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New disease surveillance tool helps detect any human virus

Computational method helps scientists examine microbes at a larger, more comprehensive scale than previously possible

During the Zika virus outbreak of 2015-16, public health officials scrambled to contain the epidemic and curb the pathogen's devastating effects on pregnant women. At the same time, scientists around the globe tried to understand the genetics of this mysterious virus.

The problem was, there just aren't many Zika virus particles in the blood of a sick patient. Looking for it in clinical samples can be like fishing for a minnow in an ocean.

A new computational method developed by Broad Institute scientists helps overcome this hurdle. Built in the lab of Broad Institute researcher Pardis Sabeti, the "CATCH" method can be used to design molecular "baits" for any virus known to infect humans and all their known strains, including those that are present in low abundance in clinical samples, such as Zika.

The approach can help small sequencing centers around the globe conduct disease surveillance more efficiently and cost-effectively, which can provide crucial information for controlling outbreaks.

The new study was led by MIT graduate student Hayden Metsky and postdoctoral researcher Katie Siddle, and it appears online in Nature Biotechnology.

"As genomic sequencing becomes a critical part of disease surveillance, tools like CATCH will help us and others detect outbreaks earlier and generate more data on pathogens that can be shared with the wider scientific and medical research communities," said Christian Matranga, a co-senior author of the new study who has joined a local biotech startup.

Scientists have been able to detect some low-abundance viruses by analyzing all the genetic material in a clinical sample, a technique known as "metagenomic" sequencing, but the approach often misses viral material that gets lost in the abundance of other microbes and the patient's own DNA.

Another approach is to "enrich" clinical samples for a particular virus. To do this, researchers use a kind of genetic "bait" to immobilize the target virus's genetic material, so that other genetic material can be washed away.

Scientists in the Sabeti lab had successfully used baits, which are molecular probes made of short strands of RNA or DNA that pair with bits of viral DNA in the sample, to analyze the Ebola and Lassa virus genomes.

However, the probes were always directed at a single microbe, meaning they had to know exactly what they were looking for, and they were not designed in a rigorous, efficient way.

What they needed was a computational method for designing probes that could provide a comprehensive view of the diverse microbial content in clinical samples, while enriching for low-abundance microbes like Zika.

"We wanted to rethink how we were actually designing the probes to do capture," said Metsky.

"We realized that we could capture viruses, including their known diversity, with fewer probes than we'd used before. To make this an effective tool for surveillance, we then decided to try targeting about 20 viruses at a time, and we eventually scaled up to the 356 viral species known to infect humans."

Short for "Compact Aggregation of Targets for Comprehensive Hybridization," CATCH allows users to design custom sets of probes to capture genetic material of any combination of microbial species, including viruses or even all forms of all viruses known to infect humans.

To run CATCH truly comprehensively, users can easily input genomes from all forms of all human viruses that have been uploaded to the National Center for Biotechnology Information's GenBank sequence database. The program determines the best set of probes based on what the user wants to recover, whether that's all viruses or only a subset. The list of probe sequences can be sent to one of a few companies that synthesize probes for research.

Scientists and clinical researchers looking to detect and study the microbes can then use the probes like fishing hooks to catch desired microbial DNA for sequencing, thereby enriching the samples for the microbe of interest.

Tests of probe sets designed with CATCH showed that after enrichment, viral content made up 18 times more of the sequencing data than before enrichment, allowing the team to assemble genomes that could not be generated from un-enriched samples. They validated the method by examining 30 samples with known content spanning eight viruses.

The researchers also showed that samples of Lassa virus from the 2018 Lassa outbreak in Nigeria that proved difficult to sequence without enrichment could be "rescued" by using a set of CATCH-designed probes against all human viruses. In addition, the team was able to improve viral detection in samples with unknown content from patients and mosquitos.

Using CATCH, Metsky and colleagues generated a subset of viral probes directed at Zika and chikungunya, another mosquito-borne virus found in the same geographic regions.

Along with Zika genomes generated with other methods, the data they generated using CATCH-designed probes helped them discover that the Zika virus had been introduced in several regions months before scientists were able to detect it, a finding that can inform efforts to control future outbreaks.

To demonstrate other potential applications of CATCH, Siddle used samples from a range of different viruses. Siddle and others have been working with scientists in West Africa, where viral outbreaks and hard-to-diagnose fevers are common, to establish laboratories and workflows for analyzing pathogen genomes on-site.

"We'd like our partners in Nigeria to be able to efficiently perform metagenomic sequencing from diverse samples, and CATCH helps them boost the sensitivity for these pathogens," said Siddle.

The method is also a powerful way to investigate undiagnosed fevers with a suspected viral cause. "We're excited about the potential to use metagenomic sequencing to shed light on those cases and, in particular, the possibility of doing so locally in affected countries," said Siddle.

One advantage of the CATCH method is its adaptability. As new mutations are identified and new sequences are added to GenBank, users can quickly redesign a set of probes with up-to-date information. In addition, while most probe designs are proprietary, Metsky and Siddle have made publicly available all of the ones they designed with CATCH. Users have access to the actual probe sequences in CATCH, allowing researchers to explore and customize the probe designs before they are synthesized.

Sabeti and fellow researchers are excited about the potential for CATCH to improve large-scale high-resolution studies of microbial communities. They are also hopeful that the method could one day have utility in diagnostic applications, in which results are returned to patients to make clinical decisions.

For now, they're encouraged by its potential to improve genomic surveillance of viral outbreaks like Zika and Lassa, and other applications requiring a comprehensive view of low-level microbial content.

The CATCH software is publicly accessible on GitHub. Its development and validation, supervised by Sabeti and Matranga, is described online in Nature Biotechnology.

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Enlarged prostate could actually be stopping tumor growth, simulations show

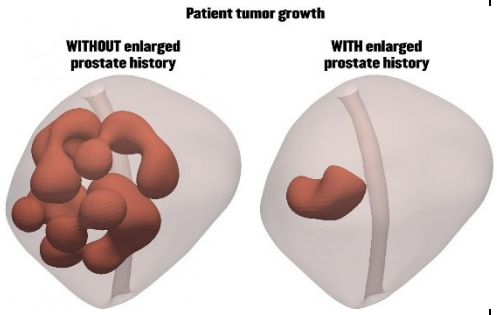
New study shows that in some men with prostate cancer, a larger prostate actually impedes tumor growth

WEST LAFAYETTE, Ind. -- For men older than about 60, an enlarged prostate means feeling the urge to make a pit stop way too often throughout the day.

But a new study shows that if these men also happen to have prostate cancer, the larger prostate actually impedes tumor growth.

The findings suggest that it might be a bad idea to downsize an enlarged prostate through surgery or drugs, because doing so could lead to faster growth of prostate cancer. While the five-year survival rate for prostate cancer is generally very high, it is still one of the leading causes of death among men in the U.S., according to the Prostate Cancer Foundation.

Computer simulations of patient data offer a possible explanation of why an enlarged prostate might be a life saver: because a prostate can only grow so much within a confined space, force accumulates and puts pressure on the tumor, effectively keeping it small.



Computer simulations show for the first time that when a patient has history of an enlarged prostate, tumors in the prostate barely grow at all. **University of Pavia/Guillermo Lorenzo**

"It's already known that forces and stresses have an impact on tumor growth, and that patients with enlarged prostates tend to have slower cancer growth, but it wasn't known why," said Hector Gomez, associate professor of mechanical engineering at Purdue University, who builds models and simulations for understanding tumor growth, cellular migration and blood flow.

The study, published in the Proceedings of the National Academy of Sciences, is the first to simulate the possible effects of benign prostatic hyperplasia, a disease that causes the prostate to enlarge progressively, on the tumors of prostate cancer.

Guillermo Lorenzo, a former doctoral student of Gomez who is now a postdoctoral researcher at the University of Pavia in Italy, performed most of the research and ran the simulations. Alessandro Reali and Pablo Dominguez-Frojan also participated in the study and are coauthors of the paper.

Gomez and Thomas Hughes, a professor of aerospace engineering and engineering mechanics at The University of Texas at Austin, began the project as part of their work on using computer simulations to improve the diagnosis and prognosis of prostate cancer.

"Current diagnosis and prognosis methods have had a hard time differentiating between patients who are under serious risk of prostate cancer and those who aren't," Gomez said. "This has led to people getting overtreated or undertreated."

Looking at the relationship between prostate enlargement and prostate cancer could bring new insights.

The study looked at data from patients in medical studies who had a history of both an enlarged prostate and prostate cancer. To perform the simulations, Lorenzo extracted a three-dimensional anatomy of the prostate and locations of the tumors from MRI images.

At the end of a one-year period, the simulations showed that the tumor of a patient with history of an enlarged prostate barely grew at all. When the researchers removed history of an enlarged prostate in the program, the tumor had grown to be over six times larger at the end of the same time period.

"But now we know that the mechanical stresses that originate as prostates enlarge impede tumor growth," Hughes said.

Realistically, these findings would need to be clinically validated in humans through a long-term observational study before doctors take action. In the meantime, the researchers plan to extend their model to incorporating the effects of drugs that downsize the prostate, as well as use the model's information on the deformation of the prostate to help detect cancer.

Gomez, Hughes and Lorenzo are listed as co-inventors of this technology on a patent application filed by The University of Texas at Austin. The work received financial support from the European Research Council, Xunta de Galicia and Fondazione Cariplo-Regione Lombardia.

This research aligns with Purdue's Giant Leaps celebration, acknowledging the university's global advancements made in health, longevity and quality of life as part of Purdue's 150th anniversary. This is one of the four themes of the yearlong celebration's Ideas Festival, designed to showcase Purdue as an intellectual center solving real-world issues.

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Excess immune pruning of synapses in neural cells derived from patients with schizophrenia

Study finds evidence that synaptic pruning is excessive in individuals with schizophrenia

A study led by Massachusetts General Hospital (MGH) investigators finds evidence that the process of synaptic pruning, a normal part of brain development during adolescence, is excessive in individuals with schizophrenia. While previous studies have found structural abnormalities in the brains of people with schizophrenia that suggested a role for abnormal synaptic pruning, this study - published in Nature Neuroscience - is the first to directly observe excessive synaptic pruning using cells from patients with schizophrenia.

"This approach lets us model at least one of the abnormalities of schizophrenia 'in a dish'," says Roy Perlis, MD, MSc, of the MGH Department of Psychiatry and the Center for Genomic Medicine, senior author of the report. "It is one of the first indications in cells from patients of what is contributing to the abnormalities in pruning that have been suspected. And we hope to use these cells to screen for new treatments that may ultimately address that abnormality."

Studies in recent years have revealed that microglia, which are innate immune cells active within the central nervous system, play an important role in brain development by removing unneeded synapses - points of communication between brain cells - and other neural structures. This process is particularly active during adolescence and early adulthood, the time of life when symptoms of schizophrenia and other mental illnesses often first appear.

A new system developed by Perlis's team has made it possible, for the first time, to study synaptic pruning in patient-derived human cells. In an earlier study the investigators described creating induced microglia-like (iMG) cells from monocytes derived from blood samples cultured under special conditions. They then developed a way to measure synaptic pruning by observing those cells devour synaptic structures called synaptosomes isolated from cultured neurons. In the current study they used iMG cells and synaptosomes obtained from men with schizophrenia and from healthy control participants to determine patient versus control differences in the model of synaptic pruning. In addition, they validated their findings in by growing microglia together with neurons, directly measuring the uptake by microglia of synaptic markers from the neurons.

Their experiments showed that the engulfment and elimination of synapses by iMG cells was most rapid and extensive when both microglia and synapses were derived from men with schizophrenia. Microglia from patients with schizophrenia more extensively pruned synapses from either patients or controls, while control microglial cells ingested the fewest synapses of all. The results suggest that factors from both microglia and neurons contribute to increased synaptic pruning in people with schizophrenia.

Several gene variants have been associated with an increased risk of schizophrenia, and one of those most strongly associated relates to the complement system, which contributes to the ability of immune cells to remove microbes and dying cells. The investigators found

that increased expression in neurons of a specific complement protein variant was associated with increased synaptic uptake by iMG cells, although that variant is not the only contributor to increased microglial uptake.

Since preclinical research has suggested that the antibiotic drug minocycline might have benefits against neurodegenerative diseases, although the mechanism is not known, the investigators pretreated microglial cell cultures with a range of minocycline doses before applying the cells to neurons derived from patients with schizophrenia and from controls. The highest minocycline doses almost totally eliminated synaptic engulfment.

To investigate whether minocycline, which is often prescribed to treat acne, might also decrease schizophrenia risk in humans by reducing synaptic pruning during adolescence, the researchers analyzed data from up to 10 years of electronic health records from two academic medical centers. Of more than 22,000 individuals prescribed at least one of five common antibiotics between the ages of 10 and 18, 203 subsequently were diagnosed with a psychotic disorder. The more than 3,800 individuals who were treated with minocycline or the related antibiotic doxycycline for at least 90 days had a significantly reduced risk of a subsequent psychotic disorder diagnosis than did those receiving other antibiotics.

"As encouraged as we are by these initial results, they represent a first step," says Perlis, a professor of Psychiatry at Harvard Medical School. "Although we studied cells from more patients than any previous study we're aware of, we need even larger numbers to better understand what is different in cells from individuals with schizophrenia. There is reason to be hopeful that we are starting to understand what causes this devastating disorder as a first step towards developing strategies to prevent, not just treat it. But there is also much more work to be done."

The lead author of the Nature Neuroscience paper, Carl Sellgren, MD, PhD, formerly a postdoctoral fellow on Perlis's team, is now at the Karolinska Institutet in Stockholm, Sweden. Another key contributor was Steven Sheridan, PhD, director of the cellular modeling platform in Perlis's lab at MGH. Support for the study includes National Institute of Mental Health/National Human Genome Research Institute grant P50 MH106933; Swedish Research Council grants 2017-02559 and MMW 2017.0118; and a National Institute of Mental Health Biobehavioral Research Award for Innovative New Scientists grant R01 MH113858.

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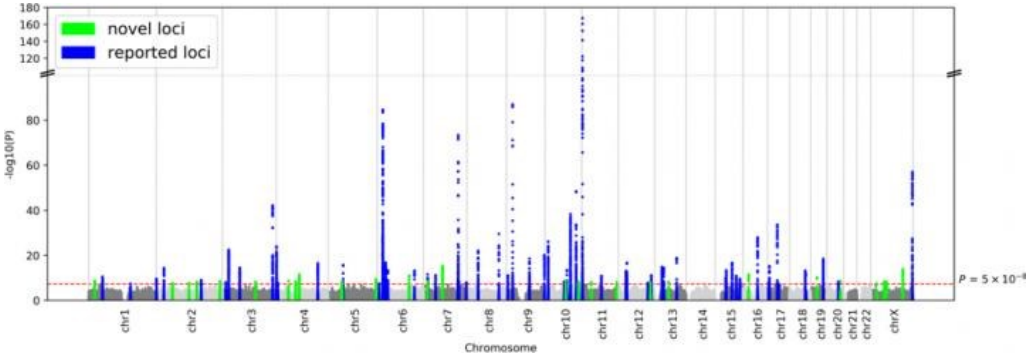
Large-scale study reveals genetic risk of diabetes in the Japanese population

Researchers have combined data from genetic studies and revealed 28 new genomic regions associated with type 2 diabetes, some variants of which are not found in other ethnic groups

Osaka, Japan - The genetic and genomic revolutions have led to an abundance of data about the genetic factors that confer a predisposition to type 2 diabetes (T2D), alongside environmental and lifestyle-related causes. However, most of the studies were based on individuals of European descent, meaning that the findings, and any treatments based on them, may not be optimal for other ethnic groups.



Manhattan plot of genome-wide association results of the meta-analysis in 36,614 cases and 155,150 controls. Association signals that reached genome-wide significance (P < 5.0 × 10−8) are shown in green if novel and blue if previously reported. **Suzuki et al. (2019)** ***Nature Genetics***

A new study performed by researchers from Osaka University, The University of Tokyo, RIKEN, and others and published in the journal

Nature Genetics has shed more light on the genetics of diabetes in the Japanese population by analyzing data on over 36,000 sufferers of T2D and over 150,000 controls of Japanese ancestry. Their work has revealed 28 novel genomic regions associated with T2D, as well as related molecular pathways and cells, with some of these associations being specific to individuals of Japanese descent.

The team conducted a type of study called a meta-analysis, which involves combining the data from a number of independent studies in order to increase the amount of available data and thus the statistical power. As shown by this new study, this approach can potentially provide novel findings that aren't unearthed by constitutive studies, each with a smaller sample size.

"We incorporated the data on links between type 2 diabetes and over 12 million variants across the whole genome from four different genome-wide association studies in the Japanese population," Yukinori Okada says. "We found 88 genomic regions significantly associated with this disease, including 28 new ones, some of which are not found in European populations in previous reports."

The group then looked in more detail at the identified genes, the effects of mutations on them and the proteins they encode, along with the associated pathways and cells. Examples of genetic factors linked to T2D include mutations in the GLP1R, involved in glucose-dependent insulin secretion, and in the genes CPA1 and GP2, known to help certain pancreatic cells transform into insulin-producing beta cells. Although the mutant forms of these genes were linked to T2D in this study, these mutations actually do not exist or are extremely rare in previous reports on European populations.

"Our findings indicate that some of the genetic underpinnings and molecular pathways of type 2 diabetes in the Japanese population may differ from those in European populations, which is unsurprising considering that, when comparing individuals of the same body mass index, Japanese are more prone to this disease," lead author Ken Suzuki says. "Our work could lead to Japanese- or Asian-specific therapeutic measures being developed to more effectively prevent or treat diabetes in this ethnic group."

The article "Identification of 28 new susceptibility loci for type 2 diabetes in the Japanese population" is published in Nature Genetics at DOI: https://doi.org/10.1038/s41588-018-0332-4.

http://bit.ly/2MQGowo

New Map Shows Brain Changes Associated with Alzheimer's

The protein expression data, which are freely available online, could help identify new drug targets for the disease.

Catherine Offord

Researchers in the UK and New Zealand have created the largest-ever database of protein expression changes associated with Alzheimer's disease, according to a study published today (February 4) in *Communications Biology*. The data, which are freely available to researchers online, reveal new insights into the brain areas affected by Alzheimer's, as well as the molecular pathways leading to the disease.

"This database provides a huge opportunity for dementia researchers around the world to progress and to follow-up new areas of biology and develop new treatments," study coauthor Richard Unwin of the University of Manchester says in a statement. "It's very exciting to be able to make these data public so scientists can access and use this vital information."

The team analyzed the expression data of more than 5,500 proteins spanning six brain regions in postmortem tissue of nine healthy and nine Alzheimer's-affected patients. The results provide a map of changes associated with the disease, identifying certain areas of the brain as more affected than others.

Heavily affected areas include the hippocampus, the entorhinal cortex, and the cingulate gyrus, the analysis showed. The researchers

also found that the cerebellum, an area of the brain thought to be less damaged by Alzheimer's disease, showed substantial changes in protein expression, but that these changes qualitatively differed from those in other regions.

"That the changes in [the cerebellum] are different from those seen elsewhere in the brain raises the possibility that, rather than being 'spared', the [cerebellum] is affected in a different way to other brain regions and that, given it shows little pathology, these changes may reflect some level of active protection," the authors write in their paper.

Rosa Sancho, who was not involved in the study but works as head of research at Alzheimer's Research UK, the study's funder, notes in the statement that "making this information freely available online will help researchers to navigate the complex and changing environment of the brain in Alzheimer's and identify processes that could be targeted by future drugs."

http://bit.ly/2GeseEC

Why Alexander the Great May Have Been Declared Dead Prematurely (It's Pretty Gruesome)

Alexander the Great may have been killed by Guillain-Barré syndrome, a rare neurological condition in which a person's own immune system attacks them, says one medical researchers.

By Owen Jarus, Live Science Contributor

The condition may have led to a mistaken declaration of the king's death and may explain the mysterious phenomenon in which his body didn't decay for seven days after his "death."

Alexander the Great was king of Macedonia between 336 and 323 B.C. During that time, he conquered an empire that stretched from the Balkans to modern-day Pakistan. In June 323, he was living in Babylon when, after a brief illness that caused fever and paralysis, he died at age 32. His senior generals then fought each other to see who would succeed him.

According to accounts left by ancient historians, after a night of drinking, the king experienced a fever and gradually became less and less able to move until he could no longer speak. One account, told by Quintus Curtius Rufus, who lived during the first century A.D., claims that Alexander the Great's body didn't decay for more than seven days after he was declared dead, and the embalmers were hesitant to work on his body.

Ancient historians reported that many people believed that Alexander the Great was poisoned, possibly by someone working for Antipater, a senior official of Alexander's who was supposedly quarreling with the king. In 2014, a research team found that the medicinal plant white hellebore (*Veratrum album)* could have been used to poison Alexander.

Guillain-Barré syndrome

Based on the symptoms recorded by ancient historians, Katherine Hall, a senior lecturer in the Department of General Practice and Rural Health at the University of Otago in New Zealand, believes that it's possible that Alexander actually died of Guillain-Barré syndrome. The condition, Hall said, may have left Alexander in a deep coma that may have led doctors to declare, mistakenly, that he was dead, something that would explain why his corpse supposedly didn't decompose quickly, noted Hall in her paper published recently in the journal Ancient History Bulletin.

The syndrome "is an autoimmune disorder where the patient's own immune system has become confused in differentiating between an invading organism, such as a bacteria, virus, or (very rarely) vaccine products, and the patient's own body," Hall wrote in her paper.

While globally it occurs in, at most, one out of every 25,000 people per year, the incidence rate is higher in modern-day Iraq, particularly during spring and summer, Hall wrote in her paper, noting that Babylon is in modern-day Iraq and that Alexander died in June.

There are several more clues that point to Guillain-Barré syndrome in Alexander's death, Hall wrote. "The most striking feature of Alexander the Great's death is that, despite being extremely unwell, he was reported to have remained compos mentis [sane] until just before his death," she wrote, noting that this is something seen in people suffering from Guillain-Barré . The gradual paralysis that Alexander supposedly experienced is also seen in patients with that syndrome.

Reactions

Live Science talked to several scientists not involved with the research who discussed their thoughts on Hall's claim.

It's "an interesting idea" that Alexander was killed by Guillain-Barré syndrome said Hugh Willison, a professor at the University of Glasgow College of Medical, Veterinary and Life Sciences, Institute of Infection, Immunity and Inflammation. "Although from the historical evidence available, it is not possible to establish this with any degree of certainty," he added.

Another professor, Michael Baker, said: "Based on a quick scan [of the article] I think the theory is quite plausible," Baker, a professor in the Department of Public Health at the University of Otago, told Live Science. To say anything more definitive, Baker said he'd need more time to review the paper.

The theory is "very interesting," said Pat Wheatley, a professor of classics at the University of Otago. Hall took some of Wheatley's classes, and the two have been discussing the theory for about a year, Wheatley said. However, Wheatley urged caution when looking at the accounts left by ancient historians, noting that the surviving accounts date to well over a century after Alexander's death, and some of the details may be inaccurate. Still, the "the theory is certainly worth floating," Wheatley said.

http://bit.ly/2UMnNEy

Specific Gut Microbes Linked with Depression: Study

The research is among the first to find the connection in humans.

Ashley Yeager

Two types of bacteria, *Coprococcus* and *Dialister*, are depleted in people with depression, researchers report today (February 4) in *Nature Microbiology*. The study also found that many gut bacteria can produce compounds that act on the nervous system. If confirmed, the results could lead to a deeper understanding of the gut-brain connection, and possibly open avenues to new treatments for mental illness.

“This is the first time this kind of work has been done in such a large scale in humans. Most previous work has been done in animal models,” study coauthor Jeroen Raes, a systems biologist at The Flanders Institute of Biotechnology, tells *Forbes*. Because most previous studies on a possible connection between gut microbial metabolism and mental health had been done in animals, the relationship has been controversial.

To find out whether the link applies to humans, Raes and his colleagues analyzed the microbiomes of 1,054 people enrolled in a study known as the Flemish Gut Flora project, as well as self-reported and physician-diagnosed depression data on the same subjects. The results revealed several types of bacteria that are negatively or positively correlated with mental health, with *Coprococcus* and *Dialister* among those that were more common in people without depression. An analysis of fecal metagenome data also showed that better mental health was associated with the gut microbiome’s ability to produce a metabolite of the human neurotransmitter dopamine called DOPAC.

John Cryan, a neuroscientist at University College Cork in Ireland who was not involved in the study, tells *Science* that the work is “the real first stab” at determining how a microbe’s metabolites influence

mood, and that it pushes the field forward. Still, Raes is cautious, noting in *Forbes* that "we don't yet know whether these neuroactive compounds produced in the gut can reach the brain. Can they traverse the blood-brain-barrier? Or perhaps they act directly on the vagus nerve in the stomach, which sends signals directly to the brain."

Adding to the complexity is the fact that not all human gut microbes have been identified yet. Today in *Nature Biotechnology*, for example, a separate group of researchers announced they had grown bacterial strains from 20 fecal samples from people in the UK and the US. DNA sequencing revealed more than 100 strains that had never been isolated before. "This study has led to the creation of the largest and most comprehensive public database of human health-associated intestinal bacteria," study coauthor Samuel Forster of the Wellcome Sanger Institute and Hudson Institute of Medical Research says in a statement. "The gut microbiome plays a major role in health and disease. This important resource will fundamentally change the way researchers study the microbiome."

http://bit.ly/2GbI0Ah

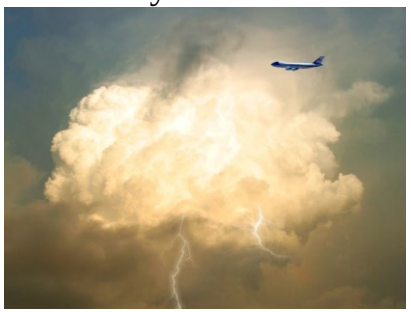
Study: Airplanes Flying Over Rain, Snow Can Intensify Precipitation by 10-Fold

Planes landing in or departing from an airport could locally increase precipitation rate by 6-14 times

By analyzing several years of weather radar observations in Finland, a research team led by University of Helsinki scientists has discovered that planes landing in or departing from an airport could locally increase precipitation rate by 6-14 times. The observations show that falling ice crystals from upper clouds could seed lower clouds and therefore increase rain or snowfall intensity through the process called snowflake aggregation; during this process bigger faster falling particles are formed by ice particles colliding and sticking together.

"The interesting thing about this feature is that it is caused by aircraft, but it is not caused by pollution," said study lead author Dr. Dimitri Moisseev, a researcher at the University of Helsinki and the Finnish Meteorological Institute.

"Even if there would be absolutely ecological airplanes, which don't have any combustion, no fuel or anything, it would still happen."



Airplanes wring extra snow and rain out of clouds. **Michael Bryant-Mode.**

Both water droplets and ice crystals form clouds. Pure water can stay liquid down to minus 40 degrees Fahrenheit (minus 40 degrees Celsius) without dust particles or other suitable surfaces present to seed crystallization into ice. So water droplets that condense into clouds can be much colder than the typical freezing point of 32 degrees Fahrenheit (0 degrees Celsius). Such supercooled liquid clouds are common in low- to mid-level cloud layers.

Air pressure changes from passing aircraft can trigger these supercooled water droplets to freeze into ice crystals. Air expands abruptly in the wake of wing and propeller tips, causing a dramatic local drop in pressure and temperature.

Inside a cloud of water droplets that is already supercooled between 5 and minus 4 degrees Fahrenheit (minus 15 and minus 20 degrees Celsius), the passing aircraft can drop the temperature below minus 40 degrees Fahrenheit and instigate the formation of ice crystals.

The new ice crystals help freeze more supercool water droplets, setting off a chain reaction of crystal formation in a widening circle around the path of the aircraft.

When the crystals fall, they create holes or streaks of clear air in the cloud, sometimes opening a window of blue sky if the cloud layer is thin. In most cases, the ice crystals evaporate before they reach the ground.

Meteorologists have known that passing aircraft can freeze water droplets into ice crystals and previous work had suggested that the process could enhance rain and snow in underlying clouds, but the effect had not been captured in detail.

In the new study, Dr. Moisseev and his co-authors from the Finnish Meteorological Institute, Vaisala Oyj, the Universities of Reading and Helsinki reviewed 11 years of dual-polarization weather radar observations in the Helsinki region and found 17 days with repeat cases of the characteristic linear streamers between December 2008 and January 2018.

The researchers examined flightpaths near the Helsinki-Vantaa airport to see whether the streamers could be caused by passing aircraft.

Flightpaths archived to 2011 confirmed aircraft passed within 1-6 miles (2-10 km) of the intense precipitation streamers in most of the cases observed.

“The intensified precipitation basically follows the track of an airplane above the cloud,” Dr. Moisseev said.

“It could extend over hundreds of miles, but the cross-section would be maybe 328 feet (100 m). So it’s a very narrow, long feature.”

The additional ice crystals raise the rate at which crystals collide to form larger snowflakes, intensifying snowfall.

This could happen if an airplane flies directly through a precipitating cloud, but the scientists suspect something more complicated is going on, because their data locates the starting height of rain and snow enhancement far above the layer that is already precipitating.

“The airplane-generated ice crystals most likely fall from a supercooled upper cloud layer into a lower layer that is actively raining or snowing, begetting more rain or snow from the lower cloud layer,” they said.

The study is published in the *Journal of Geophysical Research: Atmospheres*.

http://bit.ly/2BzlPjN

Ovarian cysts should be 'watched' rather than removed

Women may not need to undergo surgery for non-cancerous ovarian cysts, avoiding potential surgical complications.

This is the finding of new research, by a team of international scientists from institutions including Imperial College London and KU Leuven, published in The Lancet Oncology.

The two-year study followed 1919 women from 10 different countries, including the UK, Belgium, Sweden and Italy, who were diagnosed with non-cancerous ovarian cysts.

Ovarian cysts are fluid-filled sacs that develop on a woman's ovary. They're very common and usually don't cause any symptoms. However, in some cases they can trigger pelvic pain and bloating.

Doctors refer patients with these symptoms for ultrasound scans, where the cysts are classified as benign (non-cancerous), or cancerous tumours. In the event of suspected cancer, the cysts are always removed and analysed.

In the case of cysts that are thought to be benign, women are still often recommended to have the cysts surgically removed. This is because it has been thought that there is a risk of serious complications such as the cyst bursting, or causing the ovaries to twist. There have also been concerns that benign cysts may "turn cancerous" if left in place or that a cyst may have been misclassified at the initial ultrasound scan.

However, an alternative to surgery is so-called 'watchful waiting', where doctors do not remove the cysts, but monitor their size and appearance with regular ultrasound scans. This is because many cysts shrink and disappear or do not change over time.

Opinion is still divided on watchful waiting, with many doctors across the world believing benign cysts should be surgically removed in the majority of cases.

This latest study is the largest to date on the 'watchful waiting' approach, which followed nearly 2,000 women as they were scanned in the years after a benign cyst diagnosis.

Out of the 1919 women in the trial, one in five (20 per cent) had cysts that disappeared of their own accord, and 16 per cent underwent surgery. Overall, in 80 per cent of case either the cyst resolved or did not need intervention. The average age of the women in the study was 48, and the average size of the cyst was 4cm.

Only 12 women were subsequently diagnosed with ovarian cancer, making the risk of cancer 0.4 per cent. However, the researchers caution this may be due to the tumours being initially misdiagnosed as non-cancerous on the initial ultrasound scan, rather than a benign cyst turning cancerous.

The rate of other complications, such as ovarian twisting or cyst rupture was 0.4 per cent and 0.2 per cent respectively.

The research team say these risks must be assessed alongside the risks of surgical removal. The risk of complications, such as bowel perforation, for surgical removal of cysts among women aged 50-74 is between 3 and 15 per cent.

Professor Dirk Timmerman, lead author from KU Leuven explained: "Despite these surgical risks being small, if the women in this age group underwent surgery in our study then we could speculate that 29 to 123 of them could have suffered severe surgical complications. Instead, only 96 of them underwent surgery, which means severe complications may have been avoided in between 29 to 123 women."

Professor Tom Bourne, lead researcher from Imperial College London said this study suggests watchful waiting is suitable for most women when an ovarian cyst is initial classified as being benign: "Our results may lead to a paradigm shift resulting in less surgery for non-cancerous ovarian cysts - on condition that trained ultrasound examiners reliably exclude cancer."

The study was funded by the Research Foundation-Flanders, the Swedish Research Council, The Malmo General Hospital Foundation for fighting against cancer, the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre and the Linbury Trust.

http://bit.ly/2SfKvrS

Five warning signs of overdiagnosis

Being labelled with a serious illness can cause psychological distress.

Alexandra Barratt* **Katy Bell****

We've had it drummed into us over decades that early detection is key to treating diseases early, before they have a chance to turn into something really nasty.

But we've since learnt the flip-side of this is overdiagnosis, where people are diagnosed with diseases that won't harm them. Overdiagnosis is often followed by overtreatment, where procedures or other therapies are offered that won't benefit the patient and may cause harm.

The chance discovery of a small thyroid cancer in someone's neck, for instance, is likely to result in a total thyroidectomy (removal) and lifelong thyroid hormone replacement. But this cancer is very unlikely to have caused harm had it been left alone. And studies have found dramatic increases in thyroid cancer worldwide, without changes in death rates.

Overdiagnosis may also begin with a new, more sensitive test. Such tests can expand the number of people who are classified as "diseased" and send them down a path of additional invasive tests such as biopsies, as well as surgery and medication.

After the introduction of a new test for pulmonary embolism, for instance, more people were diagnosed with these lung blood clots and started on blood thinning drugs. Some suffered complications such as gut and brain haemorrhages. And despite more people being diagnosed and treated for pulmonary embolism, there was no impact on how many people died from them.

But overdiagnosis is difficult to detect. It can take years for the data to be collected to prove there's a problem with the new way of diagnosing a disease, based on the new test, compared to the old way.

To speed up the detection process, we have collated a list of five markers to indicate overdiagnosis may be occurring. The markers, published today in the journal Annals of Internal Medicine, can help researchers, health authorities, clinicians and even patients determine whether new tests are candidates for overdiangosis. Here they are as a set of questions:

1. ***is there potential for more diagnoses with the new test?***
2. ***are more people actually being diagnosed by the new test?***
3. ***do the additional people diagnosed have milder or harmless forms of the disease?***
4. ***are more people being treated?***
5. ***might the harms of being treated outweigh the benefits?***

A better way to detect heart disease? Not quite

When we applied these questions to a new blood test for acute heart disease – highly sensitive cardiac troponin (HS-cTn) – we found we answered yes to most of them.

This new test was evaluated in a large trial in Scotland. The trial found that among patients presenting to hospital with a possible heart attack, the new test (HS-cTn) led to more people being told they had suffered injury to their heart muscle.

It also led to more people being given additional tests, such as coronary angiogram (a type of X-ray imaging), and prescribed anti-platelet (blood-thinning) and other drugs to prevent heart disease. The risks of coronary angiogram are rare but include heart attack, stroke, arrhythmia, infection and bleeding. A major side effect of anti-platelet medication is bleeding.

Surprisingly, the new test didn't mean fewer people died of a heart attack over the following year as was expected, despite the additional people being treated. That possibility, or other more long-term benefits, weren't ruled out by the trial though, so we were unable to answer the last question with confidence.

The new test, HS-cTn, was introduced into Australia in 2010 and is now widely used in Australia, Europe, and the United States. But we still don't know whether using it improves patients' lives.

We can't say for sure whether overdiagnosis is occurring as a result of this new test, but there are enough red flags to identify that it could be a problem. We need to evaluate the new test further.

More scrutiny of new tests needed

While we used the example of HS-cTn, the same reservations and uncertainties apply to the introduction of many new tests.

New tests aren't generally subject to the same standards of proof of benefit as medications, before being allowed (and often promoted) on the market. It's time to change the rules.

Potential harms, as well as benefits, need to be considered before new tests are used in routine clinical practice. At a minimum, processes should be set up to collect and monitor the data needed to answer the five questions.

Regulators should only allow the provisional use of the test in the years immediately after it becomes available; for a limited time period, for instance, or in research contexts.

Further funding would be dependent on proof the test is overall beneficial rather than harmful for patients once both benefits and harms are established.

Without these safeguards, the introduction of new tests will continue to put patients at risk of harm from the very tests and treatments they expect will help them.

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http://bit.ly/2SdEoUV

A new culprit of cognitive decline in Alzheimer's disease

Study finds blood protein destroys memory storage sites in the brain and may lead to new treatments

SAN FRANCISCO, CA- It has long been known that patients with Alzheimer's disease have abnormalities in the vast network of blood vessels in the brain. Some of these alterations may also contribute to age-related cognitive decline in people without dementia. However, the ways in which such vascular pathologies contribute to cognitive dysfunction have largely remained a mystery. Until now, that is.

Scientists at the Gladstone Institutes, led by Senior Investigator Katerina Akassoglou, PhD, showed for the first time that a blood-clotting protein called fibrinogen is responsible for a series of molecular and cellular events that can destroy connections between neurons in the brain and result in cognitive decline.

Akassoglou and her team used state-of-the-art imaging technology to study both mouse brains and human brains from patients with Alzheimer's disease. They also produced the first three-dimensional volume imaging showing that blood-brain barrier leaks occur in Alzheimer's disease.

In their study, published in the scientific journal *Neuron*, the researchers found that fibrinogen, after leaking from the blood into the brain, activates the brain's immune cells and triggers them to destroy important connections between neurons. These connections, called synapses, are critical for neurons to communicate with one another.

Previous studies have shown that elimination of synapses causes memory loss, a common feature in Alzheimer's disease and other dementias. Indeed, the scientists showed that preventing fibrinogen from activating the brain's immune cells protected mouse models of Alzheimer's disease from memory loss.

"We found that blood leaks in the brain can cause elimination of neuronal connections that are important for memory functions," explains Akassoglou, who is also a professor of neurology at UC San Francisco (UCSF). "This could change the way we think about the cause and possible cure of cognitive decline in Alzheimer's disease and other neurological diseases."

The team showed that fibrinogen can have this effect even in brains that lack amyloid plaques, which are the focus of diverse treatment strategies that have failed in large clinical trials. The researchers showed that injecting even extremely small quantities of fibrinogen into a healthy brain caused the same kind of immune cell activation and loss of synapses they saw in Alzheimer's disease.

"Traditionally, the build-up of amyloid plaques in the brain has been seen as the root of memory loss and cognitive decline in Alzheimer's disease," says Mario Merlini, first author of the study and a staff research scientist in Akassoglou's laboratory at Gladstone. "Our work identifies an alternative culprit that could be responsible for the destruction of synapses."

The scientists' data help explain findings from recent human studies in which elderly people with vascular pathology showed similar rates of cognitive decline as age-matched people with amyloid pathology. However, patients with both types of pathology had much worse and more rapid cognitive decline. Other studies also identified vascular pathology as a strong predictor of cognitive decline that can act independently of amyloid pathology.

"Given the human data showing that vascular changes are early and additive to amyloid, a conclusion from those studies is that vascular changes may have to be targeted with separate therapies if we want

to ensure maximum protection against the destruction of neuronal connections that leads to cognitive decline," says Akassoglou.

Interestingly, Akassoglou and her colleagues recently developed an antibody that blocks the interaction between fibrinogen and a molecule on the brain's immune cells. In a previous study, they showed this antibody protected mouse models of Alzheimer's disease from brain inflammation and neuronal damage.

"These exciting findings greatly advance our understanding of the contributions that vascular pathology and brain inflammation make to the progression of Alzheimer's disease," said Lennart Mucke, MD, co-author of the study and director of the Gladstone Institute of Neurological Disease. "The mechanisms our study identified may also be at work in a range of other diseases that combine leaks in the blood-brain barrier with neurological decline, including multiple sclerosis, traumatic brain injury, and chronic traumatic encephalopathy. It has far-reaching therapeutic implications."

About the Study

The paper "Fibrinogen Induces Microglia-Mediated Spine Elimination and Cognitive Impairment in an Alzheimer's Disease Model" was published by the journal Neuron *on February 5, 2019: https://www.cell.com/neuron/fulltext/S0896-6273(19)30015-7.*

Other authors include Victoria A. Rafalski, Pamela E. Rios Coronado, T. Michael Gill, Maya Ellisman, Gayathri Muthukumar, Keshav S. Subramanian, Jae Kyu Ryu, Catriona A. Syme, and Dimitrios Davalos from Gladstone, as well as William W. Seeley from UCSF, and Robert B. Nelson from Lundbeck Research USA.

The work was supported by the National Institute of Neurological Disorders and Stroke, the Swiss National Science Foundation, the Race to Erase MS, the American Heart Association, the Ray and Dagmar Dolby Family Fund, H. Lundbeck A/S, and the Conrad N. Hilton Foundation.

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A taste for fat may have made us human, says study

Long before human ancestors began hunting large mammals for meat, a fatty diet provided them with the nutrition to develop bigger brains, posits a new paper in Current Anthropology.

The paper argues that our early ancestors acquired a taste for fat by eating marrow scavenged from the skeletal remains of large animals that had been killed and eaten by other predators. The argument challenges the widely held view among anthropologists that eating meat was the critical factor in setting the stage for the evolution of humans.

"Our ancestors likely began acquiring a taste for fat 4 million years ago, which explains why we crave it today," says Jessica Thompson, the paper's lead author and an anthropologist at Yale University. "The reservoirs of fat in the long bones of carcasses were a huge calorie package on a calorie-poor landscape. That could have been what gave an ancestral population the advantage it needed to set off the chain of human evolution."

Thompson, who recently joined Yale's faculty, completed the paper while on the faculty at Emory University.

While focusing on fat over meat may seem like a subtle distinction, the difference is significant, Thompson says. The nutrients of meat and fat are different, as are the technologies required to access them. Meat eating is traditionally paired with the manufacture of sharp, flaked-stone tools, while obtaining fat-rich marrow only required smashing bones with a rock, Thompson notes.

The authors review evidence that a craving for marrow could have fueled not just a growing brain size, but the quest to go beyond smashing bones with rocks to make more sophisticated tools and to hunt large animals.

"That's how all technology originated -- taking one thing and using it to alter something else," Thompson says. "That's the origin of the iPhone right there."

Co-authors of the paper include anthropologists Susana Carvalho of Oxford University, Curtis Marean of Arizona State University, and Zeresenay Alemseged of the University of Chicago.

The human brain consumes 20% of the body's energy at rest, or twice that of the brains of other primates, which are almost exclusively

vegetarian. It's a mystery to scientists how our human ancestors met the calorie demands to develop and sustain our larger brains.

A meat-centered paradigm for human evolution hypothesizes that an ape population began more actively hunting and eating small game, which became an evolutionary stepping stone to the human behavior of hunting large animals.

The paper argues that this theory does not make nutritional sense. "The meat of wild animals is lean," Thompson says. "It actually takes more work to metabolize lean protein than you get back."

In fact, eating lean meat without a good source of fat can lead to protein poisoning and acute malnutrition. Early Arctic explorers, who attempted to survive on rabbit meat exclusively, described the condition as "rabbit starvation."

This protein problem, coupled with the energy required for an upright ape with small canines to capture and eat small animals, would seem to rule out eating meat as a pathway to fueling brain growth, Thompson says.

The new paper presents a new hypothesis, going back about 4 million years, to the Pliocene. As the human ancestor began walking primarily on two legs, heavily forested regions of Africa were breaking into mosaics, creating open grasslands.

"Our human ancestors were likely awkward creatures," Thompson says. "They weren't good in trees, like chimpanzees are, but they weren't necessarily all that good on the ground either. So, what did the first upright walking apes in our lineage do to make them so successful? At this stage, there was already a small increase in the size of the brains. How were they feeding that?"

Thompson and her co-authors propose that our early ancestors wielded rocks as they foraged on open grassland. After a predator had finished eating a large mammal, these upright apes explored the leftovers by smashing them and discovered the marrow hidden in the limb bones.

"The bones sealed up the marrow like a Tupperware container, preventing bacterial growth," Thompson says. And the only things that could crack open these containers, she adds, were the bone-cracking jaws of hyenas or a clever ape wielding a rock.

The hypothesis offers an explanation for how the human ancestor may have garnered the extra calories needed to foster a larger brain, long before there is evidence for controlled fire, which could have mitigated the problem of bacteria in rotting, scavenged meat. The fat hypothesis also predates by more than 1 million years most evidence for even basic toolmaking of simple stone flakes.

Scientists ought to begin looking for evidence of bone-smashing behavior in early human ancestors, Thompson said.

"Paleoanthropologists are looking for mostly complete bones, and then concentrating on identifying the animal that died," Thompson says. "But instead of just wondering about the bone's creature of origin, we should be asking, 'What broke this bone?' We need to start collecting tiny pieces of shattered bone to help piece together this kind of behavioral information."

http://bit.ly/2WIyJEZ

When did kangaroos start to hop?

Scientists have long wondered when the kangaroo's distinctive leap first appeared.

By Alex Fox Feb. 5, 2019 , 7:01 PM

But ancient kangaroo skeletons are so rare that the hop's origin has remained a mystery. Now, newly discovered 20-million-year-old fossils reveal kangaroo ancestors got their hop on some 10 million years earlier than previously thought.

Before ancient kangaroos started to hop, they got by clinging to tree branches and plucking fruit from the canopies of a lusher, wetter Australia. Hopping is thought to have emerged as this possumlike ancestor transitioned to life on the ground some 10 million years ago, after a dramatic climatic shift dried out the land down under.

Researchers reasoned that the simultaneous expansion of grasslands and deserts drove the evolution of the hop—an efficient way to quickly cover the long distances from food source to food source.

But when one of the study authors was sifting through a pile of fossil fragments recovered from northwest Queensland in Australia, he discovered one of the world's oldest kangaroo fossils. To find out how this ancient kangaroo moved, he and colleagues analyzed the shape and size of fossilized toe and ankle bones. They then used that information to estimate the creature's range of motion. When the scientists compared it to those of living kangaroos, some of which also climb, they found similarities to modern species adapted for both hopping and climbing.

This extinct animal, not yet named, could move in a variety of ways, including hopping, climbing, and walking, researchers report today in *Royal Society Open Science*. These results push back the origin of hopping to at least 20 million years ago—and suggest the climatic changes that reshaped the Australian landscape 10 million years later may have simply provided ideal conditions for hoppers to prosper.

http://bit.ly/2MZUETI

Marijuana smoking linked with higher sperm concentrations

Men who have smoked marijuana at some point had significantly higher concentrations of sperm when compared with men who have never smoked marijuana

Men who have smoked marijuana at some point in their life had significantly higher concentrations of sperm when compared with men who have never smoked marijuana, according to new research led by Harvard T.H. Chan School of Public Health. The study, conducted in the Fertility Clinic at Massachusetts General Hospital, also found that there was no significant difference in sperm concentrations between current and former marijuana smokers.

"These unexpected findings highlight how little we know about the reproductive health effects of marijuana, and in fact of the health effects of marijuana in general," said Jorge Chavarro, associate professor of nutrition and epidemiology at Harvard Chan School. "Our results need to be interpreted with caution and they highlight the need to further study the health effects of marijuana use."

The study will be published on February 5, 2019 in Human Reproduction.

It is estimated that 16.5% of adults in the U.S. use marijuana, and support for legal recreational use of marijuana has increased dramatically in recent years. Understanding the health effects associated with marijuana use is important given the growing perception that it poses few health hazards.

The researchers hypothesized that marijuana smoking would be associated with worse semen quality. Previous studies on marijuana have suggested that it is associated with negative effects on male reproductive health, but most of those studies had focused on animal models or on men with histories of drug abuse.

For this study, researchers collected 1,143 semen samples from 662 men between 2000 and 2017. On average, the men were 36 years old, and most were white and college educated. Additionally, 317 of the participants provided blood samples that were analyzed for reproductive hormones. To gather information on marijuana use among study participants, researchers used a self-reported questionnaire that asked the men a number of questions about their usage, including if they had ever smoked more than two joints or the equivalent amount of marijuana in their life and if they were current marijuana smokers.

Among the participants, 365, or 55%, reported having smoked marijuana at some point. Of those, 44% said they were past marijuana smokers and 11% classified themselves as current smokers.

Analysis of the semen samples showed that men who had smoked marijuana had average sperm concentrations of 62.7 million sperm per milliliter of ejaculate while men who had never smoked marijuana had average concentrations of 45.4 million sperm per milliliter of ejaculate. Only 5% of marijuana smokers had sperm concentrations below 15 million/mL (the World Health Organization's threshold for "normal" levels) compared with 12% of men who had never smoked marijuana.

The study also found that among marijuana smokers, greater use was associated with higher serum testosterone levels.

The researchers cautioned that there are several potential limitations to the findings, including that participants may have underreported marijuana use given its status as an illegal drug for most of the study period.

The researchers emphasized that they do not know to what extent these findings may apply to men in the general population as the study population consisted of subfertile men in couples seeking treatment at a fertility center. Additionally, they noted that there are few similar studies to compare their results against.

"Our findings were contrary to what we initially hypothesized. However, they are consistent with two different interpretations, the first being that low levels of marijuana use could benefit sperm production because of its effect on the endocannabinoid system, which is known to play a role in fertility, but those benefits are lost with higher levels of marijuana consumption," said Feiby Nassan, lead author of the study and a postdoctoral research fellow at Harvard Chan School. "An equally plausible interpretation is that our findings could reflect the fact that men with higher testosterone levels are more likely to engage in risk-seeking behaviors, including smoking marijuana."

Other Harvard Chan School study authors included Mariel Arvizu, Lidia Mínguez-Alarcón, Paige Williams, and Russ Hauser.

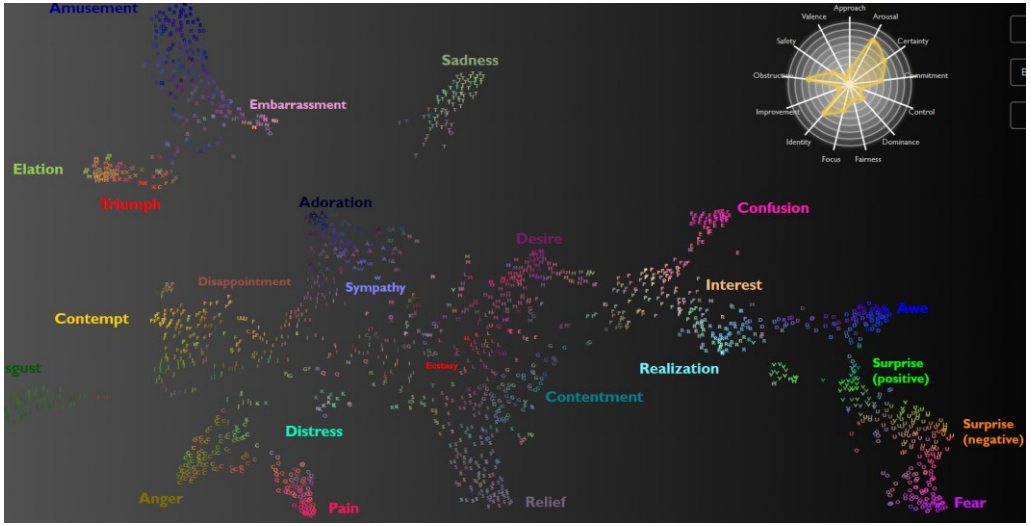
http://bit.ly/2THAhNw

Gasp! First audio map of oohs, aahs and uh-ohs spans 24 emotions

Those spontaneous nonverbal exclamations we make speak volumes

Ooh, surprise! Those spontaneous sounds we make to express everything from elation (woohoo) to embarrassment (oops) say a lot more about what we're feeling than previously understood, according to new research from the University of California, Berkeley.

Proving that a sigh is not just a sigh, UC Berkeley scientists conducted a statistical analysis of listener responses to more than 2,000 nonverbal exclamations known as "vocal bursts" and found they convey at least 24 kinds of emotion. Previous studies of vocal bursts set the number of recognizable emotions closer to 13.



Audio map of vocal bursts across 24 emotions. To visit the online map and hear the sounds, go to https://s3-us-west-1.amazonaws.com/vocs/map.html# and move the cursor across the map.... view more **Courtesy of Alan Cowen**

The results, recently published online in the American Psychologist journal, are demonstrated in vivid sound and color on the first-ever interactive audio map of nonverbal vocal communication.

"This study is the most extensive demonstration of our rich emotional vocal repertoire, involving brief signals of upwards of two dozen emotions as intriguing as awe, adoration, interest, sympathy and embarrassment," said study senior author Dacher Keltner, a psychology professor at UC Berkeley and faculty director of the Greater Good Science Center, which helped support the research.

For millions of years, humans have used wordless vocalizations to communicate feelings that can be decoded in a matter of seconds, as this latest study demonstrates.

"Our findings show that the voice is a much more powerful tool for expressing emotion than previously assumed," said study lead author Alan Cowen, a Ph.D. student in psychology at UC Berkeley.

On Cowen's audio map, one can slide one's cursor across the emotional topography and hover over fear (scream), then surprise (gasp), then awe (woah), realization (ohhh), interest (ah?) and finally confusion (huh?).

Among other applications, the map can be used to help teach voice-controlled digital assistants and other robotic devices to better recognize human emotions based on the sounds we make, he said.

As for clinical uses, the map could theoretically guide medical professionals and researchers working with people with dementia, autism and other emotional processing disorders to zero in on specific emotion-related deficits.

"It lays out the different vocal emotions that someone with a disorder might have difficulty understanding," Cowen said. "For example, you might want to sample the sounds to see if the patient is recognizing nuanced differences between, say, awe and confusion."

Though limited to U.S. responses, the study suggests humans are so keenly attuned to nonverbal signals - such as the bonding "coos" between parents and infants - that we can pick up on the subtle differences between surprise and alarm, or an amused laugh versus an embarrassed laugh.

For example, by placing the cursor in the embarrassment region of the map, you might find a vocalization that is recognized as a mix of amusement, embarrassment and positive surprise.

A tour through amusement reveals the rich vocabulary of laughter and a spin through the sounds of adoration, sympathy, ecstasy and desire may tell you more about romantic life than you might expect," said Keltner.

Researchers recorded more than 2,000 vocal bursts from 56 male and female professional actors and non-actors from the United States, India, Kenya and Singapore by asking them to respond to emotionally evocative scenarios.

Next, more than 1,000 adults recruited via Amazon's Mechanical Turk online marketplace listened to the vocal bursts and evaluated them based on the emotions and meaning they conveyed and whether the tone was positive or negative, among several other characteristics.

A statistical analysis of their responses found that the vocal bursts fit into at least two dozen distinct categories including amusement, anger, awe, confusion, contempt, contentment, desire, disappointment, disgust, distress, ecstasy, elation, embarrassment, fear, interest, pain, realization, relief, sadness, surprise (positive) surprise (negative), sympathy and triumph.

For the second part of the study, researchers sought to present real-world contexts for the vocal bursts. They did this by sampling YouTube video clips that would evoke the 24 emotions established in the first part of the study, such as babies falling, puppies being hugged and spellbinding magic tricks.

This time, 88 adults of all ages judged the vocal bursts extracted from YouTube videos. Again, the researchers were able to categorize their

responses into 24 shades of emotion. The full set of data were then organized into a semantic space onto an interactive map.

"These results show that emotional expressions color our social interactions with spirited declarations of our inner feelings that are difficult to fake, and that our friends, co-workers, and loved ones rely on to decipher our true commitments," Cowen said.

In addition to Cowen and Keltner, co-authors of the study are Hillary Anger Elfenbein at Washington University in Missouri and Petri Laukka at Stockholm University in Sweden.

https://nyti.ms/2UT7DJA

Before Global Warming, Humans Caused Global Cooling, Study Finds

The huge number of deaths of native populations in the Americas after colonization is believed by some researchers to have contributed to the "Little Ice Age"

By Niraj Chokshi

When they arrived in the Americas centuries ago, European colonists brought pestilence and death. Their arrival was so devastating, in fact, that it may have contributed to a period of global cooling, according to a new study.

The research, to be published in the March issue of the journal Quaternary Science Reviews, represents an ambitious attempt to show that, through a series of events, human activity was affecting the climate long before the industrial revolution and global warming.

The authors found that disease and war wiped out 90 percent of the indigenous population in the Americas, or about 55 million people. The earth, they argue, then reclaimed the land that these populations left behind. The new vegetation pulled heat-trapping carbon dioxide from the atmosphere and into the land, contributing to what scientists refer to as the "Little Ice Age."

"It was a drastic change in the earth's system," said Alexander Koch, the study's lead author and a Ph.D. candidate at the University College London Department of Geography.

The study stemmed from Mr. Koch's decision about three years ago to wade into a debate in geological science over how to define the start of the Anthropocene, the name for Earth's most recent, human-dominated time period.

At the time, Mr. Koch was beginning his graduate studies and came across research that had linked a dip in atmospheric carbon dioxide centuries ago to carbon sequestered in the land. If colonization had spurred that dip, as others had hypothesized, then that period would be a good candidate for when the Anthropocene should begin.

"I thought that sounds like quite an interesting topic to research," he said. "It's quite interdisciplinary."

In the end, Mr. Koch and his colleagues pulled from a wide range of disciplines for the study, synthesizing the latest credible estimates on population, land use, mortality and the carbon uptake of plants and trees throughout the Americas.

What on Earth Is Going On?

Sign up for our weekly newsletter to get our latest stories and insights about climate change — along with answers to your questions and tips on how to help.

Based on 119 regional estimates, the authors concluded that 60.5 million people lived in North and South America before Christopher Columbus arrived in the Bahamas in 1492. By 1600, though, that population had been decimated.

At the same time, carbon stored on land increased and carbon dioxide in the air decreased, supporting the hypothesis that colonization may have been to blame.

The approach is imperfect, but several scientists who study past climates, known as paleoclimatologists, said the study was a careful and compelling review of the literature.

"It's hard to piece together what the world was like," said Bianca Perren, a paleoclimatologist for the British Antarctic Survey. "This

adds just another puzzle piece to figuring out the complexity of this whole period."

But the research isn't without critics.

Robert Rohde, the lead scientist for the independent climate research group Berkeley Earth, said that while the authors clearly took care to assemble the estimates, the study, and some media coverage of it, overstated the role colonization played in the Little Ice Age.

"At best, it explains a portion of part of the Little Ice Age," he said.

The Little Ice Age was centuries in the making and, he said, other factors like weak solar activity and increased volcanic activity were more likely culprits. (There is disagreement over when the Little Ice Age began and ended, though some say it lasted from about A.D. 1400 to 1900.)

Mr. Koch and his colleagues acknowledged those other factors, which they say accounted for about half of the decrease in atmospheric carbon dioxide. But the other half, they argued, could be accounted for only by a large increase in vegetation caused by the effects of colonization.

In the end, they found that the deaths caused by colonization led to a drop of about 3.5 parts per million of carbon dioxide in the atmosphere.

That finding can be instructive, Ms. Perren said. It not only reinforces that human activity can affect the climate, but it also shows that there are natural ways to address the modern global warming problem.

"We're always searching for these great technologies that will do it on a megascale, but the most efficient way you can pull CO_2 out of the atmosphere is with trees," she said.

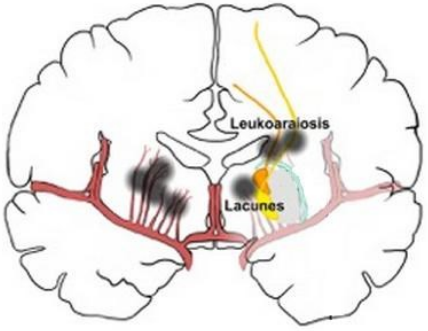
Still, the effect that the authors describe pales compared to the toll modern humanity has taken — in the opposite direction.

While the cascading effects of colonization reduced atmospheric carbon dioxide by about 3.5 parts per million over more than a century, atmospheric carbon dioxide today is increasing at a rate of about 2.3 parts per million each year, warming the earth.

http://bit.ly/2WOhLFf

Absentmindedness points to earlier warning signs of silent strokes among people at risk

Adults who notice that they frequently lose their train of thought or often become sidetracked may in fact be displaying earlier symptoms of cerebral small vessel disease, otherwise known as a 'silent stroke,' suggests a Baycrest study



A diagram of a brain with cerebral small vessel disease, otherwise known as silent stroke. **Provided by Baycrest's Rotman Research Institute**

Adults who notice that they frequently lose their train of thought or often become sidetracked may in fact be displaying earlier symptoms of cerebral small vessel disease, otherwise known as a "silent stroke," suggests a recent study.

Researchers uncovered that individuals with damage to the brain's white matter, caused by silent strokes, reported poor attentiveness and being distracted more frequently on day-to-day tasks, according to a recently published paper in the journal Neurobiology of Aging. Despite these complaints, about half of the people with identified white matter damage scored within the normal range on formal laboratory assessments of attention and executive function (a person's ability to plan, stay organized and maintain focus on overall goals).

"Our results indicate that in many cases of people who were at a higher risk of silent stroke and had one, they saw a notable difference in their ability to stay focused, even before symptoms became detectable through a neuropsychological test," says Ayan Dey, lead

author on the paper and a graduate student at Baycrest's Rotman Research Institute (RRI) and the University of Toronto. "If a person feels this may be the case, concerns should be brought to a doctor, especially if the person has a health condition or lifestyle that puts them at a higher risk of stroke or heart disease."

Cerebral small vessel disease is one of the most common neurological disorders of aging. This type of stroke and changes in the brain's blood flow (vascular changes) are connected to the development of vascular dementia and a higher risk of Alzheimer's disease and other dementias.

The strokes are "silent" since they don't cause lasting major changes seen with an overt stroke, such as affecting a person's ability to speak or paralysis. Despite a lack of obvious symptoms, cerebral small vessel disease causes damage to the brain's white matter (responsible for communication among regions), which can cause memory and cognitive issues over time.

Typically, this type of stroke is uncovered incidentally through MRI scans or once the brain damage has worsened, says Dey.

"There are no effective treatments for Alzheimer's disease, but brain vascular changes can be prevented or reduced through smoking cessation, exercise, diet and stress management, as well as keeping one's blood pressure, diabetes and cholesterol under control," says Dr. Brian Levine, senior author on the paper, RRI senior scientist and professor of Psychology and Neurology at the University of Toronto. "With the right diagnosis, these interventions and lifestyle changes give older adults who are at risk for cognitive decline some options for maintaining brain health."

The study looked at results from 54 adults (between the ages of 55 to 80), who also possessed at least one risk factor for a stroke, such as high blood pressure, high cholesterol, diabetes, sleep apnea, a history of smoking, past mini strokes and advanced age above 75.

Research participants had their brains scanned by MRI and scientists analyzed brain tissue damage, specifically in relation to white matter, to determine injuries caused by cerebral small vessel disease. They also took part in a number of neurocognitive tests and questionnaires that assessed their attention and executive function.

Following up on this study, researchers will analyze functional brain imaging and electrical brain activity from participants to look at the differences in brain networks. They hope to uncover why some people are still able to perform well on cognitive assessments, despite damage to the brain.

"The question that remains is whether overcoming these changes in the brain is a natural ability some people have or if this is something that can be built up over time," says Dey. "If it's something that can be developed, is it something we can train?"

Support for this study was provided by the Canadian Institutes for Health Research and the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery.

http://bit.ly/2GAW2ek

Plastics are being glued together in the ocean

Glue-like substances secreted by bacteria are sticking tiny particles of plastic together in the ocean to form larger masses.

As part of the NERC-funded RealRiskNano project, scientists from Heriot-Watt University used natural waters, collected from the Fore-Shetland Channel and the Firth of Forth, to perform experiments in an attempt to understand the behaviour of nano and microplastics in the marine environment. They found that these tiny particles joined with bacteria, algae and other organic particles within minutes.

Scientists believe this could lead to larger items being mistaken for food by marine mammals. They also fear this could alter the flow of food from the surface to the seafloor, potentially leading to deep sea creatures being starved.

Team member Dr Stephen Summers said:

"This is a first step towards understanding how nanoplastics interact with natural biopolymers throughout the world's oceans. This is very important, as it is at this small scale that much of the world's biogeochemistry occurs.

"We found that the biopolymers envelope or engulf the nanoplastic particles, which caused the plastics to agglomerate into clumps. The nanoplastics, which are 100-200 times smaller than a bacterial cell, were actually incorporated into the agglomerates, which became visible to the naked eye in our lab experiments."

Dr Tony Gutierrez from Heriot-Watt University, who led the study, said:

"The agglomerates form in something similar to marine snow, the shower of organic detritus that carries carbon and nutrients from the surface to the ocean floor and feeds deep-sea ecosystems.

"It will be interesting to understand if nano- and micro-scale plastics of different densities could affect the food flux from the upper to lower reaches of the ocean.

Heavier plastics could drive marine snow to fall at a faster rate to the sea floor, while the opposite could happen with lighter forms of plastics in making it more buoyant and to fall more slowly. In that case, deep-sea ecosystems could become starved of food."

Professor Ted Henry, also from Heriot-Watt University and leader of the NERC RealRiskNano project, said:

"The discovery and characterisation of nano and microplastic agglomerates increases our understanding of how these particles behave within the environment and how they interact with marine organisms. The agglomerates are much more complex than simple pieces of plastic.

"Research like this is beginning to fill the gaps in scientists' knowledge, but we need more evidence in order to prioritise and manage plastic pollution effectively."

http://bit.ly/2I5AN6G

Dying bacteria absorb antibiotic, allowing others to survive and grow

Dying cells absorb large amounts of antibiotic, allowing their neighbors to survive and continue growing

by Molly Sharlach, Princeton University

Bacteria have multiple strategies to survive antibiotics: developing genetic resistance to the drugs; delaying their growth; or hiding in protective biofilms. New results from researchers at Princeton and California State University-Northridge (CSUN) have shed light on yet another approach: self-sacrifice.

In a population of E. coli bacteria treated with a particular antimicrobial molecule, the researchers found, some dying cells absorbed large amounts of the antibiotic, allowing their neighbors to survive and continue growing. The researchers created a modified, green fluorescent version of the antibiotic of interest, a peptide molecule known as LL37 that is naturally produced by human skin, airways and other organs that frequently contact bacteria from the outside world. Tracking the glowing molecule's movements through a population of bacteria, as shown in the figure above, revealed that the antibiotic was accumulating in a subset of dying cells.

Andrej Košmrlj, an assistant professor of mechanical and aerospace engineering at Princeton, collaborated with the CSUN team to develop a mathematical model to more fully explain the phenomenon and aid further investigations.

The model describes the dynamics of bacterial populations facing different concentrations of the antimicrobial, showing how dead cells sequester the dangerous molecule and predicting the delayed growth of surviving cells—calculations borne out by experiments in the laboratory of Sattar Taheri-Araghi, an assistant professor of physics at CSUN and co-senior author of the study along with Košmrlj.

"The model provided a physical explanation for how this actually works," said Košmrlj. "We had a surprising observation that the critical inhibitory concentration of antimicrobial peptides depends on the number of bacteria, and our model was able to explain why this happens."

Despite this new understanding, questions remain about what is happening at the molecular level, said Taheri-Araghi. "This research opens the doors to a lot of questions that were never asked before. Our findings have profound implications for the evolution of bacteria—which have been around for billions of years—as well as in medicine for the design and administration of novel antibiotics."

The researchers reported their results in a paper published Dec. 18, 2018, in *eLife*.

More information: *Mehdi Snoussi et al. Heterogeneous absorption of antimicrobial peptide LL37 in Escherichia coli cells enhances population survivability, eLife (2018). DOI: 10.7554/eLife.38174*

https://wb.md/2UTUIah

Works in Mice, but Then? Publish Clinical Trial Data Alongside

Sacrifice patients make taking part in clinical trials should be honored by publication of all trial results

Liam Davenport

The sacrifice patients make to take part in clinical trials should be honored by publication of all trial results, whether they are positive or negative, say experts in an essay published online in the *Annals of Oncology* on January 31.

Particularly in the field of oncology, promising results from preclinical studies — for example, in mouse models of disease — raise hopes for a "cure for cancer," only for these hopes to be crushed all too often once the therapy is tested in humans. But the link between the early promise in mice and failure in humans is often not clearly recorded, and the concepts are "lost in translation," the authors suggest.

Of greatest benefit to the oncology field and to patients would be to publish all clinical trials, however they turn out, alongside the original preclinical data, they continue.

Ideally, the clinical results should be published in the same journal that published the preclinical research in an "online-only" format beneath the original article, they add.

"A direct benefit for the journal is another citation that adds to their impact factor," they comment. They note that a successful clinical trial "could give credit to the basic science."

Saving Money, Resources, and Lives

In their essay, Vivek Subbiah, MD, Department of Investigational Cancer Therapeutics, the University of Texas MD Anderson Cancer, Center, Houston, and colleagues highlight how a huge proportion of the results of clinical trials never see the light of day, particularly if those results are negative.

Publishing clinical trial results alongside the corresponding preclinical data would save money, resources, and lives and would benefit scientific endeavor, say the authors.

"Clinical investigators would be rewarded for their work and not the result of their study," the authors write. "Basic scientists would be able to see their ideas put into practice.

"Most important, this would ensure transparency in the scientific process.... Patients, dollars, and resources can be saved and diverted to other trials."

As to whether journals would follow this suggestion, Subbiah told *Medscape Medical News* that publishing clinical and preclinical data together would be "feasible, as almost all journals are online."

Although he feels that colleagues involved in drug development as well as investigators conducting first-in-human clinical trials would

agree to the proposal, he did wonder whether journals would take this seriously and make it happen.

"I am not sure. But we need to raise awareness so that journals eventually listen," he told *Medscape Medical News*.

"Ultimately, we need the correct information disseminated for the benefit of mankind. The goal should be cures in humans and not in mice," Subbiah added.

Less Than One Fifth of Clinical Trials Published

The authors point out that less than a fifth of clinical trials are published, owing in many cases to either the fact that the results were negative or the investigator thought that the results were not relevant to the field.

Many of these clinical trials — the majority of which are industry driven — follow "promising" preclinical studies, typically in mouse models. Often, however, the preclinical results do not translate into humans.

Indeed, half of all phase 3 clinical trials, many of which are in oncology, do not reach their primary endpoint, despite initial optimism, the authors point out.

In their essay, they give the example of a highly motivated patient they encountered in their clinic who had a gastrointestinal stromal tumor (GIST) that had a *KIT* exon 11 mutation.

This patient had read a preclinical article that showed that, in a mouse model, immunotherapy and imatinib (*Gleevec*, Novartis) were better than imatinib alone in treating GIST. The article suggested that KIT inhibition and immunotherapy have a synergistic effect.

He was "buoyed by immunotherapy news in other tumors" and cited the preclinical article. The patient was enrolled in a clinical trial of ipilimumab (*Yervoy*, Bristol-Myers Squibb) and imatinib, but he experienced rapid disease progression and symptomatic disease progression.

"The patient, spouse and their children were very distraught and raised the question of how valid a mouse model is in relation to human disease," the authors write.

Those preclinical data led to two clinical trials, which together involved 63 patients, and yielded results that were negative overall, they add.

Mark of Honor and Reverance

Even when negative clinical trial results are published, they may be "relegated to a poorly circulated journal," despite the fact that preclinical studies were published in a high-impact journal, Subbiah and colleagues comment.

They remind readers that a great deal of oncology research is funded by taxes and donations, "with the noble goal to end cancer."

They consequently feel that it would be "a mark of honor and reverence to the patients who volunteered for the trial, for the benefit of future patients, and as a part of the continuum in the scientific community" that clinical studies be published alongside the preclinical studies.

Doing so would acknowledge the "mental agony and physical side effects" that patients and their families experience when taking part in clinical trials.

Publishing all clinical trial findings would, they write, "pay it forward," not only by extracting as much data as possible but also by preventing "more patients from needlessly giving of themselves to a futile effort."

Subbiah reports receiving research funding for clinical trials from Novartis, Bayer, GlaxoSmithKline, Nanocarrier, Vegenics, Celgene, Northwest Biotherapeutics, Berghealth, Incyte, Fujifilm, Pharmamar, D3, Pfizer, Multivir, Amgen, Abbvie, Alfasigma, Agensys, Boston Biomedical, Idera Pharma, Inhibrx, Exelixis, Blueprint medicines, Loxo Oncology, Takeda, Roche/Genentech, the National Comprehensive Cancer Network, NCI-CTEP, and the University of Texas MD Anderson Cancer Center. He has also received travel grants from Novartis, Pharmamar, and AstraZeneca/Medimmune. The other authors have disclosed no relevant financial relationships.

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http://bit.ly/2TJuKWC

Earth Once Swallowed Its Own Superocean. Could It Happen Again?

The ancient supercontinent of Rodinia turned inside out as the Earth swallowed its own ocean some 700 million years ago, new research suggests.

By Stephanie Pappas, Live Science Contributor

Rodinia was a supercontinent that preceded the more famous Pangea, which existed between 320 million and 170 million years ago. In a new study, scientists led by Zheng-Xiang Li of Curtin University in Perth, Australia, argue that supercontinents and their superoceans form and break up in alternating cycles that sometimes preserve the ocean crust and sometimes recycle it back into Earth's interior.

Around 320 million years ago, the supercontinent Pangea formed. **Shutterstock**

"We suggest that the Earth's mantle structure only gets completely reorganised every second supercontinent [or every other cycle] through the regeneration of a new superocean and a new ring of fire," Li wrote in an email to Live Science. The "Ring of Fire" is a chain of subduction zones around the Pacific, where the crust of the ocean grinds underneath the continents. Volcanoes and earthquakes are frequent around the Ring of Fire, lending it its name..

Deep history

The history of supercontinents is a bit murky, but geoscientists are increasingly convinced that the continents merge into one giant landmass every 600 million years, on average. First came Nuna, which existed between 1.6 billion and 1.4 billion years ago. Then Nuna broke apart, only to coalesce as Rodinia about 900 million years ago. Rodinia broke up 700 million years ago. Then, around 320 million years ago, Pangea formed.

There are patterns in the circulation of the mantle (the layer beneath Earth's crust) that seem to match nicely with this 600 million-year cycle, Li said. But some mineral and gold deposits and geochemical signatures in ancient rock reoccur in a longer cycle — one that's closer to a billion years. In a new paper in the April issue of the journal Precambrian Research and just published online, Li and his colleagues argue that the Earth actually has two concurrent cycles running: a 600 million-year-long supercontinent cycle and a billion-year-long superocean cycle. Each supercontinent breaks up and reforms by two alternating methods, the researchers hypothesize.

A rare view of the divide between two continental plates is visible at Thingvellir National Park in Iceland. This chasm divides the Eurasian continent from the North American continent. **Kuznetsov Alexey/Shutterstock**

An alternating pattern?

The two methods are called "introversion" and "extroversion." To understand introversion, imagine a supercontinent surrounded by a single superocean. The continent begins to split into pieces separated by a new, internal ocean. Then, for whatever reason, subduction processes begin in this new, internal ocean. At these fiery spots, oceanic crust dives back into Earth's hot mantle. The internal ocean is chewed back into the planet's interior. The continents come back together again. Voilà — a new supercontinent, surrounded by the same old superocean that was there before.

Extroversion, on the other hand, creates both a new continent and a new superocean. In this case, a supercontinent rifts apart, creating

that internal ocean. But this time, the subduction occurs not in the internal ocean, but in the superocean surrounding the rifting supercontinent. The Earth swallows the superocean, dragging the rifting continental crust clear around the globe. The supercontinent essentially turns inside out: Its former coastlines smash together to form its new middle, and its torn-apart middle is now the coast. Meanwhile, the once-interior ocean is now a brand-new superocean surrounding the new supercontinent.

Li and his colleagues used modeling to argue that over the past 2 billion years, introversion and extroversion have alternated. In this scenario, the supercontinent Nuna broke apart and then formed Rodinia via introversion. Nuna's superocean thus survived to become Rodinia's superocean, which scientists have dubbed Mirovoi. Nuna and Rodinia had similar configurations, Li said, which bolsters the notion that Nuna simply broke apart and then came back together again.

But then, the oceanic crust of Mirovoi began to subduct. Rodinia pulled apart as its superocean disappeared. It slammed back together on the other side of the planet as Pangea. The new ocean that formed as Rodinia rifted, and then it became Pangea's superocean, known as Panthalassa.

Earth's future

Pangea, of course, rifted apart to become the continents we know today. Panthalassa's remnants survive as the Pacific oceanic crust.

The past 2 billion years of history posited in the new research are plausible, said Mark Behn, a geophysicist at Boston College and Woods Hole Oceanographic Institution, who studies Earth's deep history but was not involved in the new research. However, it's hard to know whether the cycles studied represent a true, fundamental pattern.

"You only have three iterations, so you're trying to extrapolate trends out of not very many cycles," Behn said.

If the alternating pattern holds, Li said, the next supercontinent will form by introversion. The internal oceans created by Pangea's rifting — the Atlantic, the Indian and the Southern oceans — will close. The Pacific will expand to become the new continent's single superocean. Scientists call this theoretical future supercontinent Amasia. (At this moment in time, the Pacific is actually shrinking slightly via subduction, but that pattern may or may not continue over hundreds of millions of years.)

Earth's supercontinent future remains unclear. Models that attempt to combine the movements of Earth's continents with the internal dynamics of the mantle could help determine if the introversion/extroversion assembly methods are realistic, Li said. The methods used by Li and his colleagues, which involved studying molecular variation patterns in ancient rocks, are probably on the right track for tackling these fundamental questions of plate tectonics, Behn said.

Ultimately, Behn said, the question comes down to what drives plate tectonics. No one knows what triggers the start of subduction at a particular place and time, he said. There is even debate about when Earth's plates started sashaying around. Some scientists think plate tectonics began soon after Earth formed. Others think it started 3 billion, 2 billion or a billion years ago.

"The data for these things is just coming of age," Behn said, "and we're only now being able to start pulling the pieces together."

http://bit.ly/2BF4plR

"Grandmother Hypothesis" Gets Some Support

New studies suggest forebears' age and physical proximity matter when it comes to their grandkids' survival.

Ashley Yeager

Grandmas often help out a lot with grandkids. That may be why women live long past reproductive age and why menopause, which is rare among animals, evolved—an idea called the "grandmother

hypothesis." Now, two new studies published today (February 7) in *Current Biology* offer some evidence that supports the hypothesis, with some caveats. In some 17th- and 18th-century communities, the studies found, the younger a grandma was and the closer she lived to her grandkids the better chance they had of surviving early childhood. "Grandmother help is central to human families all around the world, but we find that the opportunity and ability to provide help to young grandchildren declines with grandmother age," Virpi Lummaa of the University of Turku in Finland, a coauthor of the one of the studies, says in a statement.

Lummaa and her colleagues studied the records of Finnish churchgoers born from 1731 to 1895, including 5,815 children. If maternal grandmothers living in close proximity to their extended families were 50 to 75 years old, their grandchildren aged 2 to 5 years old had a better chance of survival—a 30 percent boost—than kids with no maternal grandmas. Having a paternal grandmother over age 75 raised the odds of dying before age 2 by 37 percent compared with a child whose paternal grandmother was no longer alive.

"We said it as a joke when we had the idea for this study. 'Oh killer grandmothers, wouldn't that be such a great story?'" Simon Chapman, an evolutionary biologist at the University of Turku in Finland tells *Science News*. "Then we found it."

David Coall, a biological anthropologist at Australia's Edith Cowan University who was not involved in the study, suggests the decreased survival rate for kids with older paternal grandparents was due to conflict between parents having to care for young babies, as well as their own aging parents. "What we are likely seeing here is a historical version of the sandwich generation," he says, referencing the phenomenon of people simultaneously raising children and taking care of their parents.

Having grandmas that lived far away didn't seem to help either, another group of researchers reported in a second study. Using data from Canada's St. Lawrence Valley, which included information on 3,382 maternal grandmothers and 56,767 grandchildren living sometime between 1608 and 1799, the team found that as distance between moms and daughters increased, the daughters had fewer babies—an average of 0.5 fewer kids for every 100 kilometers to be exact.

Melissa Melby, a medical anthropologist at the University of Delaware in Newark who was not involved in either study, tells *Science News* that the research offers a good look at the life of communities in North America and Europe in the 1600s and 1700s. But she says she's not convinced this is solid evidence for the grandmother hypothesis, suggesting menopause may have evolved by accident. It may have been a result of older men fathering babies that then inherited longevity genes. Or, at least in the case of the data from Canada, it could be because women were having babies later in life, until age 40, and so grandmothers survived because they were still raising their own offspring.

http://bit.ly/2GBLlbs

New 'Trojan horse' cancer treatment shows early promise in multiple tumor types

A brand new type of cancer drug that acts as a 'Trojan horse' to get inside tumour cells has shown promise in patients with six different cancer types.

In patients with advanced, drug-resistant cancers, over a quarter with cervical and bladder tumours, and nearly 15 per cent with ovarian and lung tumours, responded to the new treatment.

The innovative new drug, called tisotumab vedotin (or TV for short), releases a toxic substance to kill cancer cells from within. The results have been so positive the drug has now moved forward to phase II trials in cervical cancer and will be tested in a range of additional solid tumour cancers.

A team at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust led a phase I/II global clinical trial of nearly 150 patients with a variety of cancer types who had stopped responding to standard treatments.

The study was published in *The Lancet Oncology* and funded by Genmab and Seattle Genetics.

The researchers found that a significant minority of cancer patients responded to the drug, with their tumours either shrinking or stopping growing.

They saw responses in 27 per cent of patients with bladder cancer, 26.5 per cent with cervical cancer, 14 per cent ovarian cancer, 13 per cent with oesophageal, 13 per cent with non-small cell lung and 7 per cent with endometrial cancer (although not in any men with prostate cancer).

Responses lasted an average of 5.7 months, and up to 9.5 months in some patients.

The main side effects reported from the study were nose bleeds, fatigue, nausea and eye problems - but halfway through the trial the researchers adjusted the protocol to reduce these eye-related effects.

TV is made up of a toxic drug attached to the tail end of an antibody. The antibody is designed to seek out a receptor called 'tissue factor' - present at high levels on the surface of many cancers cells and linked with worse survival.

Binding to tissue factor draws the drug inside cancer cells, where it can kill them from within.

The trial initially recruited 27 patients to assess safety and establish the right dose, before expanding to a further 120 patients primarily to look at whether the drug was hitting the right target but also at what effect it had on tumours.

The majority of patients in the early trial had advanced stage cancer (spread locally or around the body) that had already been treated with, and became resistant to, an average of three different types of treatment.

TV is now being trialled in other cancer types including bowel, pancreatic, squamous cell lung and head and neck, as well as in a phase II trial as a second-line treatment for cervical cancer.

Biopsy samples taken at the start of the trial are currently being analysed for expression of tissue factor on tumour cells to see if it could be used as a marker to select patients most likely to respond to the drug.

Professor Johann de Bono, Regius Professor of Cancer Research at The Institute of Cancer Research, London, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust, said:

"What is so exciting about this treatment is that its mechanism of action is completely novel - it acts like a Trojan horse to sneak into cancer cells and kill them from the inside. Our early study shows that it has the potential to treat a large number of different types of cancer, and particularly some of those with very poor survival rates.

"TV has manageable side effects, and we saw some good responses in the patients in our trial, all of whom had late-stage cancer that had been heavily pre-treated with other drugs and who had run out of other options.

"We have already begun additional trials of this new drug in different tumour types and as a second-line treatment for cervical cancer, where response rates were particularly high. We are also developing a test to pick out the patients most likely to respond."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"We've seen major advances against cancer in recent decades, but many tumour types remain very difficult to treat once the cancer has begun to spread. We desperately need innovative treatments like this one that can attack cancers in brand new ways, and remain effective even against tumours that have become resistant to standard therapies.

"It's exciting to see the potential shown by TV across a range of hard-to-treat cancers. I look forward to seeing it progress in the clinic and hope it can benefit patients who currently have run out of treatment options."

After the embargo, you can access the journal article here:
http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30859-3/fulltext

http://bit.ly/2tj6RKa

Aggressive clearance key to best outcome after a brain hemorrhage

MISTIE III trial confirms need to remove at least 70 percent of an intracerebral clot

In the first study to identify specific surgical goals for the treatment of an intracerebral hemorrhage--the deadliest and most disabling type of stroke--a team of neurosurgeons found that at least 70 percent of the hemorrhage has to be removed for patients to make a meaningful recovery.

Worldwide, more than 1 million people each year develop an intracerebral hemorrhage. It occurs when a diseased blood vessel within the brain bursts, allowing blood to leak inside the brain. Hemorrhagic strokes make up about 12 percent of all strokes, but they cause about 40 percent of all stroke deaths. The most common risk factor is high blood pressure.

In this study, the researchers found that removing 70 percent or more of the hemorrhage could produce better outcomes. Ideally, there should be no more than 15 milliliters, about a tablespoon of clotted blood, remaining at the site of the injury. Anything less than that was even better.

This is the first surgical trial to connect specific volume-reduction goals with improved functional outcomes. Prior to this trial, known as MISTIE III (Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation), there was no specified goal for clot removal.

"We found that for surgeons treating a brain hemorrhage, it is critical to maximize the amount of blood the surgeon can safely remove from the site," said study leader Issam Awad, MD, the John Harper Seeley Professor in Neurological Sciences and Director of Neurovascular Surgery at the University of Chicago Medicine. "Unless at least 70 percent of the clot is promptly removed and only a very small residual amount of blood remains, the potential benefits of surgery will not be realized."

"This cannot be taken for granted," he added. "Intracerebral hemorrhage is a catastrophic illness. When surgery is performed, we must be certain that the blood is in fact removed. Surprisingly, this had not been considered in assessing the effectiveness of surgery. This is the first surgical trial to demonstrate a clear and urgent goal for reduction of intracerebral hemorrhage volume."

Two research teams will present data from MISTIE III in back-to-back "late-breaking-science" presentations at the American Heart Association's International Stroke Conference in Honolulu, on Thursday, Feb. 7, 2019. Awad will report on the ability of aggressive clot removal to produce better functional outcomes. Daniel Hanley, MD, from Johns Hopkins Medicine, will present data on overall analyses of safety and efficacy of the surgery.

The trial involved 78 hospitals in North America, Europe and Asia. Between December 30, 2013 and August 15, 2017, researchers enrolled 506 patients at least 18 years old who had suffered a spontaneous, non-traumatic, intracerebral hemorrhage in the previous 24 hours. Patients were promptly treated and periodically evaluated at regular intervals for one year.

About half (255) of the patients enrolled in the trial were randomly assigned to the MISTIE surgical procedure. The other 251 patients were assigned to the study's medical arm, which includes ICU care but no surgical intervention. Thirteen patients left the surgical arm

for various reasons, so 242 patients received the procedure and were available for evaluation.

The surgical approach to an intracerebral hemorrhage relies on careful mapping of the injury with computed tomography (CT) guidance. The surgical team then drills a small hole in the patient's skull and inserts a tiny rigid cannula. The surgeons maneuver the cannula to the blood that has accumulated in the brain and aspirate as much of it as possible.

Since the blood has already clotted, it cannot all be suctioned, so a softer catheter is placed in the remaining clot, secured in place, and the clot-busting drug alteplase (marketed as Activase®) is given through the catheter to loosen the clot and allow it to drain into a bag. This removes as much of the damage-causing blood as possible.

The surgery itself takes about an hour, but the alteplase injection is repeated every eight hours. Treatment averaged 2 days after the stroke, with a range of 1-4 days. Prior to this study, it was not known how much of the blood must be removed to gain the benefit of the procedure.

In 59 percent of the cases in the MISTIE III trial, the teams succeeded in reducing the clot to 15 milliliters or less. With the removal of each additional milliliter of clotted blood, the odds of a good outcome improved 10 percent.

Some of these operations "were remarkable," Awad said. Many of the surgeons were able to approach "a clot the size of a tennis ball and gently reduce it to less than 5 milliliters."

Patients could survive with less surgery and manipulation, Awad suggested. "If you get half of the clot out, you can save the person's life," he said. "But to get real functional benefit, you have to go all the way. You have to remove most, if not all, of the clot."

The MISTIE III trial was sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health. Trial results will be published in The Lancet *and* Neurosurgery. *Additional authors include Sean Polster, Julián Carrión-Penagos, Ying Cao, Agnieszka Stadnik, Maged Fam, Janne Koskimäki, and Romuald Girard from the University of Chicago; Richard Thompson, Karen Lane, Nichol McBee, Wendy Ziai and Yi Hao from Johns Hopkins University; Patricia Money and Mario Zuccarello, from the University of Cincinnati; Robert Dodd and Andrew P. Carlson from Stanford University; Paul Camarata from the University of Kansas; Jean-Louis Caron from the University of Texas; Mark R. Harrigan from the University of Alabama; and David Mendelow from the Institute of Neuroscience at Newcastle upon Tyne, UK.*

http://bit.ly/2RTTutA

Vaccinations jump 500% in antivax hotspot amid measles outbreak

"I would rather it not take an outbreak for this to happen."

Beth Mole

Demand for measles vaccines leapt 500 percent last month in Clark County, Washington—a hotbed for anti-vaccine sentiment that has now become the epicenter of a ferocious measles outbreak.

As of February 6, the county—which sits just north of the border from Portland, Oregon—has tallied 50 confirmed cases and 11 suspected cases of measles since January 1. The case count is rising swiftly, with figures more than doubling in just the last two weeks. On January 18, the county declared a public health emergency due to the outbreak.

Health officials have long feared an outbreak in the area, given the rampant skepticism of vaccines driven by misinformation and fear-mongering by anti-vaccine advocates. Only 76.5 percent of kindergarteners in Clark County had all the standard immunizations during the 2017-2018 school year. Overall, the county's population is below the 92-percent to 94-percent range some experts consider necessary to curb the spread of disease.

But, that might be about to change. As the threat of measles has become all too real in Clark County, residents are lining up for vaccines, according to data first reported by Kaiser Health News. Orders of measles vaccines in the county reached 3,150 in January. That is nearly a 500-percent jump in orders from January last year, when the total was just 530. Statewide vaccine figures also reflect a

boost. Orders for measles vaccine climbed 30 percent in Washington overall, from 12,140 doses in January last year to 15,780 doses in January of this year.

Though health officials are glad to see the surge in life-saving immunizations, the motivation is less encouraging. “I would rather it not take an outbreak for this to happen,” Alan Melnick, the Clark County health officer overseeing the response, told KHN.

Still, the response is unsurprising, according to Virginia Ramos, infection control nurse with Sea Mar Community Health Center, which runs six sites that offer vaccines in Clark County. “During an outbreak is when you see an influx of patients who would otherwise be vaccine-hesitant,” she said.

The Clark County health department has stressed the dangers of measles, which is an extremely contagious, air-borne viral disease. The health department notes on its website that:

The virus travels through the air and can stay up to two hours in the air of a room where a person with measles has been. If other people breathe the contaminated air or touch a contaminated surface, then touch their eyes, noses or mouths, they can become infected. Measles is so contagious that if one person has it, 90 percent of the people close to that person who are not immune will also become infected.

Measles usually starts with a high fever, cough, and runny nose, as well as red, watery eyes, according to the Centers for Disease Control and Prevention. It progresses to the telltale measles rash three to five days later, which breaks out all over the body and can be accompanied by fever spikes above 104 degrees Fahrenheit. Common complications include diarrhea and ear infections that can cause permanent hearing loss in children. Severe complications include pneumonia, which can be fatal, and encephalitis (swelling of the brain), which can lead to convulsions, hearing loss, and intellectual disabilities in children. Measles can also cause pregnant women to give birth prematurely or deliver a low-birth-weight baby.

The outbreak in Washington state is one of three ongoing in the US, with the other two in New York City and New York state. Cases have also been documented in California, Colorado, Connecticut, Georgia, Illinois, New Jersey, Oregon, and Texas since the start of the year.

https://nyti.ms/2BxcZCO

The Patient Had Bone Cancer. The Diagnosis Arrived 240 Million Years Too Late.

The fossil of an ancient animal teaches a sad lesson: Cancer has been around for a very, very long time.

By Asher Elbein

Certainly the patient never knew where the hip pain came from, or why its left leg stopped working. The diagnosis arrived only 240 million years later, when a femur turned up in an ancient lake bed in Germany, one side marred by a malignant bone tumor.

The cancerous leg bone of a 240-million-year-old Pappochelys, a shell-less ancestor of turtles, is the oldest known case of cancer in an amniote, a group that includes reptiles, birds and mammals. **Brian Engh**

Cancer seldom appears in the fossil record, and its history among vertebrates is poorly understood. On Thursday, a team of researchers writing in JAMA Oncology have described the femur as the oldest known case of cancer in an amniote, the group that includes reptiles, birds and mammals.

Modern cancers are often diagnosed through soft-tissue examinations or biopsies, but that is a difficult prospect for cancer-hunters working with cold, hard fossils. Instead, it takes luck.

“When it comes to our understanding of cancer in the past, we’re really just at the beginning,” said Michaela Binder, a bioarchaeologist at the Austrian Archaeological Institute who’s

researched cancer in ancient humans. “It’s not like people say, ‘Oh, I want to go study cancer in ancient turtles or in fossil mammoths,’ because we have so little evidence.”

The discovery of the femur was a stroke of luck. Originally collected by Rainer Schoch of the Stuttgart State Museum of Natural History, it belonged to a wide-bodied, long-tailed animal called Pappochelys, a shell-less relative of modern turtles.

The femur and its jagged growth caught the attention of Yara Haridy, a former medical student and paleontologist at the Natural History Museum, Berlin.

While many paleontologists look for the cleanest — or at least most representative — remains, Ms. Haridy said, the marks left by illness and injury also can shed light on the lives of ancient animals. The study of such fossils is called paleopathology, and it combines aspects of modern forensic and medical practices.

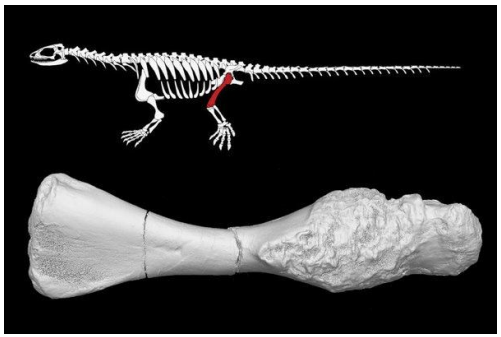
“I basically go through an elimination process, which is kind of how diagnostics in humans work,” Ms. Haridy said. “You go from the most general possibility to more specific and really strange diagnoses.”

Ms. Haridy and her colleagues brought the femur to Dr. Patrick Asbach, a radiologist at the Charité, a university hospital in Berlin. Examining micro-CT scans of the bone, the researchers began running through a checklist of possible causes.

“If you looked externally, you could easily think this was an incorrectly healed bone,” Ms. Haridy said. “I thought initially this animal had a broken femoral head or some sort of really bad shin splints.”

Healed injuries are the most common type of fossil pathology, yet the micro-CT scans showed that underneath the growth, the bone was unbroken.

So Ms. Haridy considered other possibilities. A congenital abnormality would have been present on both sides of the femur, not just one. And while friction and excessive pressure can cause bone growth, the femur would have been protected by muscles. That left the possibility of disease. But most diseases eat away at bone instead of building it up, or lead to infections that warp and wear away the underlying surface.



A drawing of the skeleton of Pappochelys and a scan of its cancerous leg bone. **Rainer Schoch/Museum für Naturkunde Berlin**

Benign tumors can sometimes grow on bones, but they tend to be formed from cartilage and look quite different: “They either make a bunch of cartilage or start to actually reabsorb bone,” Ms. Haridy said.

The team identified the swelling as an osteosarcoma, a type of bone cancer also found in humans. According to the National Organization for Rare Disorders, an estimated 750 to 1,000 cases are diagnosed in the United States every year.

The find is an important data point when it comes to learning more about cancer in the vertebrate family tree, Dr. Binder said.

The lack of evidence for prehistoric cancer has sometimes led researchers to speculate that the disease is a modern phenomenon related to unhealthy living, pollutant-filled environments or people getting much older than they used to in the past.

Other specialists have suggested the possible presence of a tumor-suppressor gene in vertebrates, the failure of which allows benign tumors to metastasize. In the absence of fossil evidence, however, there has been no proof.

Adding to the uncertainty, some animal lineages seem less susceptible to cancer than others: Crocodiles and a few other reptiles, along with sharks and naked mole rats, are rarely troubled by the

disease, while tumors in invertebrates don't much resemble those of vertebrates.

Still, there are other recent finds that suggest cancer's antiquity. In 2001, a team of Russian paleontologists identified a possible cranial osteosarcoma in an Early Triassic amphibian, while a benign jaw tumor from a 255-million-year-old mammal forerunner was reported in 2016.

"What makes this really cool is that now we understand that cancer is basically a deeply rooted switch that can be turned on or off," Ms. Haridy said. "It's not something that happened recently in our evolution. It's not something that happened early in human history, or even in mammal history."

http://bit.ly/2tjbtQu

Hate needles? This ingestible pill painlessly injects drugs into your gut

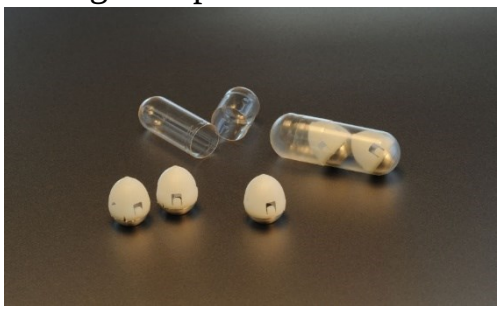
Researchers aimed to replace insulin shots, but it could work with other drugs.

Beth Mole

If the sight of a doctor flicking a needle makes you cringe, you may be better off going with your gut, according to a team of researchers at MIT and Harvard.

The team is working to knock out the need for painful, anxiety-inducing shots by having patients gulp a pill instead. But not just any pill, but an autonomous one that can right itself in your gut while packing a tiny, spring-loaded shot of drugs that it then injects directly into the thick wall of your stomach. The painless prick could deliver therapeutic payloads that normally wouldn't survive the harsh, acidic environment of the stomach. By doing so, it would make life a lot easier for needle-fearing patients and for those who depend on frequent drug injections, such as people with diabetes who take daily insulin shots, the researchers say.

In a report in the February 8 issue of *Science*, the researchers reveal a prototype of their autonomous pill along with positive results from tests in pig stomachs where they tried delivering insulin. While the research is still in the very early stages, the data so far hints that their self-righting pill—about the size of a pea—could one day work in patients.



***Enlarge** / Self-righting capsule orients itself in the gastric cavity and delivers biologic molecules to the tissue wall.* **Science | Felice Frankel**

"The drug delivery efficacy achieved with this technology suggests that this method could supplant subcutaneous injections for insulin and justifies further evaluation for other biomacromolecules," the researchers concluded.

To come up with their prototype, the researchers cribbed the wobbly, self-orienting design from the leopard tortoise. The reptiles' knobby shells help them roll out of life-threatening danger when they find themselves upside down. Taking the basic idea, the researchers engineered a capsule, vaguely acorn shaped, that will teeter to an upright position from any other position.

For safe ingestion, the researchers made the capsule out of a biodegradable polyester already approved for medical devices and drug delivery—polycaprolactone (PCL)—as well as stainless steel, which had also already been safety tested for use in dental braces. Then, they kept the knobbed shell empty to load it up with drugs.

In the first tests, the researchers tried delivering insulin. They engineered the capsule to have a spring-loaded, 1.7-millimeter needle, made of compacted, dried insulin. The compressed spring sits at the top of the knob with a vent to the outside world. It's fixed in place with caramelized sugar, which dissolves on exposure to stomach acid, unleashing the spring and the drug spike. And because

the capsule is self-orienting, the shot of drug is set up to fire directly into the 4mm- to 6mm-wall of the stomach, which has no pain receptors.

In tests in pigs, the pokey pill successfully delivered a gut punch, even when the researchers tilted and rotated the animals. The pigs' blood-sugar levels went down, suggesting that insulin delivery worked. Further testing showed that the insulin was shelf stable for 16 weeks, and the researchers saw no evidence of damage or perforation of the pig's stomachs.

But there was one big hiccup—one that's a bit hard to swallow. The pill only worked when the animals were fasting. If they had food or liquid in their tummies, the pill didn't work. The researchers suggest that the failure may be due to food particles and other gunk clogging up the capsule's vent, thus preventing the spring from firing. They designed a valved silicone membrane to try to prevent that, but the capsule will need far more testing. Further testing should also address if repeated or daily gut pricks could lead to inflammation or injury, the researchers note.

"Still, the [pill] represents a platform with the potential to deliver a broad range of biologic drugs, including but not limited to other protein- and nucleic acid–based therapies," the researchers conclude.

Science, 2018. DOI: 10.1126/science.aau2277 (About DOIs).

http://bit.ly/2WNIxNQ

Lightning's electromagnetic fields may have protective properties

Extremely low frequency fields may have played an evolutionary role in living organisms, say Tel Aviv University researchers

Lightning was the main electromagnetic presence in the Earth's atmosphere long before the invention of electricity. There are some 2,000 thunderstorms active at any given time, so humans and other organisms have been bathed in extremely low frequency (ELF) electromagnetic fields for billions of years.

These electromagnetic fields -- the result of global lightning activity known as Schumann Resonances -- are weak and difficult to detect. Scientists never suspected that they had any tangible impact on life on Earth. But a new Tel Aviv University study finds that these fields may have protective properties for organisms living under stress conditions.

Research for the study was led by Prof. Colin Price of TAU's Porter School of the Environment and Earth Sciences and conducted by his doctoral student Gal Elhalel in collaboration with Profs. Asher Shainberg and Dror Fixler of Bar Ilan University. It was published in *Nature Scientific Reports* on February 7.

"We found that under controlled conditions, the Schumann Resonance fields certainly had an effect on living tissues," Prof. Price says. "The most important effect was that the atmospheric ELF fields actually protected cells under stress conditions. In other words, when biological cells are under stress -- due to lack of oxygen, for example -- the atmospheric fields from lightning appear to protect them from damage. This may be related to the evolutionary role these fields have played on living organisms."

In the course of numerous laboratory experiments, in which the scientists induced fields similar to those in the atmosphere, they witnessed significant effects on living heart cells of rats within 30-40 minutes. Extremely weak magnetic fields in the 7.6-8Hz frequency range induced a number of effects when applied to rat cardiac cells, including reductions in spontaneous contractions, calcium transients and the release of Creatine Kinase (CK). (The release of CK into the liquid medium around the cardiac cells is a measure of damage to cardiac cells, which also occurs during heart attacks.) The scientists found that the effects were temporary, as the induced cell changes reversed when the fields were turned off.

"It is the first study that demonstrates a link between global lighting activity and the Schumann Resonances and the activity of living

cells," Prof. Price says. "It may explain why all living organisms have electrical activity in the same ELF spectral range, and it is the first time such a connection has been shown. This may have some therapeutic implications down the line, since these ELF fields appear to protect cells from damage, but this requires further research."

Prof. Price and his team are expanding their research to other types of biological cells to see if there is a similar effect of these electromagnetic fields on other cell types.

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Fluconazole makes fungi sexually active

Resistant fungal cells can quickly switch to sexual reproduction in the presence of fluconazole

The yeast *Candida albicans* occurs in most healthy people as a harmless colonizer in the digestive tract. However, it can also cause life-threatening infections, especially in immunocompromised patients.

These infections are usually treated with the drug fluconazole, which inhibits the synthesis of ergosterol in *Candida*. Ergosterol fulfils similar important functions in fungi as cholesterol in humans.

Candida albicans can, however, become resistant to this drug. Scientists have uncovered the main mechanisms of fluconazole resistance in recent years. The group of Professor Joachim Morschhäuser from the Institute for Molecular Infection Biology at Julius-Maximilians-Universität Würzburg (JMU) in Bavaria, Germany, has contributed important findings.

The fungus succeeds in becoming resistant with numerous mechanisms. For example, it uses pumps to transport the drug out of its cells. "Highly resistant *Candida albicans*, in which fluconazole therapy fails, usually use a combination of several of these mechanisms," says Morschhäuser.

New combinations of resistance mechanisms

Normally *Candida albicans* reproduces asexually by cell division. Morschhäuser's research group has now discovered that resistant fungal cells can quickly switch to sexual reproduction in the presence of fluconazole. In this case, the cells fuse and unite their genetic material. In the offspring cells, different resistance mechanisms are newly combined and the fungal population thus becomes even less sensitive to fluconazole.

"In our investigations, we found out that the cells that retained the advantageous resistance characteristics are selected and become dominant in the population when treated with fluconazole," says first author Christina Popp. Fluconazole not only selects for resistance mutations, but can also lead to changes in the genome that make the normally asexual fungus "mating-competent", thereby enabling the cells to combine individually acquired resistance mechanisms and produce highly resistant offspring.

Knowledge about the molecular mechanisms of drug resistance can be useful for the development of better and new drugs and help overcome resistance.

Morschhäuser assumes that the resistance mechanisms described here are only one example of how *Candida albicans* can change in its host. Next, his team wants to investigate whether other forms of adaptation can also contribute in a similar way to the successful establishment of the fungus in different host niches.

This research was funded by the German Research Foundation (DFG) and the Open Access Publication Programme of DFG and JMU.

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Innovative, simple treatment to combat the Candida albicans fungus

A study led by the UPV/EHU-University of the Basque Country has for the first time shown the antifungal activity of uterine stem cells

The research is being led by Guillermo Quindós, professor of Microbiology at the UPV/EHU's Faculty of Medicine, and funded by the Foundation for Uterine Stem Cell Research (FICEMU). This study opens up an alternative for treating vaginal candidiasis, a disease that is extremely prevalent in the female population.

Vaginal candidiasis is not life-threating, but it reduces the life quality and restricts the activity of women affected by it because it is terribly unpleasant, owing to its symptoms (at times unbearable itching and stinging).

What is more, nearly one in five women who suffer a bout of vaginal candidiasis becomes a chronic carrier of the *Candida* fungus, and goes on to suffer fresh bouts of this unpleasant infection. These repeat bouts of candidiasis tend to be resistant to the usual treatments, and it is here where the results of this research are opening up a significant window of hope.

The conditioned medium of uterine stem cells (hUCESC-CM) inhibits the growth of various sensitive strains of *Candida* isolated from the vagina of various patients, but what is much more important, it inhibits the growth of *Candida albicans* in nearly 80% of cases in patients with chronic vaginal candidiasis that is resistant to treatment. It has to be remembered that *Candida albicans* is responsible for over 80% of cases of vaginal candidiasis.

Yet uterine stem cells also inhibit the growth of *Candida albicans* (strains sensitive to as well as resistant to treatment) originating in the blood of immunosuppressed patients.

Sepsis (blood infections) by fungi are a significant cause of death in this group of patients, above all when they become resistant to the few, not particularly effective medical treatments currently available to combat them.

The reason why this particular strain of Human Uterine Cervical Stromal Stem Cells (hUCESCs) is more active in combating *Candida albicans* may be found in its origin.

Uterine stem cells come from a very specific area, known as the "transformation zone of the uterine cervix", which is biologically highly vulnerable, and is in permanent contact with the vaginal medium and the threats harboured by the latter: fungi, bacteria, viruses, plus all the pathogenic microbes entering from outside, generally through sexual intercourse.

In this context, throughout the evolution of our species, the mesenchymal stem cells of the uterine cervix have been able to develop powerful defence mechanisms in the form of a cocktail of molecular factors that are released into the external medium for the purpose of combatting all these potential threats and preserving our species.

The possible use of the conditioned medium of Human Uterine Cervical Stromal Stem Cells (hUCESC-CM) as a totally innovative means of antimicrobial treatment is important not only from the conceptual point of view, but also from the practical point of view, since it does not entail the difficulty of treatments based on the use of stem cells themselves.

Uterine stem cells or mesenchymal stem cells of the uterine cervix (hUCESCs) are obtained in a fairly non-invasive way using cervical brushing like that used in routine gynaecological examinations.

In addition, the researchers have provided evidence in previous studies that its secretome/conditioned medium (set of molecules secreted by these cells) has an anti-tumour potential in breast cancer, a regenerative one in corneal injuries, plus a potential immunoregulator.

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http://bit.ly/2I83Ia9

Researchers discover corn plants call in hungry nematodes when resistant rootworms attack

Nematodes are an indirect defensive strategy used by hybrid plants that provides some recourse against rootworms

Someday – in some scientifically savvy encyclopedia perhaps – the word "resilience" may include a photograph of the Western Corn Rootworm. This crafty, intrepid rootworm has found a way to circumvent just about every defense a corn plant and its advocates have thrown at it.

This is why its street name is "Billion Dollar Bug" in many agricultural circles, a name that reflects the size of this insect's annual bite into the coffers of U.S. corn growers, who last year year planted 89.1 million acres of the crop, according to the U.S. Department of Agriculture. Not all of that acreage is at risk. But the rootworm is considered the most important pest in the Midwest's Corn Belt, where corn production is highest, led by Iowa, Illinois, Nebraska and Minnesota.

Consider this rootworm's impressive record: It has survived granular insecticides and sprayed insecticides. It has figured out how to beat crop-rotation practices, which discourage rootworm population increases. And, scientists say, it has developed resistance to hybrid corn plants that were engineered with toxins released when the rootworms attacked, a defense that had proven effective for at least a decade.

Now researchers at the University of Delaware and the USDA have discovered an indirect defensive strategy used by the hybrid plant that provides some recourse against this stubborn creature. Ivan Hiltpold, assistant professor of entomology and wildlife ecology in UD's College of Agriculture and Natural Resources, and the USDA's Bruce Hibbard, who leads plant genetics research at the University of Missouri, published their findings in the *Journal of Economic Entomology*.

Western Corn Rootworms encountered significant setbacks when growers started planting hybrid corn plants, genetically engineered to produce insecticidal toxins from a bacterium called Bacillus thuringiensis – or Bt for short. When a susceptible rootworm attacked a hybrid corn plant, the toxin usually killed it, arresting the damage.

After about a decade of effectiveness, Western Corn Rootworms developed resistance to Bt corn.

But it turns out that Bt corn wasn't helpless.

Hiltpold and Hibbard found that when a resistant rootworm chomps boldly into this plant, causing advanced damage, the hybrid sends out a specific chemical signal that is something like throwing chum into the ocean as shark bait. In this case, the organic compound sent out by the corn plant attracts nematodes, small wriggling wormlike creatures that feed on these rootworm larvae.

You might call it the nematode dinner bell defense. The chemicals tell every nematode within range that dinner is ready and rootworm larvae are on the menu.

This is great news for the nematodes, but a new vulnerability for the resistant rootworm – something agricultural economists call a "fitness cost," a tradeoff that explains how a newly acquired trait costs an organism something in development or ability to reproduce. Breeding corn to grow bigger ears, for example, may have implications for the corn's future. It may lose certain traits that smaller-eared corn maintains.

"This is the first case where we saw some sort of fitness cost associated with resistance – and it's a different slant on fitness cost than anybody thought of before," Hibbard said. "The only reason the nematodes are targeting these resistant insects is that they are doing more damage."

The Western Corn Rootworm's resistance to this hybrid corn has exposed it to another layer of defense – the compounds that are emitted only to beckon nematodes when this resistant rootworm attacks. The compounds are not emitted when non-resistant insects attack the corn because the damage to the plant is not great enough to trigger the defense.

"So if you use the right cultivar with these nematodes, you have a chance to control this resistant population," Hiltpold said. "It's a way to manage this resistant pest and it is less likely to evolve further resistance."

Nematodes are expensive to introduce as an applied defense, though, Hiltpold said. They are not an economical way of prophylactically managing Western Corn Rootworm populations.

But they can be used to treat problem areas and pockets of resistance, he said.

Some growers are suspicious of nematodes and reluctant to encourage them in any way, Hiltpold said. And to be sure, certain nematodes are a threat to soybeans, for example. But the nematodes drawn by these corn plants are not plant eaters. They are insectivores. And they can be another weapon in the corn grower's arsenal.

"This is just another component of an integrated pest management approach," said Hibbard. "This will help kill some resistant insects. But right now, the natural populations of nematodes aren't big enough to manage rootworms well. You need multiple approaches."

The Western Corn Rootworm is not a significant problem for corn in Delaware, Hiltpold said. It does not like sandy soil. But he is interested in exploring whether nematodes could be helpful to another big Delaware crop – watermelons.

"The more angles you use to control insects or pests, the more sustainable your management will be," Hiltpold said.

More information: *Ivan Hiltpold et al. Indirect Root Defenses Cause Induced Fitness Costs in Bt-Resistant Western Corn Rootworm, Journal of Economic Entomology (2018).* *DOI: 10.1093/jee/toy220*

http://bit.ly/2WVchbS

Drug companies are sitting on generics—43% of recently approved aren't for sale

You pay more for medicine because hundreds of generics aren't for sale.

Beth Mole

Of the more than 1,600 generic drugs approved by the Food and Drug Administration since January of 2017, more than 700—or 43 percent—are not for sale in the US, according to a new analysis by Kaiser Health News.

The finding means that many pricy, brand-name drugs are not facing the competition that could help drive down soaring prices. Among the drugs missing in action are generic versions of the expensive blood thinner Brilinta and the HIV medication Truvada. Moreover, of the approved drugs that would offer a brand-name drug its first competition, 36 percent are being held off the market, the analysis found.

Experts told KHN that the reasons drug makers may withhold an approved generic from the market are varied. Industry consolidation has made buying, manufacturing, and distributing generics more difficult in recent years. Generic drug makers also, as always, face patent litigation from brand-name makers. Then there's potentially anti-competitive deals, in which brand-name drug makers simply pay generic makers to keep their product off the market for a while—a so-called "pay for delay" tactic.

Lastly, there are internal decisions within a generic company that can lead to shelving a drug. For instance, a drug maker may shift its business strategy while it's waiting for the drug to get approved, or the maker may delay a drug's entry to the market until a strategic time.

Whatever the reason, keeping approved generics from the market is "a real problem because we're not getting all the expected

competition," FDA Commissioner Scott Gottlieb said in an interview with KHN.

Generic approvals at the FDA have ramped up in recent years, and the agency is cracking down on anti-competitive tactics, Gottlieb said. Still, it's a difficult problem to solve with so many factors at play, he said.

He added that an FDA analysis found that on average it takes the introduction of five generic versions of a drug to the market to drive down a drug's price to 33 percent of the original branded price.

https://bbc.in/2RUjZ20

Herbal history: Five garden plants with a hidden past

Many garden plants we're familiar with today have a hidden history.

By Helen Briggs BBC News

Grown centuries ago for their reputed healing powers, they became garden staples, valued for their beauty, form or scent.

Pulmonaria, with its spotted leaves, was thought to symbolise diseased lungs, and used for chest infections.

And the mint now found in a pot by the door was recommended to "stayeth bleeding" by early herbalists and apothecaries.

There's more to garden plants than just their aesthetics, says Fiona Davison, head of libraries and exhibitions at the Royal Horticultural Society, RHS.

Plants generally don't get into gardens by accident, she says - they have a long relationship with people.

Image copyright RHS Lindley Collections Image caption Valerian: A flowering plant with sweetly scented pink or white flowers

"It's been a long story of people choosing particular plants, nurturing them, growing them, breeding them, making choices of which seedling they would select to carry on growing," she says.

"And a lot of times those choices have been made on aesthetics, but a lot of times those choices have been made on the basis of what they thought the plant would do for you, from a medicinal point of view."

Healing spaces

Studies of plants by ancient herbalists paved the way for the formal study of plants by the first botanists, many of whom were also physicians. Today, at least 28,000 plant species are recorded as being of medicinal use.

Fiona Davison says the long story of the "healing garden" is coming full circle and we're now thinking of gardens holistically as "healing spaces", where, by spending time in them, we're getting some well-being benefit.

Here are five garden plants that you can still find in your garden, that were once recommended by ancient herbalists. (Note: These plants may not be recommended for medical use today and may have side-effects or be harmful if ingested.)

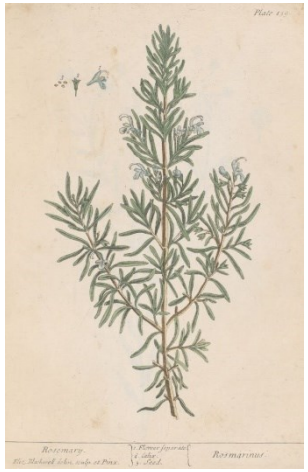
Common name: Yarrow

Scientific name: *Achillea millefolium*

The yarrow plant is a herbaceous flowering perennial. The name comes from Achilles, because it was believed Achilles used it on the battlefield to staunch bleeding.

Common name: Rosemary

Scientific name: *Rosmarinus officinalis*



Rosemary: Woody, perennial herb with fragrant, evergreen, needle-like leaves **RHS Lindley Collections**

Rosemary has long been recommended by herbalists for improving memory. According to English herbalist John Parkinson, the herb could remedy "all other cold diseases of the head and braines, as the giddiness or swimming therein, drowsiness or dulnesse of the minde and senses like a stupidnesse".

Common name: Valerian
Scientific name: *Valeriana officinalis*

Valerian was recommended for sickness, pain and insomnia by many early herbalists. Nicholas Culpeper recommended both herb and root, for cough and plague.

Valerian: A flowering plant with sweetly scented pink or white flowers **RHS Lindley Collections**

Common name: Honeysuckle
Scientific name: *Lonicera periclymenum*

Honeysuckle was once recommended for skin problems and to "cleanse the face and skinne from morphew, sunburne, freckles, and other discolouring".

Honeysuckle: Valued as garden plants, for their ability to climb and cover walls and outbuildings **RHS Lindley Collections**

Common name: Peony
Scientific name: genus Paeonia

The roots of this plant has historically been used to treat a variety of ailments, including pains in the belly, bladder and kidneys. They were recommended for children with epilepsy, with the roots "either taken inwardly, or hung about their necks".

Peony: Herbaceous perennial plant or woody shrub **RHS Lindley Collections**

An exhibition on the healing garden can be seen at RHS Garden Wisley; RHS Garden Harlow Carr, Yorkshire; RHS Garden Hyde Hall, Essex; and RHS Garden Rosemoor, Devon until 4 March.