinction between incorrect diagnoses and uncertainty. "The latter is part of the basis for a referral to a specialist," he noted.

Poll results indicated that NPs and PAs in the poll reported slightly higher rates of daily diagnostic uncertainty than did physicians.

Table. Frequency of Diagnostic Uncertainty by Provider

Frequency	% Physicians	% NPs/PAs
Every day	**52**	**64**
About once a week	**20**	**21**
Several times a month	**13**	**9**
Once a month	**14**	**5**
Never	**0**	**0**

Uncertainty rates were similar for male and female physicians.

Reasons for Errors

Physicians and NPs/PAs agreed on the top three reasons diagnostic errors occur. One was "lack of feedback on diagnostic accuracy" (38% of physicians and 44% of NPs/PAs listed that as a top factor). Another was time constraints, listed by 37% of physicians and 47% of NPs and PAs. Rounding out the top three was "a culture that discourages disclosure or errors" (27% physicians, 33% NPs/PAs).

Emergency medicine physicians were more likely than physicians in general (76% vs 52%) and NPs/PAs (64%) to say they experienced diagnostic uncertainty daily.

An emergency medicine physician who commented on the poll offered an explanation for uncertainty in his specialty: "I dare say we in EM cannot give a definitive diagnosis in the majority of undifferentiated presentations we see," he said.

"Our primary objective is to perform a 'medical screening exam' to rule out to a reasonable degree of certainty that an Emergency Medical Condition is not the cause of the patient's acute chest pain, abdominal pain, headache, etc. We focus on making the safest disposition through evidence-based risk stratification processes. It is a system that works fairly well sorting the emergent from the non-urgent," he said. "We strive to be honest in that we often don't know the definitive cause of the low risk chest pain, headache,

abdominal pain, etc. Often our most important intervention is simply reassurance that it is safe to follow up with the specialist for further testing — we are dispositionalists more often than we are diagnosticians."

Asked at what point they experienced diagnostic uncertainty, the greatest percentages of providers (70% of physicians and 76% of NPs/PAs) answered that it was when making the actual diagnosis. The second most frequent time for uncertainty was when deciding what tests to order (34% for physicians and 50% for NPs/PAs).

An internist said one cause of uncertainty in diagnosis was not listed as an option in the poll — "the inherent nature of biological systems." Not all symptoms or conditions can be diagnosed, at least in a timely manner, he said.

"We are not 'omnipotent,' " he wrote. "We do not understand in totality human physiology/pathology. Just because a diagnostic 'label' cannot be applied to a patient within a certain time, or that a reasonable diagnosis was applied that turns out to be 'incorrect,' does not mean an 'error' occurred."

A veterinarian who responded to the poll said that artificial intelligence (AI) may one day bridge the gaps in diagnosis for healthcare providers of all kinds.

"There are so many variables and possibilities I'm convinced, even for seasoned practitioners, our salvation will be A.I. and we will collaborate with our computerized 'partners,' " he said.

http://bit.ly/2mqqF7m

Ground-breaking method to reconstruct the evolution of all species

An evolution revolution has begun after scientists extracted genetic information from a 1.77 million-year-old rhino tooth - the largest genetic data set this old to ever be confidently recorded.

Researchers identified an almost complete set of proteins, a proteome, in the dental enamel of the now-extinct rhino and the resulting genetic information is one million years older than the oldest DNA sequenced from a 700,000-year-old horse.

The findings by scientists from the Faculty of Health and Medical Sciences, University of Copenhagen, and St John's College, University of Cambridge, are published today in Nature. They mark a breakthrough in the field of ancient molecular studies and could solve some of the biggest mysteries of ancient animal and human biology by allowing scientists to accurately reconstruct evolution from further back in time than ever before.

'For 20 years ancient DNA has been used to resolve questions about the evolution of extinct species, adaptation and human migration but it has limitations. For the first time we have retrieved ancient genetic information which allows us to reconstruct evolution way beyond the usual time limit of DNA preservation', Professor Enrico Cappellini, Associate Professor in Palaeoproteomics at the Globe Institute, University of Copenhagen, and first author on the paper, says.

'This new analysis of ancient proteins from dental enamel will start an exciting new chapter in the study of molecular evolution.'

For example, the reliance on DNA analysis allowed to genetically track the processes of evolution behind the origins of our species that occurred approximately in the last 400,000 years. However, considering the lineages leading to our species and to the chimp (the living species closest to us) branched apart approximately six to seven million years ago, it means that we currently have no genetic information from more than 90% of the path of evolution that led to us.

Accordingly, we still don't know what exactly is the genetic relation between us and, for example, Homo erectus - the oldest known species of humans to have had modern human-like body proportions -, or between us and the Australopithecus group of

species, which includes the iconic fossil commonly referred to as Lucy.

Ancient protein sequencing, based on a ground-breaking technology called mass spectrometry, has now been able to retrieve genetic information from a 1.77 million year old Stephanorhinus - an extinct rhinoceros which lived in Eurasia during the Pleistocene. The researchers extracted protein remains of dental enamel from a fossil tooth, which was discovered in Dmanisi, Georgia, and used mass spectrometry to sequence the ancient proteins and retrieve genetic information previously unobtainable using DNA sequencing.

Tooth enamel is the hardest material present in mammal body. In this study researchers discovered that the set of proteins it contains lasts longer than DNA and is genetically more informative than collagen, the only other ancient protein so far retrieved in fossils older than one million year.

Ultimately, mass spectrometry-based ancient protein sequencing expands the possibilities of retrieving reliable and rich genetic information from mammal fossils to those which are millions, rather than just thousands, of years old.

'With the new, protein-sequencing based method the possibilities of genetic information have been stretched beyond ancient DNA', Professor and co-corresponding author, Jesper Velgaard Olsen from the Novo Nordisk Foundation Center for Protein Research explains. 'Basically, this approach can tell us not only the species and the gender of an ancient fossil, but we can also draw an evolutionary line - all from a single tooth', he says. 'Dental enamel is extremely abundant and it is highly durable, which is why a high proportion of fossil records are teeth', Enrico Cappellini adds.

'We have been able to find a way to retrieve genetic information that is more informative and reliable than any other source of comparable age before, and it's from a material that is abundant in the fossil records so the potential of the application of this approach is extensive.'

The sequencing of the ancient proteome from the Dmanisi Stephanorhinus fossil has led the researchers to integrate it in the evolutionary tree including other extinct and extant rhinoceros species and to define its genetic relation with them, lead author on the paper Professor Eske Willerslev explains. Eske Willerslev holds positions at St John's College, University of Cambridge, and is director of The Lundbeck Foundation Centre for GeoGenetics at the University of Copenhagen.

'There are extinct species of early humans that we haven't been able to get any DNA from - species like Homo Erectus. The remains we have are too old and too poorly preserved for the DNA to survive', he says.

'This research is a game-changer that opens up a lot of opportunities for further evolutionary studies in terms of humans as well as mammals. It will revolutionise the methods of investigating evolution based on molecular markers and it will open a complete new field of ancient molecular studies.'

This rearranging of the evolutionary lineage of a single species may seem like a small adjustment but identifying changes in numerous extinct mammals and humans could lead to massive shifts in our understanding of the way animal life has evolved. The team of scientists are already implementing the findings in their current research.

The discovery could enable scientists across the globe to collect the genetic data of ancient fossils and to build a bigger, more accurate picture of the evolution of hundreds of species including our own.

http://bit.ly/2mgzZRV

Infant with deadly leukemia saved by drug for adult liver cancer

Identifying genetic mutations may unlock cure for challenging malignancies

UCSF Benioff Children's Hospitals have successfully treated a months-old infant with a rare childhood leukemia using a targeted therapy approved for adults with inoperable liver cancer and advanced kidney cancer.

The decision to use the drug, sorafenib, was made after pathologists identified a unique mutation in the form of two genes being fused together instead of on separate chromosomes -- according to a case study publishing in the journal *Leukemia* on Sept. 11, 2019.

The patient, now a thriving toddler, personifies a growing shift in cancer treatment: the genes fueling the cancer, rather than the type of cancer itself, may determine optimal therapy, say researchers, led by senior author Elliot Stieglitz, MD, a physician scientist in the UCSF Division of Pediatric Hematology/Oncology and the Helen Diller Family Comprehensive Cancer Center.

The authors report that the infant presented with the hallmarks of leukemia, including enlargement of the liver and spleen, and elevated white blood cell counts.

The child was believed to have JMML, or juvenile myelomonocytic leukemia, an aggressive type of blood cancer most commonly affecting infants and toddlers, and occurring in about 1.2 children per million, per year. JMML is treated with a stem cell transplant, in which intense chemotherapy is given to wipe out JMML cells, followed by a transplant of donated stem cells from a closely matched donor into the recipient's bone marrow, where they produce healthy blood cells. However, up to 50 percent of JMML patients relapse after transplantation.

Live-Saving Treatment Stalled When Infant's Condition Declined

Chemotherapy was initiated in an attempt to reduce the disease burden before stem cell transplant, said Stieglitz. "Unfortunately, the patient did not respond to chemotherapy and his symptoms worsened. The stem cell transplant was no longer an option."

Facing shrinking options, Stieglitz's team conducted molecular profiling of the child's cancer cells, in the hope that mutations could be identified and matched with targeted therapies. They used both UCSF 500, a cancer gene panel that sequences DNA from a patient's cancer cells and compares them to normal tissue, and a second tool that analyzes RNA, which offers a more sensitive measurement of gene expression and may identify novel features, including fusion genes. None of the mutations associated with JMML were found. However, the pathologists were surprised to discover a mutation known as an FLT3 fusion -- something that had never before been reported in a pediatric malignancy, the authors said.

"We know that fusions are more likely to respond to targeted therapies than other types of mutations," said Mignon Loh, MD, a co-author and Chair in Pediatric Molecular Oncology, who was involved in the patient's care. "Sorafenib, which was developed at UCSF, is a type of targeted therapy known as a kinase inhibitor that works by blocking the action of an abnormal protein that signals cancer cells to multiply."

After two weeks on sorafenib, the patient's white blood cell counts plummeted to within the normal range. After 10 weeks' treatment, the infant was well enough to undergo a stem cell transplant. Sorafenib was stopped after nearly two years. The patient remains in remission months later.

"The patient's history reveals that the one-size-fits-all treatment approach does not work well for all children with JMML," said

Stieglitz. "The course of JMML is highly variable. In rare cases, children spontaneously go into remission with minimal treatment, while half of all patients suffer from a highly aggressive form of the disease that fails to respond to stem cell transplant."

Most JMML patients present with genes that hyperactivate the Ras pathway, said Stieglitz, referring to a chain of proteins within the cell that communicates a signal from a receptor to the DNA in the nucleus.

"Recently there have been reports of JMML patients who have lacked these Ras mutations, but have fusions like our patient," he said. "We recommend that all patients without Ras mutations undergo RNA sequencing to identify any fusions that might be treated with targeted therapies."

Co-authors: *First author is Alexander Chao of the UCSF Department of Pediatrics. Co-authors are Julia Meyer, PhD, Alex G. Lee, PhD, Anna Hecht, MD, Theodore Tarver, Jessica Van Ziffle, PhD, Ashley Koegel, MD, Carla Golden, MD, Benjamin Braun, MD, PhD, E. Alejandro Sweet-Cordero, MD, Catherine C. Smith, MD, Christopher Dvorak, MD, and Mignon Loh, MD, all of UCSF.*

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Disclosures: *Smith received research funding from FujiFilm and Astellas Pharma; Chao received an honorarium from Bio-Rad. There are no further conflicts of interest.*

http://bit.ly/2kAiBY1

Papillomaviruses may be able to be spread by blood

Raises the possibility that human papillomavirus (HPV) may also be transferable by blood in humans

UNIVERSITY PARK, Pa. -- Papillomavirus has traditionally been considered strictly a sexually transmitted disease, but a recent study found that rabbit and mouse papillomaviruses could be transferred by blood to their respective hosts. Penn State researchers on the study said this raises the possibility that human papillomavirus (HPV) may also be transferable by blood in humans.

According to the Centers for Disease Control and Prevention, HPV is the most common sexually transmitted disease in humans, with an estimated 79 million individuals infected in the United States alone. While HPV is often harmless and goes away on its own, it can sometimes result in genital warts or progress to cervical or oral cancer.

Jiafen Hu, assistant professor of pathology and laboratory medicine at Penn State College of Medicine, said the team's results suggest more research is needed to determine whether HPV can be spread through blood in humans, specifically through blood transfusions.

"People who are receiving blood transfusions typically have immune systems that aren't working optimally, so their systems are more vulnerable," Hu said. "We might want to think about adding HPV to the list of viruses for which blood donations are screened, as well as researching whether the typical viral load of HPV in human blood would be sufficient to cause infection."

The results were recently published in the journal Emerging Microbes & Infections.

The study came about after an observation made in 2005 prompted one of the study authors to question how HPV is transmitted.

"Some years ago, researchers were looking at blood samples from a group of HIV-positive children, and as they were testing those samples, they found that some of them were also positive for HPV," Hu said. "Because these children were so young, it prompted the question of whether the virus could have come from blood transfusions, which some of the children had undergone."

While HPV is specific to humans and cannot be tested directly in animal models, the researchers said there are several different strains of papillomavirus that do exist in animals and can be a good approximation of how HPV may work in humans.

The researchers used two of these animal models for several experiments, including the Cottontail Rabbit Papillomavirus model,

which the researchers said is considered to be the "gold standard" for studying HPV-related infections and diseases.

First, the researchers injected virus into the bloodstream of the rabbit. They monitored the rabbits, and after four weeks, noticed tumors on the animals, which Hu said demonstrated that the virus had traveled through the bloodstream and caused an infection.

Because their first experiment used a fairly large amount of the virus -- larger than would be present in a normal infection -- the researchers repeated the experiment with a five-fold reduction of the virus. The tumors once again appeared, this time on 18 out of 32 sites on the animals.

"We were able to show that the virus in the blood caused tumors, but what about blood transfusions?" Hu said. "People receiving a transfusion may only get a very small amount of the virus. To simulate this, we injected the virus into one animal, took 10 milliliters of blood and transfused it into a second animal. We still saw tumors."

While the rabbit model showed that the virus could travel through the bloodstream to cause infections in the skin, Hu said the question remained as to whether it could cause infections in mucous membranes, like the cervix.

The researchers repeated the experiments in a mouse model and found that not only did they detect the virus in mucous membranes like the tongue and genitals, but they also found it in the stomach. Hu noted that this was a significant finding because people with cancer are sometimes found to have papillomavirus sequences in their stomach and other internal organs.

Hu said that while HPV does not cause health problems for every person who becomes infected with the virus, it is still important to know whether or not it can be spread by blood.

"We know that HPV is common and that not everyone who gets it is going to get cancer," Hu said. "The tricky part is that a lot of people who are carrying HPV and are asymptomatic still have the potential to spread the virus. If a person is getting a blood transfusion because of one health issue, you don't want to accidentally add another on top of that."

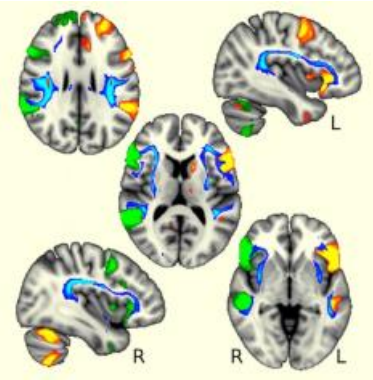
Nancy M. Cladel, Penn State; Pengfei Jiang, Wenzhou Medical University; Jingwei J. Li, Penn State; Xuwen Peng, Penn State; Timothy K. Cooper, National Institute of Allergy and Infectious Diseases; Vladimir Majerciak, National Cancer Institute; Karla K. Balogh, Penn State; Thomas J. Meyer, Frederick National Laboratory for Cancer Research; Sarah A. Brendle, Penn State; Lynn R. Budgeon, Penn State; Debra A. Shearer, Penn State; Regina Munden, Penn State; Maggie Cam, National Cancer Institute; Raghavan Vallur, Penn State; Neil D. Christensen, Penn State; and Zhi-Ming Zheng, National Cancer Institute, also participated in this work.

The National Cancer Institute, National Institutes of Health, National Institute of Allergy and Infectious Diseases and the Jake Gittlen Memorial Golf Tournament helped support this research.

http://bit.ly/2kANL1q

Scientists Identify Four Genetic Regions Associated with Left-Handedness

A team of researchers from the University of Oxford has identified four regions of the human genome associated with left-handedness in the general population and linked their effects with brain architecture.



"Throughout history, left-handedness has been considered unlucky, or even malicious," said University of Oxford's Professor Dominic Furniss.

"Indeed, this is reflected in the words for left and right in many languages. For example, in English 'right' also means correct or proper; in French 'gauche' means both left and clumsy."

The language brain regions were more coordinated in left-handers between the two sides of the brain (in green and orange) and were also connected by the white matter tracts influenced by one genetic region related to handedness (in blue). **Gwenaëlle Douaud, University of Oxford.**

"Here we've demonstrated that left-handedness is a consequence of the developmental biology of the brain, in part driven by the complex interplay of many genes. It is part of the rich tapestry of what makes us human."

Professor Furniss and colleagues identified the genetic variants associated with left-handedness by analyzing the genomes of about 400,000 people from UK Biobank, which included 38,332 left-handers. Of the four genetic regions the team identified (rs199512, rs45608532, rs13017199, and rs3094128), three of these were associated with proteins involved in brain development and structure.

In particular, these proteins were related to microtubules, which are part of the scaffolding inside cells, called the cytoskeleton, which guides the construction and functioning of the cells in the body.

Using detailed brain imaging from approximately 10,000 of these participants, the scientists found that these genetic effects were associated with differences in brain structure in white matter tracts, which contain the cytoskeleton of the brain that joins language-related regions.

"We discovered that, in left-handed participants, the language areas of the left and right sides of the brain communicate with each other in a more coordinated way," said University of Oxford's Dr. Akira Wiberg. "This raises the intriguing possibility for future research that left-handers might have an advantage when it comes to performing verbal tasks, but it must be remembered that these differences were only seen as averages over very large numbers of people and not all left-handers will be similar."

"Many animals show left-right asymmetry in their development, such as snail shells coiling to the left or right, and this is driven by genes for cell scaffolding, what we call the cytoskeleton," said University of Oxford's Professor Gwenaëlle Douaud.

"For the first time in humans, we have been able to establish that these handedness-associated cytoskeletal differences are actually visible in the brain." "We know from other animals, such as snails and frogs, that these effects are caused by very early genetically-guided events, so this raises the tantalizing possibility that the hallmarks of the future development of handedness start appearing in the brain in the womb."

The authors also found correlations between the genetic regions involved in left-handedness and a very slightly lower chance of having Parkinson's disease, but a very slightly higher chance of having schizophrenia.

However, they stressed that these links only correspond to a very small difference in the actual number of people with these diseases, and are correlational so they do not show cause-and-effect.

"Studying the genetic links could help to improve understanding of how these serious medical conditions develop," they said.

The study was published in the journal *Brain*.

Akira Wiberg et al. *Handedness, language areas and neuropsychiatric diseases: insights from brain imaging and genetics.* Brain, *published online September 5, 2019; doi: 10.1093/brain/awz257*

https://nyti.ms/2khna9d

Why Aren't Cancer Drugs Better? The Targets Might Be Wrong

Drugs can stop cancer cells if they attack the right proteins. But many of these targets were chosen with dated, imprecise technology, a new study suggests.

By Carl Zimmer

Twenty years ago, the fight against cancer seemed as if it were about to take a dramatic turn.

Traditionally, cancer doctors fought the disease with crude weapons, often simply poisoning fast-growing cells whether they were cancerous or healthy. But then a team of researchers hit on a new

strategy: drugs targeting proteins produced by cancer cells that seemed necessary to their survival.

Once such drug, Gleevec, worked spectacularly in patients with chronic myeloid leukemia. But the clinical trials that followed mostly have produced disappointments. According to a study published earlier this year, only 3 percent of cancer drugs tested in clinical trials between 2000 and 2015 have been approved to treat patients. A study published on Wednesday in the journal Science Translational Medicine offers one reason for the failure: Scientists are going after the wrong targets.

"I hope people will really wake up to the need to be much more rigorous," said Dr. William Kaelin, a professor of medicine at Harvard University who was not involved in the new study.

Jason Sheltzer, a cancer biologist at Cold Spring Harbor Laboratory in New York State, and his colleagues made the discovery as they were trying to come up with a new test for breast cancer.

In certain forms of the disease, cancer cells make high levels of a protein called MELK. Extremely high levels can mean poor odds of survival for the patient.

Earlier studies had indicated that MELK was essential to the spread of the cancer; indeed, researchers were already testing a drug for breast cancer that targets the MELK protein.

Two undergraduates in Dr. Sheltzer's lab, Ann Lin and Christopher J. Giuliano, used Crispr, the revolutionary DNA-editing tool, to snip out the gene for MELK in cancer cells. The cells should have stopped growing, but to the surprise of the scientists, they did not.

"The cancer cells did not care whatsoever," Dr. Sheltzer said.

It was odd that the cells didn't need a supposedly essential gene. Odder still was what happened when the scientists exposed the cells to the MELK-targeting drug. It stopped the cancer cells anyway — even though they lacked the gene that the drug targeted.

Dr. Sheltzer wondered if he simply had stumbled across a peculiar case. So he widened his research, running the same experiment with 10 other drugs. All were protein-targeting medications currently in clinical trials. With each drug, the scientists got the same results. Every supposedly essential protein turned out to be expendable in the cancer cells, yet all these cells stopped growing when the scientists applied the drug.

This sort of mistake may lead to failures in clinical trials, Dr. Sheltzer said. "When you design a clinical trial, you want to pick out the patients who are most likely to respond," he said. "That trial may fail because you're picking the wrong people to give that drug to."

The mistakes Dr. Sheltzer has uncovered may have come about because the scientists who were hunting for drug targets used unreliable tools. "A lot of the drug targets that are in clinical trials today were discovered with the best technology from five or 10 years ago," he said.

That technology, known as RNAi, seemed at the time like it could zero in on cancer targets with high precision. "Everyone thought finally we had the genie in the lamp," Dr. Kaelin said.

RNAi allows scientists to craft a molecule to block cells from making a particular protein. If blocking a protein's production stopped cancer cells from growing, scientists looked for a drug that also targeted that protein.

But some critics questioned whether RNAi was all that precise. The technique may block not just a target protein, but certain others as well. Dr. Sheltzer tested this possibility with one of the drugs in his experiment, OTS964. The researchers gave the drug to colonies of cancer cells with the target protein removed. Most still died — but a few did not. The researchers sequenced the DNA of the surviving cells. It turned out they all had mutations in the same gene, which encodes a protein called CDK11B.

No one had any idea that the protein was essential to the survival of the cancer cells. But Dr. Sheltzer's experiment suggested it was: The mutant cells survived because they had an altered form of the protein, with which the drug could not interfere. When the researchers cut out the CDK11B gene, the cancer cells died — further evidence that the protein was necessary to the cancer cell.

Traver Hart, a cancer biologist at M.D. Anderson Cancer Center in Houston who was not involved in the new study, said that scientists need to take another look at cancer drugs now undergoing testing.

"There clearly exists a legacy of RNAi-guided bad targets that needs to be purged from the drug development pipeline," he said.

That doesn't mean that targeting essential proteins is pointless. Scientists just need to make sure they're going after the right ones.

Searching for mutations in the genes of cancer cells may be one way to avoid false positives. Instead of relying on hunches about what is a good target, cancer cells might speak for themselves.

"There is probably a whole universe of unexplored drug targets in the cancer cell," Dr. Sheltzer said.

http://bit.ly/2lOkFvJ

Acupuncture Causes Woman's Lung to Collapse

Although rare, piercing the lung through an acupuncture pressure point in the shoulder is a well-known risk.

By Nicoletta Lanese - Staff Writer 3 days ago Health

It's the stuff of nightmares: An acupuncturist in New Zealand accidentally pierced her patient's lungs while inserting needles into the patient's shoulder, causing the organ to collapse.

The 33-year-old woman went to the acupuncture clinic in March following arm and wrist injuries that caused pain in her shoulders. To alleviate the discomfort, her acupuncturist inserted two needles near a spot known in Chinese medicine as the Jian Jing pressure point, or Gallbladder 21, which lies near the top of the shoulders. It also rests dangerously close to the apices of the lungs — the pointed ends of the organ near the neck. At Gallbladder 21, the surface of the lung lies only 0.4 to 0.8 inches (10 to 20 millimeters) beneath the skin, according to the World Health Organization (WHO).

When the needles were inserted, the patient felt a twinge of pain and later recalled that the instruments felt "extremely deep," according to a report filed by New Zealand's Health and Disability Commissioner. The acupuncturist left the needles in for 30 minutes before twisting and removing them, an action that left the patient feeling a sudden "right-sided chest pain and shortness of breath." The patient said she also felt a "stuffy" sensation 10 minutes later, so the acupuncturist removed all of the remaining needles, administered additional treatment, and sent the patient home with instructions to rest and pay attention to her breathing.

Once home, the patient felt persistent pain in the left side of her chest and numbness in the right side. Later that night, she was admitted to the emergency department, where she was diagnosed with bilateral apical pneumothoraces, meaning both of her lungs had collapsed. The pneumothoraces were produced by the acupuncture treatment, which caused gas to be released into her chest cavity.

Although these occurrences are rare, acupuncturists occasionally pierce patients' lungs through the Jian Jing pressure point. About 30% of the cases of pneumothorax due to acupuncture are caused by the insertion of needles into that particular spot, according to a 2010 study by the WHO. Per New Zealand's Code of Health and Disability Services Consumers' Rights, this well-established risk should be spelled out for patients before any needles enter their skin.

The acupuncturist in this case reportedly failed to inform her patient of these risks and neglected to have her sign a required written

consent form. The commissioner recommended that the acupuncturist receive additional training and that the clinic audit whether other clients had received informational brochures and signed consent forms prior to treatment, according to the New Zealand Herald.

You can read more about the case in the New Zealand Herald.

https://bbc.in/2ky0ORb

Signs of a slowdown in new type 2 diabetes cases

The number of new cases of type 2 diabetes could be stabilising, or even falling, a study suggests.

The analysis looked at 47 studies from the mid-1960s up to 2014, mainly from the US and Canada and countries across Europe including the UK. A third of populations studied between 2006 and 2014 saw a fall in new cases and another third were stable.

But Diabetes UK said the challenges of obesity and unhealthy lifestyles, both linked to the condition, remained.

Prof Dianna Magliano, head of diabetes and population health at the Baker Heart and Diabetes Institute, in Melbourne, who led the study, said: "We are seeing a flattening of incidence and even a fall in many high income countries in the recent years."

'Potential plateau'

Studies between 1990 and 2005 showed the number of new cases increased in two-thirds (67%) of populations studied, was stable in 31% and decreased in 2%. But from 2006 to 2014, increases were seen in only a third, with 30% staying stable and 36% declining.

Prof Magliano said: "The most obvious conclusion to be drawn from falling incidence is that we are succeeding in reducing the risk for developing diabetes in the population."

The studies did not reveal the level of undiagnosed diabetes in populations - and a different test for type 2 diabetes was introduced around 2010. But Sarah Wild, professor of epidemiology at the University of Edinburgh, said the findings echoed what she had seen in Scotland. "There does seem to be a flattening of new cases of diabetes," she said. "Why that is seems to be a bit of a puzzle.

"It's good news. But that doesn't mean we can take our eye off the ball."

'Challenges remain'

Dr Emily Burns head of research communications at Diabetes UK, said: "This study looks at type 2 diabetes through a different lens, reporting on the number diagnosed rather than the number living with the condition - which can often be distorted by factors such as how long people live for. "With this in mind, it's promising to see that the number of people being diagnosed with type 2 diabetes might potentially be plateauing in certain parts of the world."

But she added: "The challenges posed by obesity and unhealthy lifestyles - the two main drivers for type 2 diabetes - remain significant. "That's why, while the findings are interesting, this study doesn't detract from the seriousness of the growing diabetes crisis and the vital prevention efforts under way to help tackle this."

http://bit.ly/2lPedVe

Device generates light from the cold night sky

Inexpensive thermoelectric device harnesses the cold of space without active heat input

In this photograph, the thermoelectric generator harnesses temperature differences to produce renewable electricity without active heat input. Here it is generating light. **Aaswath Raman**

An inexpensive thermoelectric device harnesses the cold of space without active heat input, generating electricity that powers an LED at night, researchers report September 12 in the journal *Joule*.

"Remarkably, the device is able to generate electricity at night, when solar cells don't work," says lead author Aaswath Raman (@aaraman), an assistant professor of materials science and

engineering at the University of California, Los Angeles. "Beyond lighting, we believe this could be a broadly enabling approach to power generation suitable for remote locations, and anywhere where power generation at night is needed."

While solar cells are an efficient source of renewable energy during the day, there is currently no similar renewable approach to generating power at night. Solar lights can be outfitted with batteries to store energy produced in daylight hours for night-time use, but the addition drives up costs.

The device developed by Raman and Stanford University scientists Wei Li and Shanhui Fan sidesteps the limitations of solar power by taking advantage of radiative cooling, in which a sky-facing surface passes its heat to the atmosphere as thermal radiation, losing some heat to space and reaching a cooler temperature than the surrounding air. This phenomenon explains how frost forms on grass during above-freezing nights, and the same principle can be used to generate electricity, harnessing temperature differences to produce renewable electricity at night, when lighting demand peaks.

Raman and colleagues tested their low-cost thermoelectric generator on a rooftop in Stanford, California, under a clear December sky. The device, which consists of a polystyrene enclosure covered in aluminized mylar to minimize thermal radiation and protected by an infrared-transparent wind cover, sat on a table one meter above roof level, drawing heat from the surrounding air and releasing it into the night sky through a simple black emitter. When the thermoelectric module was connected to a voltage boost convertor and a white LED, the researchers observed that it passively powered the light. They further measured its power output over six hours, finding that it generated as much as 25 milliwatts of energy per square meter.

Since the radiative cooler consists of a simple aluminum disk coated in paint, and all other components can be purchased off the shelf, Raman and the team believe the device can be easily scaled for practical use. The amount of electricity it generates per unit area remains relatively small, limiting its widespread applications for now, but the researchers predict it can be made twenty times more powerful with improved engineering--such as by suppressing heat gain in the radiative cooling component to increase heat-exchange efficiency--and operation in a hotter, drier climate.

"Our work highlights the many remaining opportunities for energy by taking advantage of the cold of outer space as a renewable energy resource," says Raman. "We think this forms the basis of a complementary technology to solar. While the power output will always be substantially lower, it can operate at hours when solar cells cannot."

This work is supported by the U.S. Department of Energy, as well as by the Mellon Family Foundation.

Joule, Raman et al.: "Generating Light from Darkness"
https://www.cell.com/joule/fulltext/S2542-4351(19)30412-X

http://bit.ly/2kKfwo7

Patients diagnosed with cancer afterskipping appointment more likely to die within a year

Cancer patients who miss an urgent referral appointment for their symptoms are 12% more likely to die within 12 months of diagnosis, a major new study has found

Cancer patients who miss an urgent referral appointment for their symptoms are 12% more likely to die within 12 months of diagnosis, a major new study has found.

The study, funded by Yorkshire Cancer Research, showed that male patients and those under 30 or over 85 years of age are more likely to skip their appointment, as are people who live in disadvantaged neighbourhoods and people who have been referred due to gastrointestinal problems.

The authors of the study say that more support is needed for patients at risk of non-attendance.

Led by researchers at the University of York and Hull York Medical School, the study looked at data from more than 100,000 patients who had been urgently referred by around 100 different GP practices in the North of England. The majority of patients in the study (95%) attended their referral appointment, but a significant minority (5% or 5,673 people) did not.

While the study found that only one in 18 of the patients who skipped their appointment went on to be diagnosed with cancer - compared to one in 10 of those who did attend - the outlook for patients who missed their appointment and did have cancer was significantly worse.

The study revealed that 34.6% of non-attending patients with cancer had an advanced stage of the disease at diagnosis compared to 18.4% of attenders with cancer. Having a more advanced stage of the disease is likely to be a reason why more non-attending patients with cancer died within a year of diagnosis (31.3% compared to 19.2% of attenders), the researchers say.

Dr Peter Knapp, from the Department of Health Sciences at the University of York and Hull York Medical School, said: "Our study showed cancer diagnosis was less likely in non-attending patients but those who are diagnosed have worse outcomes than attending patients with cancer. This may be due to later presentation to their GP and more advanced disease at referral.

"Non-attendance at urgent referral appointments for suspected cancer involves a minority of patients, but happens in somewhat predictable groups. For example, we found that patients with suspected gastrointestinal cancer were among the least likely to attend - this may be due to concerns about unpleasant or embarrassing procedures.

"Our research suggests that more could be done to identify individuals at risk of non-attendance and offer extra support."

The NHS's 'Two Week Wait' policy aims to ensure that patients with suspected cancer are seen by a consultant within two weeks of an urgent GP referral.

While there is more awareness around the issues of ignored cancer screening invitations and the waste of resources incurred from missed GP appointments, the study is the first to focus on non-attendance of symptomatic patients referred due to suspected cancer.

Dr Stuart Griffiths, Director of Research and Services at Yorkshire Cancer Research, said: "Early diagnosis is vital in ensuring more people survive cancer, but there are many challenges facing both doctors and patients when it comes to accessing diagnosis and treatment swiftly. The charity is looking at ways it can work with the NHS and other research partners to determine how it can address factors leading to non-attendance at urgent referral appointments."

Patient non-attendance at urgent referral appointments for suspected cancer and its links to cancer diagnosis and one year mortality: a cohort study of patients referred on the Two Week Wait pathway is published in Cancer Epidemiology.

http://bit.ly/2lRkTCh

Breaking the 'stalemate' in the most common soft tissue sarcoma in children

First randomized clinical trial to show positive results in rhabdomyosarcoma since 1974

A phase 2 clinical trial has found that combining a molecular targeted drug called temsirolimus with chemotherapy shows promise in the treatment of rhabdomyosarcoma, the most common soft tissue sarcoma in childhood. The Children's Oncology Group trial was led by Leo Mascarenhas, MD, MS, Deputy Director of the Children's Center for Cancer and Blood Diseases at Children's Hospital Los Angeles. Results were recently published online in the Journal of Clinical Oncology.

"Since the early 1990s, there's been no change in the overall survival or risk of recurrence of this disease," explains Dr. Mascarenhas, Section Head, Oncology, in the Division of Oncology, Hematology and Blood and Marrow Transplantation at CHLA. "This trial was pivotal in finding a path forward to potentially break the stalemate."

Rhabdomyosarcoma is a rare childhood cancer that arises in the body's soft tissues, such as muscle. A small group of patients--those whose tumors can be surgically removed at the time of diagnosis--have an over 90% chance of being cured. But for others, the outlook is far less certain. About half are considered "intermediate-risk," with a 60% to 70% chance of long-term survival. Roughly 25% of patients are diagnosed with disease that's already spread; these children have a poor prognosis. In addition, once rhabdomyosarcoma relapses in any patient, long-term survival plummets to under 20%.

The goal of the clinical trial was to see if a targeted drug could be paired with chemotherapy to improve patient outcomes. It was the first-ever randomized trial in rhabdomyosarcoma to test targeted agents in combination with chemotherapy in both treatment groups.

Researchers compared two targeted drugs against each other: bevacizumab, which inhibits the growth of blood vessels that feed tumors, and temsirolimus, which inhibits a pathway often active in rhabdomyosarcoma called mammalian target of rapamycin (mTOR). Both drugs are approved by the Food and Drug Administration for use in other cancers.

The multicenter trial enrolled 86 rhabdomyosarcoma patients who had relapsed for the first time. About half received bevacizumab with chemotherapy; the other half received temsirolimus with chemotherapy. The chemotherapy agents used were vinorelbine and cyclophosphamide.

Enrollment was stopped early because an interim analysis showed that the temsirolimus combination was clearly superior. After six months, the event-free survival rate of patients receiving the bevacizumab treatment was 54.6%--comparable to results expected at this point in treatment with chemotherapy alone. For patients receiving temsirolimus, it was 69.1%.

The goal of this trial was to determine which molecularly targeted agent warranted further investigation. Because the patients studied had already relapsed, most did not survive long-term on either treatment. However, the Children's Oncology Group is now conducting a multicenter, phase 3 clinical trial to study the effectiveness of the temsirolimus-chemotherapy combination in newly diagnosed, intermediate-risk patients.

Researchers are trying to see if giving this therapy early on--when the cancer is most sensitive to treatment--will improve long-term outcomes.

"Prior to these results, there were no compelling ideas on how to improve survival of newly diagnosed patients," says Dr. Mascarenhas, who directs the Sarcoma and Solid Tumor Program at CHLA and is also Associate Professor of Pediatrics at the Keck School of Medicine of USC. "There is a lot more work to be done. But we now may have a way forward."

Additional contributors include Yueh-Yun Chi of the University of Florida, Gainesville; Pooja Hingorani of Phoenix Children's Hospital; James R. Anderson of Merck Research Laboratories: Oncology; Elizabeth R. Lyden of the University of Nebraska College of Medicine; David A. Rodeberg of East Carolina University; Daniel J. Indelicato, University of Florida, Jacksonville; Simon C. Kao of the University of Iowa Carver College of Medicine; Roshni Dasgupta of Cincinnati Children's Hospital; Sheri L. Spunt of Stanford University School of Medicine; William H. Meyer of the University of Oklahoma Health Sciences Center; and Douglas S. Hawkins of Seattle Children's Hospital on behalf of the Soft Tissue Sarcoma Committee of COG

The research was supported by the Children's Oncology Group and the National Cancer Institute (U10CA180886, U10CA180899, U10CA098543, U10CA098413) and the St. Baldrick's Foundation.

https://wb.md/2kN8xdZ

Medical Devices Very Vulnerable to Hacking, FDA Experts Warn

Medical devices can be prone to hacking and to errors

Many people do not realize the cybersecurity risks associated with common medical devices, such as insulin pumps and pacemakers, but these medical devices can be prone to hacking and to errors, experts said at a meeting of the US Food and Drug Administration's (FDA's) Patient Engagement Advisory Committee (PEAC) on September 10. Physicians and healthcare providers may not know how to educate patients about these issues — if they give patients too little information, patients may not understand when to get help with their device. If providers give the patient too much information or in language they don't understand, patients may become unnecessarily anxious.

Hacking a Serious Problem

When most people envision someone hacking an electronic device, their first thought is not usually of a medical device such as an insulin pump, but at least two speakers at the advisory committee meeting described how easy it was to hack their own medical devices by reverse-engineering them.

One factor relates to how medical devices have changed over time. Many medical devices, including surgical laser systems, blood pressure cuffs, dialysis systems, and MRI machines, formerly were "standalone technologies implanted in patients or used in hospitals or clinics to diagnose, treat, or manage health conditions," according to an FDA briefing document.

Now, many of these devices have a software component and are interconnected via wireless access networks and other networks. These factors increase the devices' functionality, but they pose problems as well, including exposing patients' private information and making errors the patient is unaware of, such as administering a wrong dose of insulin. "In medical device cybersecurity, the risk is typically associated with an unauthorized person (threat) accessing the device(s) of one or more patients by exploiting a vulnerability (such as a security weakness in the device's software or firmware). Examples include inappropriate pacing or shocks from a pacemaker or inappropriate dosing from an infusion pump," according to the FDA briefing document.

Panel members discussed the types of information healthcare providers should tell patients, effective ways of communicating that information, and when and how to report problems with devices.

User-Friendly Approach Is Key

Committee members repeatedly said that many devices and the instructions that come with them are cumbersome and difficult to understand. Software updates and patches are needed to fix certain problems, but alerts to update devices such as cell phones occur frequently, and some users ignore alerts because they know that they will likely lose valuable information once they update their device.

Healthcare providers should use culturally appropriate language the patient understands and should use a translator if necessary. They should offer information in small portions to allow patients time to process and understand it. Healthcare workers should also consider using pictures and visual displays instead of words when possible.

The fact that it is impossible to predict which types of cybersecurity risks can affect a given medical device can make it more difficult for healthcare providers to have meaningful conversations about risks and benefits, but many patients prefer to have as much information as possible, one attendee said.

When to offer health education is just as important as how to deliver that information, a number of attendees said. For example, many patients will not remember information that is given to them when they are waking up from anesthesia or when they are stressed,

afraid, or in pain. In addition, patients' preferences regarding communication methods vary: some prefer to make traditional telephone calls, others like to send text messages or emails, and some prefer to receive letters in the mail. Knowing a patient's communication preference will help provide device warnings and alerts when needed and ensure the patient reads them.

Another factor to consider is that patients who live in rural areas may have limited access to the Internet, newer telephone technology, and telephone service providers.

Continuous Vigilance Needed

It is not always possible to anticipate problems or defects that may arise, because certain factors regarding cybersecurity risk are not known, several panelists said; therefore, constant vigilance for problems is necessary, as is timely, effective communication to users of medical devices regarding cybersecurity risks.

The most important factor regarding response to an attack, such as the May 2017 WannaCry ransomware attack, is planning. However, planning only for specific events is often ineffective, Natashia Tamari, associate director, Cybersecurity Incident Response, Becton Dickinson, said.

"We can take plans and make them for very specific scenarios, but that is not going to help us; we really have to make frameworks and take [into consideration] how do we communicate with each other and who needs to be in the room and what does the coordination look like, because that's really going to be what's key in preparing for these types of vulnerabilities," Tamari explained.

FDA Actions

In considering whether to issue a safety communication to the public regarding medical device cybersecurity, the FDA considers a number of factors, such as the likelihood that the device will be successfully exploited; how quickly such an attack could happen and the extent to which it could affect the patient population; and how much time it would take to initiate an effective countermeasure.

"For these reasons, FDA's communication approach regarding medical device cybersecurity has been anticipatory, forward-leaning and proactive as vulnerabilities are identified and verified before exploitation, and when there is a mitigation available, rather than waiting for a signal or indicator of harm to manifest," according to the FDA briefing document.

Several attendees stressed the role of the FDA in protecting patients and of reaching all medical device users when there are problems with the device.

"The tactics matter as much as the principle of being timely in communication," Patient Engagement Advisory Committee chair Paul T. Conway, American Association of Kidney Patients, Patient Advocacy, said at the meeting.

As important as prompt communication is when cybersecurity concerns regarding medical devices are identified, the FDA does not want to disclose such concerns prematurely, because it does not want to give information to individuals who might use it to cause harm.

Additional information about cybersecurity and medical devices, including final guidance documents on premarket and postmarket medical device cybersecurity, is available on the FDA's webpage.

http://bit.ly/2majfLY

Hormone secreted by bones may help us escape danger

When it comes with our body's stress response, adrenaline may be less important than another hormone, one that seeps out of our bones

By Emily Underwood

Adrenaline. The word is synonymous with any activity that gets our blood racing, whether it be encountering a rattlesnake or watching the latest horror movie. But a new study reveals that when it comes

with our body's stress response, adrenaline may be less important than another hormone, one that seeps out of our bones.

Our skeleton is much more than a rigid scaffold for the body, says geneticist Gérard Karsenty of Columbia University. Our bones secrete a protein called osteocalcin, discovered in the 1970s, that rebuilds the skeleton. In 2007, Karsenty and colleagues discovered that this protein acts as a hormone to keep blood sugar levels in check and burn fat. Later, his group showed that the hormone is important for maintaining brain function and physical fitness, restoring memory in aged mice and boosting performance during exercise in old mice and people. The findings led Karsenty to hypothesize that animals evolved bony skeletons to escape danger.

The new study furthers that argument. Karsenty and colleagues exposed mice to several stressors, including a mild electric shock to the foot and a whiff of fox urine, a scent that triggers an innate fear response. Then, the researchers measured the osteocalcin in the animals' blood.

Within 2 to 3 minutes of being exposed to a stressor, levels of osteocalcin in the mice quadrupled, the team reports today in *Cell Metabolism*. A classic stressor in people had a similar effect: When the researchers asked volunteers to speak in front of an audience, osteocalcin levels also spiked.

Next, Karsenty's group set out to determine whether osteocalcin is required to trigger fight-or-flight mode, an involuntary physical reaction to threat. The mode includes a racing pulse, heavier breathing, and a spike in blood sugar; the response provides the body extra fuel for a speedy escape. When the team put mice genetically engineered not to make osteocalcin through the same stressors as the nonengineered mice, the rodents barely reacted. In normal mice, a single injection of osteocalcin was enough to trigger a full flight-or-fight reaction—even without a stressor.

By probing the neural connections between the rodents' brains and their skeletons, the team discovered how osteocalcin unleashes fight-or-flight mode. When a brain region called the amygdala detects danger, it instructs bone cells called osteoblasts to release osteocalcin into the bloodstream, the researchers found. Osteocalcin, in turn, tamps down activity in the parasympathetic nervous system–nerve fibers that slow heart rate and breathing. This takes the brakes off the sympathetic nervous system, unleashing the body's stress response, including the release of adrenaline, Karsenty says.

The findings suggest osteocalcin—not adrenaline—is the gatekeeper that determines when bodies shift into fight-or-flight mode, Karsenty says. They also help explain why rodents that have had their adrenal glands removed and people who don't produce much adrenaline because of medical conditions can still experience intense physical reactions to danger.

The study is "definitely newsworthy" and supports the hypothesis that bones evolved to help animals escape predators and other threats, says Patricia Buckendahl, a bone physiologist at Rutgers University in New Brunswick, New Jersey, who was not involved with the work. Buckendahl presented the first evidence that osteocalcin acts as a stress hormone in rats 20 years ago, but no one took the idea very seriously at the time, she says. "I've always said bones are a heck of a lot more than a place to store calcium."

http://bit.ly/2mi9ATQ

Simple model captures almost 100 years of measles dynamics in London

Simple epidemiological model accurately captures long-term measles transmission dynamics in London

A simple epidemiological model accurately captures long-term measles transmission dynamics in London, including major perturbations triggered by historical events. Alexander Becker of

Princeton University in New Jersey, U.S., and colleagues present these findings in *PLOS Computational Biology*.

Previous studies have extensively explored how disease outbreaks are affected by variations in demography, such as birth rate, and variations in person-to-person contact, such those arising from school calendars. However, key historical events, such as the 1918 influenza pandemic in London and the World War II evacuation of about 1 million children from London to the countryside, have not been studied in the context of long-term trajectories of disease transmission.

For the new study, Becker and colleagues aimed to mathematically disentangle the disease transmission effects of regular demographic changes, such as variable birth rate, from larger shifts caused by historical events. They took advantage of recent advancements in statistical algorithms to mathematically analyze weekly measles incidence and mortality data reported in London from 1897 to 1991.

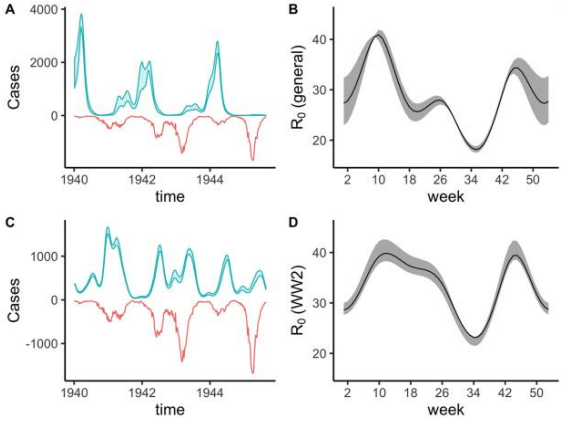


Fig 4. A comparison of predicted against observed measles dynamics for the subsetted WWII time period (1940 to 1946).

A) The predicted dynamics using the fitted model against the whole time series with the same visual fit information as Fig 2. B) The inferred seasonality across the whole-time series with mean $R_0 = 29$. C) The predicted dynamics fit to just the WWII time period with the inferred seasonality in D). D) The inferred seasonality in just the WWII time period with average $R_0 = 33$. Note the local WWII fit produces a lower amplitude seasonality pattern. In both B) and D) 95% confidence intervals (calculated using the chi-square approximation of the likelihood ratio test) on the inferred seasonality pattern are shown in shaded gray, while the inferred values are shown in solid black. Note that the seasonality pattern in D) yields a stronger fit the data while maintaining a generally lower amplitude.

https://doi.org/10.1371/journal.pcbi.1007305.g004

The researchers found that a simple mathematical model successfully captured measles transmission dynamics throughout the study period, including the effects of major perturbations caused by historical events. "The most exciting aspect of this research is showing that the London system is able to remain mathematically stable—that is, essentially, well-predicted—in spite of multiple huge perturbations such as the 1918 pandemic and the wartime evacuation," Becker says.

The findings underscore that the long-term dynamics of epidemiological systems can follow simple rules, despite major perturbations. The results could have practical implications for understanding long-term disease dynamics in other contexts, such as the resurgence of measles seen in recent years. They could also help inform understanding of other ecological dynamics, such as predator-prey interactions.

Becker AD, Wesolowski A, Bjørnstad ON, Grenfell BT (2019) Long-term dynamics of measles in London: Titrating the impact of wars, the 1918 pandemic, and vaccination. PLoS Comput Biol 15(9): e1007305. doi.org/10.1371/journal.pcbi.1007305

http://bit.ly/2kid9bR

Tuna Steaks Recalled Because They May Cause This Weird Type of Food Poisoning

Several people who ate the products developed symptoms of "scombroid fish poisoning."

By Rachael Rettner - Senior Writer

Yellowfin tuna products sold in 16 U.S. states are being recalled because they have the potential to cause an odd type of food poisoning that resembles an allergic reaction.

On Sept. 6, the company Alfa International Seafood issued a voluntary recall of its refrigerated, yellowfin tuna steak products, which were sold at Kroger grocery stores and several other chains owned by Kroger, according to a statement from the Food and Drug Administration (FDA).

The steaks were recalled because several people who ate the products developed symptoms of so-called scombroid fish poisoning. This type of food poisoning happens when people eat fish that's contaminated with high levels of histamine, a natural compound that causes allergy-like symptoms.

The contamination occurs when certain types of fish aren't properly refrigerated and bacteria break down the fish's flesh, resulting in high levels of histamine, according to the Minnesota Department of Health.

Symptoms of scombroid fish poisoning can include a tingling or burning sensation in the mouth, facial swelling, rash, hives and itchy skin, as well as nausea, vomiting and diarrhea, according to the FDA.

So far, five illnesses have been linked with the recalled products.

The recalled fish was sold between Aug. 20 and Sept. 7 at stores in Alabama, Arkansas, Georgia, Illinois, Indiana, Kansas, Kentucky, Michigan, Missouri, Mississippi, Nebraska, Ohio, South Carolina, Tennessee, Virginia and West Virginia, according to the statement.

People who purchased the recalled products should not eat them and return them to the store for a full refund, the FDA said.

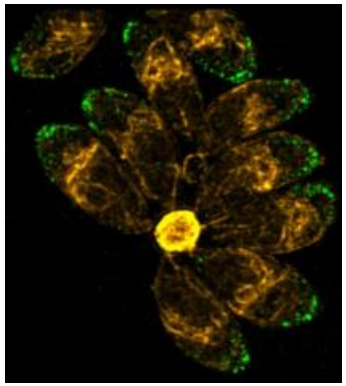
http://bit.ly/2mk0SED

Parasitology: Mother cells as organelle donors

Toxoplasma gondii, *the unicellular causative agent of toxoplasmosis, reproduces itself in an unusual fashion by means of an internal budding process.*

This entails the development of two daughter cells within the cytoplasm of the mother cell. On completion of this process, the mother cell undergoes lysis, and the daughter cells are released into the infected host cell. The daughter cells continue to proliferate until the host-cell itself finally bursts. *T. gondii* is a globally distributed infectious agent. As a rule, the infection is innocuous. However, during pregnancy, transmission of the parasite to the fetus can severely damage the development of the latter.

A group of researchers led by Markus Meissner, Professor of Experimental Parasitology at LMU in collaboration with Dr. Javier Periz at Glasgow University, has now described a phenomenon which plays an important role in asexual reproduction - during internal budding, components of a specific organelle are donated by the mother cell to the daughters. The study appears in the online journal *Nature Communications*.



***Microbiologists at LMU and UoG have discovered a recycling process in the eukaryotic parasite* Toxoplasma gondii *that plays a vital role in the organism's unusual mode of reproduction.* Source: Dr. Javier Periz, University of Glasgow.**

In order to recognize, adhere to and infect host cells, *T. gondii* makes use of organelles called rhoptries and micronemes, which secrete a set of specialized proteins that enable the parasite to invade the target cell. Once the infection has been successfully established, the parasite divides. It had been assumed up to now that the micronemes in the daughter cells are reformed from scratch. However, by specifically labelling one of the micronemal proteins, the authors of the new study were able to follow the fate of the microneme during the cell cycle with the aid of high-resolution microscopy. The observations revealed that the components of the mother cell's microneme are divided more or less equally between the daughter cells. In addition, micronemal proteins are newly synthesized in the daughter cell. The researchers assume that this recycling is not limited to the micronemes, but serves as a more general mechanism to enable the reassembly of organelles that are vital for propagation of the parasite.

"Furthermore, we have shown that recycled micronemes are transported from mother to daughter by the actin filaments of the cytoskeleton," says Markus Meissner. "This is an entirely new function for actin in the parasite. Up to now, actin was thought to be involved solely in cell motility in *T. gondii*. When we have a better understanding of how this newly discovered function of actin is regulated, we may also be able to identify novel drug targets. This is a very interesting prospect because *T. gondii* is known to possess very few actin-regulating proteins."

http://bit.ly/2lS9vGh

Extinction of Icelandic walrus coincides with Norse settlement

First use of ancient DNA analyses and C^{14}-dating to demonstrate a unique population of Icelandic walrus existed

An international collaboration of scientists in Iceland, Denmark and the Netherlands has for the first time used ancient DNA analyses and C^{14}-dating to demonstrate the past existence of a unique population of Icelandic walrus that went extinct shortly after Norse settlement some 1100 years ago. Walrus hunting and ivory trade was probably the principal cause of extinction, being one of the earliest examples of commercially driven overexploitation of marine resources.

The presence of walruses in Iceland in the past and its apparent disappearance as early as in the Settlement and Commonwealth periods (870-1262 AD) has long puzzled the scientific world. In a study recently published in the journal Molecular Biology and Evolution scientists from Denmark, Iceland and Holland have addressed the question by analysing ancient and contemporary DNA along with carbon-14 dating of walrus remains, supplemented with detailed studies of finding localities of the remains, place names and references to walrus hunting in the Icelandic Mediaeval literature, including the Icelandic Sagas.

"Natural History Museum collections provide a remarkable window into the past, which with modern day technology allow us to explore the past effects of human activities and environmental change on species and ecosystems. This can be further put into context by studying the Icelandic Mediaeval literature, historic place names and zooarchaeological sites," explains instigator of the research Hilmar J. Malmquist, Director of the Icelandic Museum of Natural History, Reykjavik, Iceland.

A long-term population of genetically unique walruses in Iceland

The scientists used carbon-14 dating of walrus remains found in Iceland to reveal that walrus inhabited Iceland for thousands of years, but disappeared shortly after the country's settlement around 870 AD by the Norse. DNA was extracted from natural finding sites and archaeological excavations of walrus samples, and compared to data from contemporary walruses, documenting that the Icelandic walrus constituted a genetically unique lineage, distinct from all other historic and contemporary walrus populations in the North Atlantic.

"Our study provides one of the earliest examples of local extinction of a marine species following human arrival and overexploitation. It further adds to the debate about the role of humans in the extinction of megafauna, supporting a growing body of evidence that wherever humans turn up, the local environment and ecosystem suffers," says Morten Tange Olsen, Assistant Professor at Globe Institute, University of Copenhagen.

Walrus ivory was a luxury good

Walrus ivory was a luxury good in high demand and widely traded across Viking Age and Medieval Europe with beautifully ornamented tusks documented as far away as the Middle East and India. Most examples of trade and human overexploitation and extinction of local marine resources are of much more recent date,

such as overfishing, and commercial whaling for the past three centuries or so.

"We show that already in the Viking Age, more than 1000 years ago, commercial hunting, economic incentives and trade networks were of sufficient scale and intensity to result in significant, irreversible ecological impacts on the marine environment, potentially exacerbated by a warming climate and volcanism. The reliance on marine mammal resources for both consumption and trade has so far been underestimated," says lead author Xénia Keighley, who is completing a PhD at the GLOBE Institute in Copenhagen and the Arctic Centre in Groningen.

Facts about the walrus

- The walrus (Odobenus rosmarus) grows up to three meters in length and live up to 40 years. The male weighs up to 1500 kilo, while the female is slightly smaller. Both males and females have tusks.
- The walrus occurs throughout the Arctic, divided in two subspecies, the Atlantic and Pacific walrus. The Atlantic walrus, to which the Icelandic belonged, numbers approximately 30.000 animals and occurs in north-eastern Canada, Greenland, Svalbard and north-western Russia.
- The Norse of the Viking Age were the first people to settle permanently in Iceland around 870 AD, and later colonised Greenland, where they also hunted walruses for food and trade with walrus tusks and hides.

The research was conducted by Xénia Keighley (University of Copenhagen and University of Groningen), Snæbjörn Pálsson (University of Iceland), Bjarni F. Einarsson (Archaeological Office in Iceland), Aevar Petersen, Meritxell Fernández-Coll (Icelandic Museum of Natural History), Peter Jordan (University of Groningen), Morten Tange Olsen (University of Copenhagen), and Hilmar J. Malmquist (Icelandic Museum of Natural History).

http://bit.ly/2metqry

Skin-crawling discovery: 'body farm' scientists find corpses move

Australian scientist has proved that human bodies move around significantly for more than a year after death

An Australian scientist has proved that human bodies move around significantly for more than a year after death, in findings that could have implications for detectives and pathologists around the world.

After studying and photographing the movements of a corpse over 17-months, Alyson Wilson told AFP on Friday that she found humans don't exactly rest in peace.

Researcher Alyson Wilson studied the movements of a corpse over 17-months and found humans don't exactly rest in peace

In one case study, arms that began held close to the body ended up flung out to the side.

"We think the movements relate to the process of decomposition, as the body mummifies and the ligaments dry out," she said.

To carry out her unusual form of people watching, Wilson took the three-hour flight from Cairns to Sydney every month to check on the progress of a cadaver.

Her subject was one of seventy bodies stored at the Southern Hemisphere's only "body farm", which sits at a secret bushland location on the outskirts of Australia's largest city.

Officially known as the Australian Facility for Taphonomic Experimental Research (AFTER), the farm is carrying out pioneering research into post-mortem movement.

Wilson and her colleagues were trying to improve a commonly used system for estimating the time of death using time-lapse cameras and in the process found that human bodies actually move around significantly. Her findings were recently published in the journal *Forensic Science International: Synergy*.

A better understanding of these movements and the rate of decomposition could be used by police to estimate time of death more accurately. She hopes the knowledge could, for example,

narrow down the number of missing persons that could be linked to an unidentified corpse.

A better understanding of post mortem movement could also help to reduce the incorrect cause of death or misinterpretation of a crime scene. "They'll map a crime scene, they'll map the victim's body position, they'll map any physical evidence which is found, and they can understand the cause of death."

The CQ University criminology graduate says she started her unique project after a trip to Mexico to help classify Mayan-era skeletal remains. "I was fascinated with death from a child and was always interested in how the body breaks down after death."

"I guess that comes about from being raised on a farm and seeing livestock die and watching that process," she said.

"Once I observed a movement in a previous study, I started researching and couldn't find anywhere in the world that looks at quantifying the movement, so I thought OK, I'm going to do this."

http://bit.ly/2kimjoL

Volcanoes kill more people long after eruptions – those deaths are avoidable

The drawn-out nature of volcanic eruptions can be most fatal—and understanding why is the key to saving lives

by Jenni Barclay, Roger Few and Teresa Armijos Burneo, The Conversation

You may think of volcanic eruptions as spectacular but brief explosions. But in reality, these destructive forces wreak havoc before headlines are made and continue long after they fade. As our new research shows, it is the drawn-out nature of volcanic eruptions that can be most fatal—and understanding why is the key to saving lives.

Most commonly, volcanoes will emit pulses of gas and solids for six to seven weeks, with quiet fizzling and rumbling punctuated by more intensive bouts of activity. Some go on for years and even decades. The recent fatal explosion in the Italian island of Stromboli is part of an eruptive sequence that officially began in 1934) but stretches back millennia—the Romans referred to the island as the "lighthouse" of the Mediterranean).

But despite this sustained risk, many who live within the reach of volatile volcanoes choose to stay in high hazard zones during an eruption, risking their lives. Studies report that between 15 and 85% of evacuated populations revisit dangerous areas while warnings are still in place.

However, research examining why so many choose to do so is limited. To better understand how to protect lives and livelihoods in the wake of eruptions, we investigated the impacts of past eruptions on the communities around volcanoes with a three-pronged approach.

Reporting on what happens to entire populations during eruptions can be a bit patchy, but what is usually well covered is when people died and where and what they were doing. We examined the circumstances of human deaths from all eruptions globally with available data over a 30-year period. We also conducted detailed interviews with people who had experienced prolonged volcanic activity in Latin America and the Caribbean. Finally, we compiled and analysed existing case studies of communities affected by recent eruptions, to understand the relevant data they had uncovered.

Data on deaths showed that where warnings were in place, about 75% of the fatalities happened inside a zone where people had been asked to to leave, or stay away from. More than 90% of these were people who were either protecting their assets or engaged in activities that contributed to their livelihoods—farming for instance. More than 70% of all fatalities happened a week or more after the initial eruption, despite warnings being in place.

Interviews gave us more insight into the pressures that might have led to those risky decisions. Most people who chose to return to evacuation zones were aware of the risks, but pressures to protect

livelihoods and well-being override those considerations. Many returned to look after property, animals or crops. Some people simply wanted to protect and be with their community and seek solace in their home. Few just returned out of curiosity.

Difficult conditions in evacuation shelters also contribute. After the Soufrière Hills Volcano on Montserrat began to erupt in 1995, some people lived for months in refuges where supplies of fresh vegetables were in short supply. By 1997, some were returning to the evacuated zone to tend to crops in an attempt to provide for not only their families but others too. In June of that year, 19 people died during an upsurge in activity in the exclusion zone.

Saving lives and livelihoods

What ours and and the other studies we analyzed show is that promoting awareness of the sustained risks of volcanoes is a good start, but it's not enough to ensure people's safety. Evacuation strategies also need to find ways of minimizing long-term impacts on livelihoods and well-being—especially when they last for more than a few days. For example, authorities could provide alternative pasture for animals, or ensure market prices don't fall if they have to sell them.

Allowing populations at risk to anticipate sudden changes in activity would also be helpful. The better we can forecast sudden upsurges in activity, the less disruption there will be to affected populations. Scientists are hopeful that new technologies such as drones, space-based monitoring and better micro-analysis of erupted rocks will soon allow us to better detect when unrest turns to more violent eruptions and, just as importantly, when a volcano will settle for a longer period of time. Improving communication networks in at-risk areas is also crucial for improved forecasting to be useful.

Of course, most important of all is that strategies are designed by working collaboratively with and for communities at risk. There are already some wonderful examples where scientists, authorities and communities collaborate to share and rapidly transmit information when activity changes. For example, at Tungurahua in Ecuador, "watchers" have direct radio contact with the local observatory and are trusted members of their community. This network enabled populations to respond rapidly when the volcano started generating pyroclastic flows between 2006 and 2014.

All of this applies not just to volcanoes, but other protracted hazards such as flooding, coastal erosion and landslides too—many of which we will face with increased frequency in the future. By truly understanding and addressing what drives people to return to dangerous zones, and helping them anticipate times of extreme risk, we can save countless lives and countless more livelihoods.

https://wb.md/2lR9n9S

Lyme Testing Gets Fast and Easy

Modified approach performed as well—if not a bit better—in detecting identifiable antibodies against Borrelia burgdorferi

Paul G. Auwaerter, MD

This transcript has been edited for clarity.

Hello. I'm Paul Auwaerter with Medscape Infectious Diseases, speaking from the Johns Hopkins University School of Medicine.

Lyme disease serologic testing has often been a difficult issue for clinicians and patients alike, both in receiving testing results on a speedy basis and dealing with the confusing presence of bands and trying to interpret what it all means.

The US Food and Drug Administration has recently approved a modified two-tier approach, whereby two enzyme immunoassays (EIAs) alone are necessary instead of the current standard (which has existed for 25 years), where a first-tier EIA is followed by an immunoblot or Western blot.[1]

This modified approach, which relies on two easy-to-run tests, offers several advantages. When the test was examined for both

early Lyme disease and later noncutaneous Lyme disease, it performed as well—if not a bit better—in detecting identifiable antibodies against *Borrelia burgdorferi*, the causative agent of Lyme disease.[2,3]

Laboratory pathologists would very much like to do away with the immunoblot components of Lyme disease testing because they are fraught with difficulties, both technical and in interpretation, whereas EIAs are much easier to run in the laboratory, provide quicker results, and may be less expensive.[4]

Instead of waiting for immunoblot testing, it's quite possible that you will get these test results back quicker with a positive, equivocal, or negative result, and you could therefore confirm whether someone has Lyme disease. However, you still run into trouble with the same IgM positivity, so you should ask your laboratory if they are running independent IgM and IgG confirmatory testing.

These advantages outweigh those of the current approach. The standard two-tier approach will still be there if needed and is offered as an alternative to this modified two-tier testing.

This modified approach also offers advantages in terms of helping clinicians and patients get to treatment earlier, and it seems to be as accurate as the standard approach—both sensitive and specific—based on assessment in a large number of specimens that have been clinically verified.[3]

This has been a long time coming. We are still looking for even more improvements in testing because these antibodies don't necessarily reflect active infection and can reflect past infection. There are needs for improvement in diagnostic testing for Lyme disease in the very earliest phases of infection that don't depend on antibodies, especially for patients without the characteristic erythema migrans rash.

Tests that track with microbiologic cure would be very reassuring to people, especially if there are concerns that they don't improve after initial testing. If a patient is not improving, you should determine whether you have an accurate diagnosis of Lyme disease.

My sense is that this approach works as well, if not better, for early Lyme disease detection. You can have confidence that the modified approach will also detect Lyme disease for patients who might have later neurologic presentations. Thanks very much for listening.

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http://bit.ly/2knvOTQ

No Laughing Matter: A Woman's Guffaw Results in a Dislocated Jaw

The woman received help from a doctor who happened to be riding on the same train.

By Nicoletta Lanese - Staff Writer 2 days ago Health

A woman aboard a train in China let out a laugh so boisterous that she dislocated her jaw, according to news reports.

While traveling to Guangzhou South Railway Station in southeast China, the unfortunate passenger got stuck with her mouth agape, drooling and unable to speak properly after a booming burst of laughter, according to the India-based news outlet News18. Unbeknown to the woman, her lower jawbone had become unhinged from her skull. A call for help was sounded over the

train's speaker system and a doctor on board named Luo Wensheng came to her aid.

Wensheng, who works at Liwan Hospital in the city of Guangzhou, rushed to the passenger and quickly assessed her condition. "I initially thought she had had a stroke," Wensheng reportedly told the Chinese news outlet Guancha. After realizing the woman's actual problem, Wensheng at first told her that she should seek help at a hospital, as he wasn't an expert on resetting jaws. But nearby passengers implored the doctor to help, saying that it would take at least an hour to reach a medical facility.

After two tries, Wensheng successfully reset the passenger's jaw. A person traveling with the woman later said that the woman had previously dislocated her jaw once before while vomiting, which likely placed her at higher risk for future dislocation, according to News18. The woman thanked Wensheng for saving her money, while the doctor urged her once again to seek care at a hospital.

Woman Stuck With Mouth Open after Dislocating Jaw From 'Laughing Too Hard'https://t.co/Gg94zQVtIISeptember 12, 2019

http://bit.ly/2kC4Jwo

Childhood behavior linked to taking paracetamol in pregnancy

Examining whether there were any effects of taking paracetamol in mid-pregnancy and the behaviour of the offspring between the ages of 6 month and 11 years

The research published today (Monday 16 September) in *Paediatric and Perinatal Epidemiology* examined whether there were any effects of taking paracetamol in mid-pregnancy and the behaviour of the offspring between the ages of 6 month and 11 years, with memory and IQ tested up until the age of 17. Paracetamol is commonly used to relieve pain during pregnancy and is recommended as the treatment of choice by the NHS.

Using questionnaire and school information from Bristol's Children of the 90s study researchers examined 14,000 children. When they were seven months pregnant 43 per cent of their mothers said they had taken paracetamol 'sometimes' or more often during the previous three months. Researchers examined results of the children's memory, IQ and pre-school development tests, temperament and behaviour measures.

They found an association between paracetamol intake and hyperactivity and attention problems as well as with other difficult behaviours with young children that were not accounted for by the reasons why the medication was taken or social factors. However, this was no longer the case by the time the children reached the end of primary school. Boys appeared to be more susceptible than girls to the possible behavioural effects of the drug.

The study was led by Professor Jean Golding OBE who also founded the University of Bristol's Children of the 90s study. She commented:

"Our findings add to a series of results concerning evidence of the possible adverse effects of taking paracetamol during pregnancy such as issues with asthma or behaviour in the offspring. It reinforces the advice that women should be cautious when taking medication during pregnancy and to seek medical advice where necessary.

"It is important that our findings are tested in other studies - we were not in a position to show a causal link, rather an association between two outcomes. It would also be useful now to assess whether older children and adults are free of difficult behavioural problems if their mother had taken paracetamol."

Notes for editors

1. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation: a longitundinal cohort study by Jean Golding, Steven Gregory, Rosie Clark et al published in Paediatric and Perinatal Epidemiology

2. Based at the University of Bristol, Children of the 90s, also known as the Avon Longitudinal Study of Parents and Children (ALSPAC), is a long-term health research project that enrolled more than 14,000 pregnant women in 1991 and 1992. It has been following the health and development of the parents, their children and now their grandchildren in detail ever since. It receives core funding from the Medical Research Council, the Wellcome Trust and the University of Bristol.

3. The current advice on taking paracetamol during pregnancy can be found here (due for review June 2021): https://www.nhs.uk/common-health-questions/pregnancy/can-i-take-paracetamol-when-i-am-pregnant/

4. Two other major European studies have used longitudinal cohorts to examine the issue of taking paracetamol during pregnancy and child behaviour. Both studies had controlled for a variety of potential confounders:

A study by Brandlistuen using the Norwegian mother and child cohort study MoBA found adverse development and behaviour of three year old children, and increased risk of diagnosis of ADHD in the offspring of women who had taken paracetamol more often than eight days during pregnancy: https://academic.oup.com/ije/article/42/6/1702/739709

A study by the University of California using the Danish National Birth Cohort also found an increased risk of ADHD and of ADHD-like behaviour at seven years old if the mothers had consumed paracetamol during pregnancy.

https://jamanetwork.com/journals/jamapediatrics/fullarticle/1833486

http://bit.ly/2lOwdip

Did the Dinosaur-Killing Asteroid Inadvertently Help Lichens?

The leafy lichens seem to have picked up where a lot of incinerated plants left off

By Jennifer Frazer

***The macrolichen* Letharia vulpina Jason Hollinger *Wikimedia* (CC-by-3.0)**

As is now pretty well known, a city-sized asteroid hurled itself into Earth near today's Yucatan Peninsula about 65 million years ago on what was an unquestionably bad day for the planet. But it wasn't a bad day for everyone.

Although terrifying (not to mention highly injurious to property values), the day that eliminated dinosaurs ultimately produced a slew of creatures that filled their vacated niches. To name but a few: anteaters, antelopes, duck-billed platypuses, slow lorises, giant sloths, saber-toothed tigers, horses, hippopotamuses, humans … and possibly also a whole lot of leafy lichens.

At least, the timing of leafy lichen diversification looks suspiciously as if they may have gotten a big assist from the Big A, according to a new study in *Scientific Reports*.

Dinosaurs weren't the only group to take a sucker punch in the summer of Just-Past-66 million BC. Plants, too – large, stationary targets that can't burrow, jump in the ocean, or relocate easily in response to instant climate change -- struggled to cope. Fungi, on the other hand, often benefited. That isn't surprising, considering many of them make a living batting cleanup on the dearly departed.

That got a scientist from Chicago's Field Museum wondering: how did lichens fare in the aftermath of the "Terminal Cretaceous Event"? Lichens are leathery or crusty co-ops that marry fungi to algae, some of which are closely related to plants. Did lichens react to the asteroid more like plants or like fungi?

Because the lichen fossil record is skimpy, Thorsten Lumbsch and a team of scientists from the United States, Thailand, and Taiwan decided to investigate by studying lichen DNA. Since the rate of mutation is usually constant, comparing the DNA sequences of various species using special software can help scientists tell how long ago various groups shared a common ancestor and when and how often new species evolved. If lichens prosper, one would expect lots of new species. If not, speciation rates should drop.

***Microlichens tend to be smaller, crustier affairs, like this:* Valugi *Wikimedia* (CC-by-3.0)**

But lichens aren't monolithic; they come in many flavors. One of the most basic ways of classifying them is by size. Macrolichens

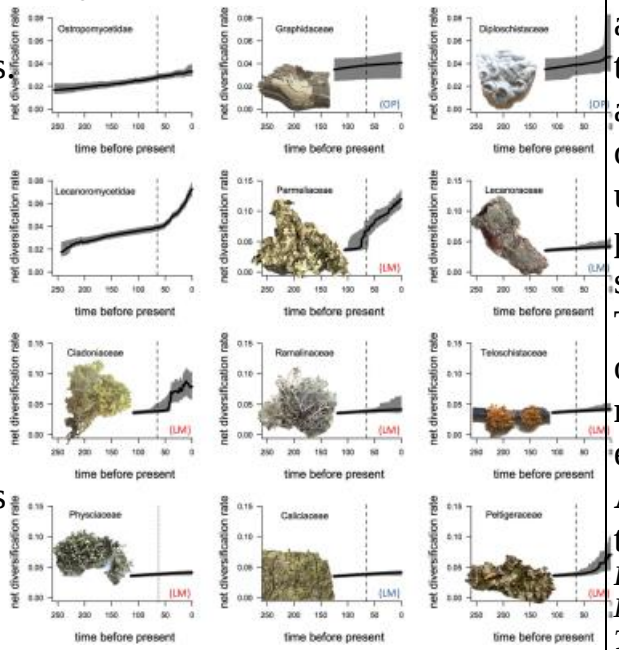
are big, but also usually leafy or shrubby, like the one pictured at the top of this post.

The scientists specifically wondered what happened to the speciation rate of macrolichens and microlichens post-asteroid, and published their results in June in the journal *Scientific Reports*.

When they crunched the DNA data, they concluded that macrolichens in at least three major families blossomed around the time of the impact. Microlichens appear not to have noticed anything happened, and continued making species at the same plodding pace they had pre-asteroid.

In the figure below, families composed predominantly of macrolichens are indicated by red lettering in the lower right corner, and microlichens by blue.

At upper left are two larger taxonomic groups called subclasses. Ostropomycetidae contains mostly microlichens, while Lecanoromycetidae is predominantly macrolichens. However, "around the time of the impact" in this case means anywhere from 100 million to 40 million years ago, so understandably, the asteroid may not have been the only factor in macrolichen diversification. You can see this in the figure above as some groups seem to diversify before or after the black dashed line of doom.



Credit: Huang et al. 2019

The 60-million-year macrolichen diversification window also encompasses the explosive evolution of flowering plants around 125-80 million years ago, and on the other side of the impact, a significant global warming that peaked at 55 million years ago. Either event may have induced lichens to diversify by providing new homes or more favorable growing conditions.

But it is also possible that the big leafy lichens all diversified simply because, as they were all related, they all inherited a shared propensity to evolve quickly. With the data so far, it's not possible to distinguish between these possibilities, the scientists say.

Assuming the asteroid did stimulate – or at least contribute to -- macrolichen evolution, why the big leafy lichens and not the small crusty ones?

Epiphytes are plants that grow on other plants. Epiphytic plants would have been particularly vulnerable to the effects of the asteroid, which may have included a global bake at pizza-oven temperatures as tiny glass beads produced by the impact re-entered and heated the atmosphere. Plants rooted in the ground stood some chance of resurrection from underground bits. Epiphytes have no underground bits. On top of that, Earth's climate post-asteroid was probably radically different from what preceded the asteroid for some time.

Thus, it may be that as with so many others, the epiphytic niche opened wide at the dawn of the Paleocene. Tough, dessication-resistant lichens may have survived the planetary flash fry and ensuing climatic trauma much better than Cretaceous ephiphytes. And from the smoking embers, new trees with invitingly naked trunks eventually grew, beckoning nearby lichens to hop onboard.

Reference

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http://bit.ly/2kOh0h1

Working memory linked to road accidents

Study prompts call for routine memory testing of teenagers.

Paul Biegler reports.

A study of young drivers in the US has found those who did worse on tests for short term "working" memory were more likely to crash in the first few years after getting their licence.

The finding has prompted the authors, led by neuroscientist Elizabeth Walshe from the University of Pennsylvania, to call for routine memory testing of teens to weed out those not ready to take the wheel. They could instead be offered extra training.

The study comes on the back of a stark set of numbers. Statistics from the Centres for Disease Control and Prevention show vehicle crashes are the leading cause of death in US teens. Six teen drivers die on the roads each day with the cost of adolescents injured in crashes topping $US13 billion in 2016.

Having a callow youth at the helm is also bad news for other youngsters in the car. More than half of children aged eight to 17 who die in crashes are in cars driven by someone under 20.

The authors' suspicion was that some teenage brains are just not up to the job.

Driving puts big demands on your working memory. That's the "scratch pad" that keeps track of things that happened in the last few seconds and helps you decide what to do next.

It is critical brain kit for drivers, who have to check their speed, read road signs and take in what the GPS is saying, all while keeping an eye on the moveable feast of stuff happening on the road. But the authors say working memory is very much a work in progress for adolescents.

One key stat shows 20-year-old drivers have fewer crashes than equally experienced 17-year-olds, suggesting the older drivers have a developmental advantage.

The authors suspected that might be in working memory.

To find out they enlisted the help of young people from the Philadelphia Trajectory Study, which tracked risky behaviour in youths aged 10 to 20 between the years 2004 and 2014.

The researchers surveyed the crash history of 84 of those young people, average age 20, who had started driving. Twenty-five of them – just shy of 30% – had been in at least one crash. Four had been in two bingles, and two drivers had more than three crashes.

But the Philadelphia study also did something that was gold for the researchers.

It measured working memory, including with the so-called "two-back" test. In one version of the test you see a stream of images one after the other; for example, a cat a fish, a spoon and a ball. The challenge is to say when the current image is the same as the one two steps back. The team dug through the files to see how the 84 youngsters had done over their decade of memory tasks.

All made gains in working memory, but it was the rate of improvement that mattered. Those with a flatter upward slope – whose memory gains were relatively poor – were significantly more likely to crash within the first three years or so of getting their license.

The American Academy of Paediatrics Teen Driver guidelines reference the higher crash rates of teens with developmental issues such as ADHD. But the authors suggest there may be a critical omission.

"To our knowledge, no evidence exists for recommendations around expected individual variation in typical neurocognitive development, including working memory capacity, which co-occurs during the period of learning to drive and early licensure," they write.

That is a deficiency, they note, that could be a new target for injury prevention in young drivers.

“Monitoring working memory development across adolescence as part of routine assessment could help to identify at-risk drivers, as well as opportunities for intervention. Attention and driving skill deficits due to insufficient working memory may be one of the most modifiable risk factors,” they conclude.

One possible intervention is extra training in a driving simulator. Given the general affinity of modern youth for anything on a screen, that should not be too tall an order.

The study appears in the journal *JAMA Network Open*.

http://bit.ly/2kjn6pw

Physicians report high refusal rates for the HPV vaccine and need for improvement

The HPV vaccine is one of only two vaccines that prevent cancer

Despite its proven success at preventing cancer, many adolescents are still not getting the HPV vaccine. A new study from the University of Colorado School of Medicine at the Anschutz Medical Campus shows that physicians' delivery and communication practices must improve to boost vaccination completion rates. Health care providers must also learn to deal with parents hesitant to get their children vaccinated with HPV vaccine.

The study, published today in *Pediatrics*, is the first to examine pediatricians and family physicians' delivery practices for the vaccine since the new 2-dose schedule came out for adolescents 11 or 12-years-old.

"A physician recommendation is one of the most important factors in vaccine acceptance by parents," said Allison Kempe, MD, MPH, lead author and professor of pediatrics at the University of Colorado School of Medicine. "However, we're seeing a lack of understanding from healthcare providers about the need for vaccination early in adolescence and high rates of refusal on the part of parents. The vaccine is underutilized, with less than half of American adolescents completing the vaccination. We need to maximize methods of introducing the vaccine that we know to be more effective, as well as the use of reminder and delivery methods at the practice in order to improve this rate."

Every year, HPV causes over 33,500 cases of cancer in women and men in the United States, according to the Centers for Disease Control and Prevention. "The earlier someone is vaccinated, the better the immune system responds. It also increases the chances of being vaccinated before having exposure to HPV strains," Kempe said. "If we can increase the rate of vaccination in early adolescence, then we can prevent cancers that develop in later years."

The study surveyed 588 pediatricians and family physicians and found that refusal rates from parents remain high, especially for 11 to 12-year-olds, the target population for vaccination.

But physicians who use a `presumptive style' approach have higher acceptance rates. Presumptive style means physicians introduce the HPV vaccine and recommend it in the same manner and as strongly as the other recommended adolescent vaccines for meningitis and Tdap. For example, a doctor could say, "We've got three vaccines today: Tdap, HPV and Meningitis," rather than isolating HPV as an option that is not as important.

Still, the survey found some encouraging signs:

- ***Despite a high refusal rate, pediatricians who strongly recommend the vaccine increased from 60% in 2013 to 85% in 2018 for 11 or 12-year-old females and from 52% to 83% for 11 to 12-year-old males.***
- ***Some 89% of pediatricians and 79% of family pediatricians reported more adolescents under age 15 are completing the HPV series now that only 2 doses are recommended.***

Along with improving physician communication styles, HPV delivery could also be optimized by increased use of standing orders and alert systems in the medical record to remind providers of the need for vaccination at the point of care.

The study was supported by a grant from the Centers for Disease Control and Prevention.