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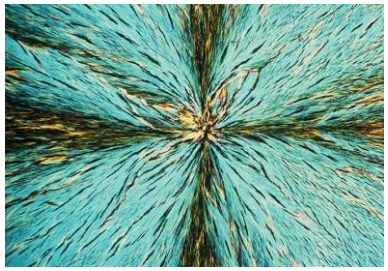
How a minty fresh flavouring could control useful genes

The cooling compound menthol sets a human protein to work, triggering a cellular cascade.



Menthol has found a purpose beyond soothing a cough. Researchers have designed a genetic circuit that can be switched on by a drop in temperature — or by menthol, which imparts a cooling sensation.

A crystal of menthol, an additive used in products including toothpaste. The compound can spur an engineered genetic circuit into action. **Sidney Moulds/Science Photo Library**

Scientists are investigating genes as treatments for genetic diseases and other medical problems, but controlling those genes in the body is a challenge.Seeking a solution, Martin Fussenegger at the Basel campus of the Swiss Federal Institute of Technology Zurich and his colleagues developed a genetic circuit based on the human protein TRPM8, which reacts to cool temperatures.

In cells the team created, TRPM8 responds both to temperatures of 15–18 ºC and to the presence of menthol — a mint-flavoured ingredient of many cough drops and other remedies — by activating a second protein. That activation, in turn, triggers the production of a third protein of the researchers' choice.

The team engineered a set of cells whose TRPM8-based circuitry stimulated production of the protein insulin, which controls blood sugar levels.

After diabetic mice implanted with these cells had menthol applied to their skin, their blood sugar levels were lower than those of diabetic mice treated with menthol alone.

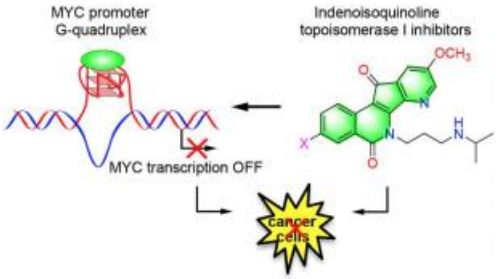
Nature Med. (2019)

http://bit.ly/32pV2lK

New anticancer agents may better control tumor growth in nearly every cancer type

Novel set of G-quadruplex stabilizers may help stop gene from driving tumor growth in hundreds of cancers

WEST LAFAYETTE, Ind. - A gene called MYC has become one of the hottest targets for cancer researchers around the world. MYC is known to drive tumor growth in nearly all cancer types - but successfully targeting the gene has proven to be a challenge. One that has been baffling researchers for more than three decades.



Purdue University researchers have discovered potential anticancer agents that stabilize the MYC promoter G-quadruplex and downregulate the expression of the MYC oncogene. **Purdue University/Danzhou Yang**

Now, researchers at Purdue University have discovered a novel set of MYC promoter G-quadruplex stabilizers that have demonstrated anticancer activity in human cancer cell cultures.

The discovery is published in the July 8 edition of the *Journal of the American Chemical Society*.

"We are striving to discover effective anticancer agents," said Mark Cushman, a distinguished professor of medicinal chemistry in Purdue's College of Pharmacy, who helps lead the research team. "The ability to incorporate MYC promoter G-quadruplex stabilizing activity into existing topoisomerase I inhibitors has shown promise in making them more potent as anticancer agents and in making cancer cells less likely to become resistant to them."

The Purdue team discovered potential anticancer agents that target the MYC promoter G-quadruplex and downregulate the expression

of the MYC oncogene, which is overexpressed in cancer and is associated with almost all aspects of cancer development.

The work has been supported by the National Cancer Institute and the National Institutes of Health.

Cushman, whose cancer research work contributed to his election as a fellow of the National Academy of Inventors, said they discovered a novel class of indenoisoquinoline MYC promoter G-quadruplex stabilizers in collaboration with Danzhou Yang.

Some of them also inhibit topoisomerase I, an enzyme that facilitates DNA replication and is produced in greater amounts in cancer cells.

"Targeting promoter G-quadruplexes offers a relatively new and exciting strategy to inhibit the critical oncogene expression in cancer cells," said Yang, the Martha and Fred Borch Chair of Cancer Therapeutics in Purdue's College of Pharmacy, who led the research with Cushman.

"We hope to combine the potency of the DNA-targeted drugs and selectivity of molecular-targeted approaches for new cancer therapeutics."

Yang and Cushman, both members of the Purdue University Center for Cancer Research, said the agents they discovered could be used in helping to treat nearly every type of cancer.

Some of the technology from their work has been licensed to Gibson Oncology LLC through the Purdue Research Foundation Office of Technology Commercialization.

Some of the work Cushman and his team previously developed led to three anticancer agents that are in clinical trials.

The MYC innovation will greatly enhance interest in these anticancer agents within the scientific community and will also contribute to the understanding of how they work.

http://bit.ly/2Llf9My

Combining antibiotics, researchers deliver one-two punch against ubiquitous bacterium

CWRU/Cleveland VA findings in mouse models could make inroads against superbugs

By combining two well-established antibiotics for the first time, a scientific team led by Case Western Reserve University School of Medicine and Louis Stokes Cleveland VA Medical Center has delivered a "double whammy" against the pervasive *Pseudomonas aeruginosa*, a potentially deadly form of bacteria that is a major source of hospital-based infections.

In a recent *Journal of Infectious Diseases* study, investigators showed using two antibiotic drugs to fight *P. aeruginosa* in mouse models was significantly more effective than either antibiotic alone. The antibiotics were ceftazidime-avibactam, a combination drug used to treat a wide variety of serious bacterial infections, and fosfomycin, used to primarily treat infections of the urinary tract.

"By successfully combining these two drugs against this widespread form of bacteria, we hope to lay a foundation for eventually eradicating the infection," said the study's lead author Krisztina M. Papp-Wallace, PhD, an assistant professor of medicine at the School of Medicine and a research scientist at the Cleveland VA Medical Center. "These findings have significant implications for further studies directed at clinical applications and could bring benefits to numerous patients worldwide."

Immunocompromised patients, such as those with cancer or cystic fibrosis, burn victims and patients on ventilators, are at particular risk from the bacterium, which can be spread by the hands of health-care workers or contaminated equipment.

Bacteria and other microorganisms have increasingly developed resistance to antibiotics, making infections harder to treat and expanding the risk of contamination to others. As a result, health-

care costs are also growing. Microorganisms that develop antimicrobial resistance are sometimes referred to as "superbugs." While such resistance typically occurs naturally over time, usually through spontaneous genetic changes, the misuse and overuse of antibiotics in humans and animals is accelerating this process.

The new approach described in the paper is directed at destroying enzymes in the cell wall of the bacterium. Homing in on a particular strain of *P. aeruginosa* known as CL232, the researchers found that, after 24 hours, the ceftazidime-avibactam-fosfomycin combination was much more effective in reducing the presence of the bacterium than the medications individually.

"Dr. Papp-Wallace's insight about combining the two antibiotics proved to be right on target," said the study's senior author, Robert A. Bonomo, MD, professor of medicine, pharmacology, molecular biology and microbiology at the School of Medicine and chief of the medical service at the Cleveland VA Medical Center. "This is superb bench-to-bedside science and has positive implications for future patients worldwide."

The study was a substantial collaborative effort that included several of the world's experts in infectious diseases. David S. Perlin, PhD, and his National Institutes of Health designated Center of Excellence in Translational Research (CETR) at Hackensack Meridian Health Center for Discovery and Innovation established the animal model to test the combination. George L. Drusano, MD, a leading specialist in pharmacokinetics/pharmacodynamics from the Institute for Therapeutic Innovation at the University of Florida determined the dosing parameters for this novel combination. Evelyn J. Ellis-Grosse, PhD, who was involved in the clinical development of intravenous fosfomycin in the United States, provided valuable input on the activity of fosfomycin. Barry N. Kreiswirth, PhD, also at Hackensack, and Derrick E. Fouts, PhD of J. Craig Venter Institute, assisted with the genetic characterization of the P. aeruginosa.

Support for this work was provided through the CETR and National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services, Louis Stokes Cleveland VA Medical Center, Veterans Affairs Merit Review Program, Department of Veterans Affairs Biomedical Laboratory Research and Development Service, and the Geriatric Research Education and Clinical Center.

Papp-Wallace, K. et al. "Ceftazidime-Avibactam in Combination with Fosfomycin: A Novel Therapeutic Strategy against Multidrug-Resistant Pseudomonas aeruginosa*."* The Journal of Infectious Diseases. *DOI: 10.1093/infdis/jiz149.*

http://bit.ly/2JyRQqe

Study finds psychiatric diagnosis to be 'scientifically meaningless'

A new study, published in* Psychiatry Research, *has concluded that psychiatric diagnoses are scientifically worthless as tools to identify discrete mental health disorders.

The study, led by researchers from the University of Liverpool, involved a detailed analysis of five key chapters of the latest edition of the widely used Diagnostic and Statistical Manual (DSM), on 'schizophrenia', 'bipolar disorder', 'depressive disorders', 'anxiety disorders' and 'trauma-related disorders'.

Diagnostic manuals such as the DSM were created to provide a common diagnostic language for mental health professionals and attempt to provide a definitive list of mental health problems, including their symptoms.

The main findings of the research were:

- ***Psychiatric diagnoses all use different decision-making rules***
- ***There is a huge amount of overlap in symptoms between diagnoses***
- ***Almost all diagnoses mask the role of trauma and adverse events***
- ***Diagnoses tell us little about the individual patient and what treatment they need***

The authors conclude that diagnostic labelling represents 'a disingenuous categorical system'.

Lead researcher Dr Kate Allsopp, University of Liverpool, said: "Although diagnostic labels create the illusion of an explanation they are scientifically meaningless and can create stigma and prejudice. I hope these findings will encourage mental health professionals to think beyond diagnoses and consider other explanations of mental distress, such as trauma and other adverse life experiences."

Professor Peter Kinderman, University of Liverpool, said: "This study provides yet more evidence that the biomedical diagnostic approach in psychiatry is not fit for purpose. Diagnoses frequently and uncritically reported as 'real illnesses' are in fact made on the basis of internally inconsistent, confused and contradictory patterns of largely arbitrary criteria. The diagnostic system wrongly assumes that all distress results from disorder, and relies heavily on subjective judgments about what is normal."

Professor John Read, University of East London, said: "Perhaps it is time we stopped pretending that medical-sounding labels contribute anything to our understanding of the complex causes of human distress or of what kind of help we need when distressed."

The full study, entitled 'Heterogeneity in psychiatric diagnostic classification', can be found here https://doi.org/10.1016/j.psychres.2019.07.005

http://bit.ly/2LNeh2u

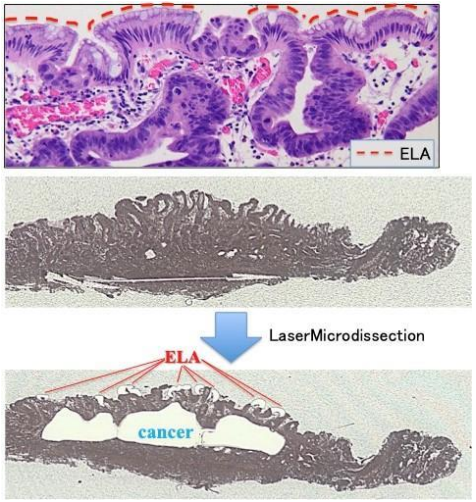
Scientists discover origin of cell mask that hides stomach cancer

A layer of cells that look like normal stomach lining on top of sites of stomach cancer can make it difficult to spot after removal of a Helicobacter pylori infection

A layer of cells that look like normal stomach lining on top of sites of stomach cancer can make it difficult to spot after removal of a Helicobacter pylori infection. In a recent study, researchers from Hiroshima University have uncovered the origin of this layer of cells: it is produced by the cancer tissue itself.

Helicobacter pylori (*H. pylori*) is a type of bacteria that lives in people's stomachs. To survive the harsh environment these bacteria can neutralize stomach acid. *H. pylori* is the leading cause of stomach cancer, one of the most common types of cancer which can have a low survival rate. The bacteria cause inflammation by injecting a toxin-like substance into mucosal cells that line the stomach. This destruction and regeneration of these cells can lead to the development of stomach cancer.

In this study Professor Kazuaki Chayama, from Hiroshima University Hospital, and his team found the origins of a strange layer of cells that was present on stomach cancer sites after treatment of *H. pylori*. This layer, called ELA (epithelium with low-grade atypia), resembled normal mucosal cells that line the stomach and acted like a mask to hide stomach cancer. Up to now, researchers were not sure where this layer came from.



The red dotted line indicates epithelium of low grade atypia (ELA) covering the surface of gastric cancer tissue in upper image. ELA (Red) and cancerous tissues (Blue) extracted by Laser Microdissection in lower image.
Hiroshima University

"It was very interesting scientifically to find that that cancer reoccurs even after eradicating causal bacteria." says Chayama.

A *H. pylori* infection is cured after a course of antibiotics that leave reddish depression in the stomach.

"*H. pylori* eradication affects the regeneration of gastric mucosa. After eradication there are many reddish depressions in the stomach, most of them are not cancer. It is difficult to identify the ELA mucosa from amongst the regular mucosa." explains Chayama.

The research group conducted a preliminary study on 10 patients after gastric operations and looked for this layer of cells. The ELA cells' DNA was intensively studied and was found to be identical to stomach cancer cells. ELA was concluded to come from the stomach cancer tissue itself.

These findings could mean that even after getting rid of *H. pylori* there is still a risk of stomach cancer for some patients. Stomach cancer can be difficult to spot due to its location and the fact that the disease can progress slowly. This is not helped by ELA that masks cancer after the causal factor is removed.

Chayama stresses that clinicians should be aware of this layer, so they don't miss potential sites of stomach cancer and that it is important for patients to continue having check-ups even after finishing treatment for *H. pylori*.

Details of the findings can be found in the team's paper, published in the Journal of Gastroenterology on June 13.

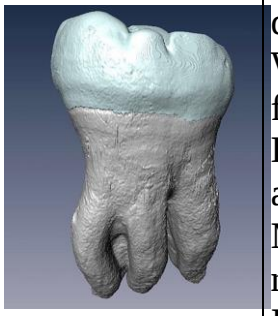
http://bit.ly/2XI8Clv

A rare dental trait lives on

Three-rooted molars in modern humans could have come from Denisovans.

Dyani Lewis reports.

A rare dental trait that is more common in Asian and Native American populations could have its origins in trysts with our archaic relatives, the Denisovans, according to new research.



Few people probably give much thought to the subterranean shape of the grinding teeth in their lower jaw, but palaeoanthropologists look to teeth – often the only surviving fossil remains of our ancient relatives – for clues to our prehistoric family tree.

***A three-rooted lower first molar and its corresponding jaw in a recent Asian individual.* Christine Lee (California State University, Los Angeles, CA).**

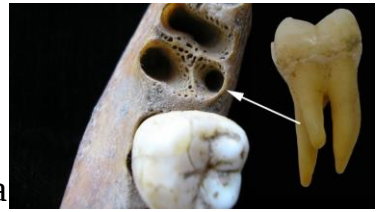
Recently, a lower jawbone found in a Tibetan cave was identified as being at least 160,000 years old and belonging to a member of the group known as the Denisovans. It bears a molar with three roots.

Another jawbone, found off the coast of Taiwan, and belonging to an archaic human – possibly a Denisovan – has a three-rooted molar, too.

Three-rooted molars are oddities in most modern dental practices. Molars generally have just two roots, but occasionally a third, smaller root grows.

In Europe and Africa, fewer than 3.5% of people have such teeth.

But rates upwards of 40% have been found in surveys of archaeological specimens from northern China and islands in the Bering Sea that were once part of a land bridge connecting Asia and North America



***A three-rooted lower second molar from a Denisovan found in Xiahe, China.* Jean-Jacques Hublin.**

Indeed, the high frequencies of three-rooted molars in these populations is a key feature that points to the Asian origins of Native Americans.

Surveys of modern Asian populations also have higher rates of the dental anomaly – up to nearly a third in some studies.

When a Denisovan genome was sequenced from a scrap of bone found in the Siberian Denisova cave, it became evident that Denisovans met and intermingled with our own prehistoric ancestors.

Modern-day populations across Asia, New Guinea and Australia retain snippets of Denisovan DNA in their genome.

In the case of present-day Tibetans, one snippet inherited from Denisovans helps them to live in the low oxygen environments of the Tibetan Plateau.

The new study, published in the journal *PNAS*, suggests that the three-rooted molars in modern-day people also derive from Denisovans.

"We now have very clear evidence that gene flow between archaic groups and *Homo sapiens* resulted in the transfer of identifiable morphological features," the authors write.

"The [three-rooted molar] is an Asian-derived character that we can definitively trace to Denisovans," they say.

Palaeoanthropologist Tanya Smith from Griffith University, who wasn't involved in the study, takes a more cautious view.

"It is a very interesting suggestion," she says, but adds that "without genetic evidence, I think it is premature to declare that this one fossil provides compelling morphological evidence of Denisovan admixture in Asian-derived populations".

Before concluding that three-rooted molars in modern humans came from Denisovans, scientists first need to be sure that most Denisovans had this trait, given that the trait can readily pop up due to mutation alone. That's a hard ask given the small number of Denisovan molars identified so far.

Identifying the genes that cause a third root in modern people's molars, and mapping that back to regions of the genome inherited from Denisovans would also make the link more air-tight, says Smith.

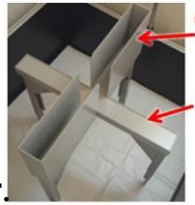
http://bit.ly/2xOj2Rn

Research shows that drinking Matcha tea can reduce anxiety

Researchers have shown anxious behavior in mice is reduced after consuming Matcha powder or Matcha extract

Many different countries have a tea culture, and Japanese Matcha tea is growing in popularity around the world. In Japan, Matcha has a long history of being used for various medicinal purposes. It has been suspected to have various beneficial effects to health, but relatively little scientific evidence supported that claim.

Now, a group of Japanese researchers from Kumamoto University has shown that anxious behavior in mice is reduced after consuming Matcha powder or Matcha extract. Its calming effects appear to be due to mechanisms that activate dopamine D1 receptors and serotonin 5-HT_{1A} receptors, both of which are closely related to anxious behavior.



Endpoint	Anxiety Level	
	High	Low
Time spent in the open arms (%)	↓	↑
Distance traveled in the open arms (cm)		

This test uses a mouse's natural preference to stay in dark and narrow places (closed arms). The longer a mouse spends in the open areas (open arms) and the more distance it travels, the more its anxiety level is thought to decrease.

Dr. Yuki Kurauchi

Matcha is the finely ground powder of new leaves from shade-grown (90% shade) *Camellia sinensis* green tea bushes. The tea (and food flavoring) is enjoyed around the world. In Japan, historical medicinal uses for Matcha included helping people relax, preventing obesity, and treatment of skin conditions. The researchers, therefore, sought to determine its various beneficial effects.

The "elevated plus maze" test is an elevated, plus-shaped, narrow platform with two walled arms that provide safety for the test subject, typically a mouse. It is used as an anxiety test for rodents with the idea that animals experiencing higher anxiety will spend more time in the safer walled-off areas. Using this test, researchers found that mouse anxiety was reduced after consuming Matcha powder or Matcha extract. In addition, when the anxiolytic activity of different Matcha extracts were evaluated, a stronger effect was found with the extract derived using 80% ethanol in comparison to the extract derived from only hot water. In other words, a poorly water-soluble Matcha component has stronger anxiolytic effects than a component that is easily soluble in water. A behavioral pharmacological analysis further revealed that Matcha and Matcha extracts reduce anxiety by activating dopamine D1 and serotonin 5-HT_{1A} receptors.

"Although further epidemiological research is necessary, the results of our study show that Matcha, which has been used as medicinal agent for many years, may be quite beneficial to the human body," said study leader, Dr. Yuki Kurauchi. "We hope that our research into Matcha can lead to health benefits worldwide."

*This research was published in the "*Journal of Functional Foods*" on 6 June 2019.*

[Source]

Kurauchi, Y. et al., *2019. Anxiolytic activities of Matcha tea powder, extracts, and fractions in mice: Contribution of dopamine D1 receptor- and serotonin 5-HT$_{1A}$ receptor-mediated mechanisms.* Journal of Functional Foods, *59, pp.301-308. Available at: http://dx.doi.org/10.1016/j.jff.2019.05.046.*

https://yhoo.it/2Jv7SYh

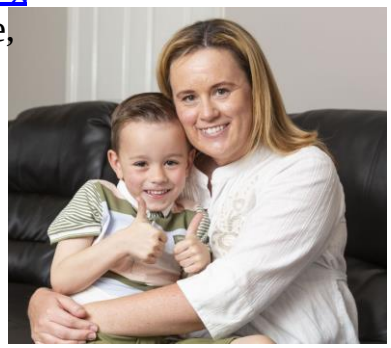
Woman's breast cancer discovered after son refuses to feed from breast with tumour

A mum has revealed how her one-year-old son discovered her breast cancer after refusing to breastfeed from the boob with the tumour.

Marie Claire Dorking

Joanne Carr, 37, breastfed her son, Dougie, since the day he was born without any problems, but after 14 months he started refusing to feed from her right side.

It prompted the mum-of-two to check her breast, where she found a pea-sized lump in her milk duct, which doctors later diagnosed as cancerous.



Joanne Carr's son Dougie, now 5, has been hailed by his mother as her 'guardian angel' **[Photo: Joanne Carr/SWNS]**

Joanne says she'd never have discovered the tumour if Dougie had not rejected her boob, which was likely a sign that something was blocking the duct or mis-shaping her breast.

Now cancer-free, Joanne, from Liverpool, has hailed her son as her "guardian angel" who saved her life.

"The doctor said it's very strange what Dougie did," she says. "He must have known somehow. He was looking out for me. "I know I wouldn't have checked if it wasn't for him."

Joanne, a nurse, gave birth to Dougie, now 5, in April 2014 at Liverpool Women's Hospital.

Everything was normal up until June 2015, when aged 14 months, Dougie's feeding habits suddenly changed and he stopped feeding from his mum's right breast. "He just wasn't interested anymore," Joanne explains. "He fed on the other one fine. I thought I might have a blocked duct or something. It was very strange."

Concerned, Joanne decided to check her breast for signs of any problems and found a small lump - immediately booking herself in to see the GP. She was given antibiotics and told to come back if it didn't go away - on her return, she was referred to specialists at the Royal Liverpool Hospital.

"I was really worried by this point," she says. "My gut feeling was that something wasn't right. I started to think the lump wasn't normal.

Following scans and a cell biopsy, Joanne was told she had an aggressive form of breast cancer known as invasive ductal cancer.

It's a common type of breast cancer which spreads to the milk ducts - the 'pipes' which carry milk from the milk-producing lobules to the nipple.

Though doctors didn't speculate on why it stopped Dougie feeding, Joanne says the 2cm lump was really close to her nipple, so she suspects Dougie felt it pressing against his mouth when he was feeding.

"I was diagnosed there and then," she continued. "They took me into a room and told me I had cancer. They said it was aggressive but treatable.

Joanne had eight rounds of chemotherapy until March last year, and lost all of her hair. But the lump shrank and surgeons removed

residual cancer cells in March 2018. Joanne was given the all-clear in April last year, and has been in remission for around a year.

Though she hasn't been able to return to work yet as she still suffers with joint pains resulting from her chemo, Joanne is hoping to start university next year to retrain to specialise in chemotherapy.

"I still think about how lucky I am to this day," she says.

"My attitude now is to just live life to the full. I owe my life to Dougie. He means the world to me."

https://wb.md/2GcFQyy

Antibiotics for Pneumonia: Short Course Is More Effective

For patients hospitalized with community-acquired pneumonia (CAP), more is not better when it comes to antibiotic therapy. In fact, it is likely worse, a study has shown.

Diana Phillips

Using data from a 43-hospital quality improvement consortium, Valerie M. Vaughn, MD, assistant professor of medicine at the University of Michigan Health System, Ann Arbor, and colleagues evaluated antibiotic prescriptions for the treatment of nearly 6500 adults with community-acquired pneumonia from 2017 to 2018.

More than two thirds of the patients received antibiotic courses that exceeded necessary durations. Typically linked to post-discharge oral stepdown therapy, the longer treatment courses did not improve patient outcomes, but did increase the risk for antibiotic-associated adverse events, the authors report in an article published online July 8 in *Annals of Internal Medicine*.

Antibiotics prescribed at discharge accounted for nearly half (49.5%) of total antibiotic days and nearly all (93.2%) of excess antibiotic days. That nearly all excess therapy resulted from antibiotics prescribed at discharge "highlights an urgent and unmet need for 'discharge stewardship,' or coordinated interventions to improve antibiotic prescribing at discharge," the researchers write.

"It is notable that only 18% of patients received 0 or 1 day of antibiotics after discharge despite it being expected for 61.6%. Instead, the clock seemed to restart, given that 44.7% received full antibiotic courses (5, 7, or 10 days) after discharge."

The researchers based their assessment of sufficient antibiotic therapy on national guidelines that recommend antibiotic treatment duration on the basis of pneumonia classification, organism, and time to clinical stability.

According to these criteria, the expected antibiotic duration for patients with CAP is at least 5 days (longer in cases where time to clinical stability was longer). The expected treatment duration for patients with healthcare-associated pneumonia (HCAP), *Staphylococcus aureus*, or a nonfermenting gram-negative bacillus is at least 7 days, the authors note.

Of the 6481 patients (median age 70.2 years) included in the analysis, 4747 had CAP and 1734 had HCAP. More than half (57.4%) had severe pneumonia, and 26.4% and 7.5%, respectively, had concurrent chronic obstructive pulmonary disease or a congestive heart failure exacerbation.

With respect to treatment duration, 67.8% of patients received excessive courses of antibiotics, including 71.8% of patients with CAP and 56.6% of patients with HCAP.

Among those with CAP and HCAP, respectively, the median antibiotic treatment duration was 8 days and 9 days, and the respective median excess duration was 2 days and 1 day. "This led to 2526 excess days of treatment per 1000 patients hospitalized with pneumonia," the authors write.

The excess treatment duration is consistent with observations from prior studies and was not explained by differences in clinical stability or disease severity. "Indeed, most patients with CAP (86.7%) stabilized quickly and thus were candidates for 5 days of

therapy, yet fewer than 24.7% received 5 (±1) days of therapy," the authors note.

Further, given that providers appeared to treat CAP and HCAP with similar durations of antibiotics, misdiagnosis of CAP as HCAP does not explain the excess treatment duration in patients with CAP. "Providers may not differentiate between CAP and HCAP because of the national movement away from the latter term or the difficulty with risk stratification at the point of care," the authors suggest.

In an analysis looking at characteristics associated with excess treatment duration, patients with sputum production were 7% more likely to have longer-than-needed antibiotic courses (rate ratio, 1.07; 95% confidence interval [CI], 1.02 - 1.13).

Multivariable analyses linked having a respiratory culture or a nonculture diagnostic test, a longer hospital stay, high-risk antibiotic use in the prior 90 days, and CAP with higher rates of excess treatment. Not having total treatment duration documented at discharge was also linked to excess treatment.

"It is unclear whether hospitals with better documentation are more likely to appropriately treat patients (for example, due to stewardship initiatives) or whether documentation itself triggers a mindful moment that leads to improved treatment duration," the authors write.

"Regardless, documentation is a core stewardship strategy, and hospitals should strive to improve it, particularly at discharge."

Academic hospitals also had lower rates of excess treatment, a finding the researchers say merits additional exploration. "Academic hospitals have more institutional support for stewardship and follow more of the Centers for Disease Control and Prevention's recommendations, which may explain this difference," they hypothesize.

They note, however, that differences in antibiotic stewardship interventions related to treatment duration might contribute to variation across hospitals.

In adjusted analyses, excess treatment duration did not improve rates of 30-day mortality, readmission, or emergency department visits, but it did increase the likelihood of adverse events associated with antibiotic treatment.

Among patients who were contacted by telephone 1 month post discharge, the odds of a patient-reported adverse event were 5% (CI, 2% - 8%) higher for each excess day of treatment. The most common adverse events were diarrhea, gastrointestinal distress, and mucosal candidiasis.

"This adds to growing literature that short-course therapy in pneumonia is safe and that longer durations are not just unnecessary but potentially harmful," the authors write. "Therefore, reducing excess treatment durations should be a top priority for antibiotic stewardship nationally."

The study findings have research and policy implications, the authors explain. "Specifically, the next iteration of CAP and HCAP guidelines should explicitly recommend (rather than imply) that providers prescribe the shortest effective duration, similar to recommendations made in the hospital-acquired and ventilator-associated pneumonia guidelines," they note.

Given that excess antibiotic prescribing continues despite national efforts to contain it, "future improvement may be more effective by focusing on discharge stewardship, including antibiotic documentation at discharge, and on patients with high rates of overuse, such as those with CAP," the authors recommend.

They also advocate for the incorporation of antibiotics prescribed at discharge into national use metrics.

Acknowledging "change is scary and medicine is a conservative profession," the authors of an accompanying editorial stress that

"we must overcome inertia and tradition and change practice when compelling evidence becomes available."

Doing so is essential in order to "live up to the expectations that our patients have for us and that we have for one another," write Brad Spellberg, MD, of the University of Southern California Medical Center in Los Angeles, and Louis B. Rice, MD, of Warren Alpert Medical School of Brown University in Providence, Rhode Island.

"After dozens of [randomized controlled trials] and more than a decade since the initial clarion call to move to short-course therapy, it is time to adapt clinical practice for diseases that have been studied and adopt the mantra 'shorter is better.'"

The findings of the current study add weight to this mantra, the editorialists write. "The cumulative evidence indicates that each day of antibiotic therapy beyond the first confers a decreasing additional benefit to clinical cure while increasing the burden of harm in the form of adverse effects, superinfections, and selection of antibiotic resistance," they state.

"The question is, where do those 2 competing trends cross, such that continuing tilts the balance to harm over benefit? For community-acquired pneumonia, the data indicate net harm somewhere around 3 to 5 days of therapy for most patients."

In the face of continued underuse of short-term antibiotic therapy, the editorialists stress, "it is time for regulatory agencies, payers, and professional societies to align themselves with the overwhelming data and assist in converting practice patterns to short-course therapy."

Support for the Michigan Hospital Medicine Safety Consortium is provided by Blue Cross Blue Shield of Michigan (BCBSM) and Blue Care Network as part of the BCBSM Value Partnerships program. Multiple study coauthors report receiving support during the conduct of the study; see study disclosures for full details. Rice reports relationships with Zavante Pharmaceuticals and Macrolide, outside the submitted work. Spellberg reports relationships with Alexion, Paratek, TheoremDx, Acurx, Shionogi, and Merck, as well as other support from Motif, BioAIM, Mycomed, and ExBaq, outside the submitted work.

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https://go.nature.com/2JDqWT4

An early dispersal of modern humans from Africa to Greece

Analysis of two fossils from a Greek cave has shed light on early hominins in Eurasia. One fossil is the earliest known specimen of Homo sapiens found outside Africa; the other is a Neanderthal who lived 40,000 years later.

Eric Delson

The origin and early dispersal of *Homo sapiens* has long been a subject of both popular and scholarly interest[1]. It is almost universally agreed that *H. sapiens* (modern humans) evolved in Africa, with the earliest known fossil representatives of our species dated to around 315,000 years ago in Morocco (at a site called Jebel Irhoud)[2] and approximately 260,000 years ago in South Africa (at Florisbad)[3]. Stone tools comparable to those found with both of these fossils have been excavated in Kenya (at Olorgesailie)[4] and dated to about 320,000 years ago. Writing in *Nature*, Harvati *et al*.[5] describe their analysis of a fossil from Apidima Cave in southern Greece that they report to be an early modern *H. sapiens* at least 210,000 years old. This fossil is the oldest known modern human in Europe, and probably in all of Eurasia, and is more than 160,000 years older than the next oldest known European fossil of *H. sapiens*[6].

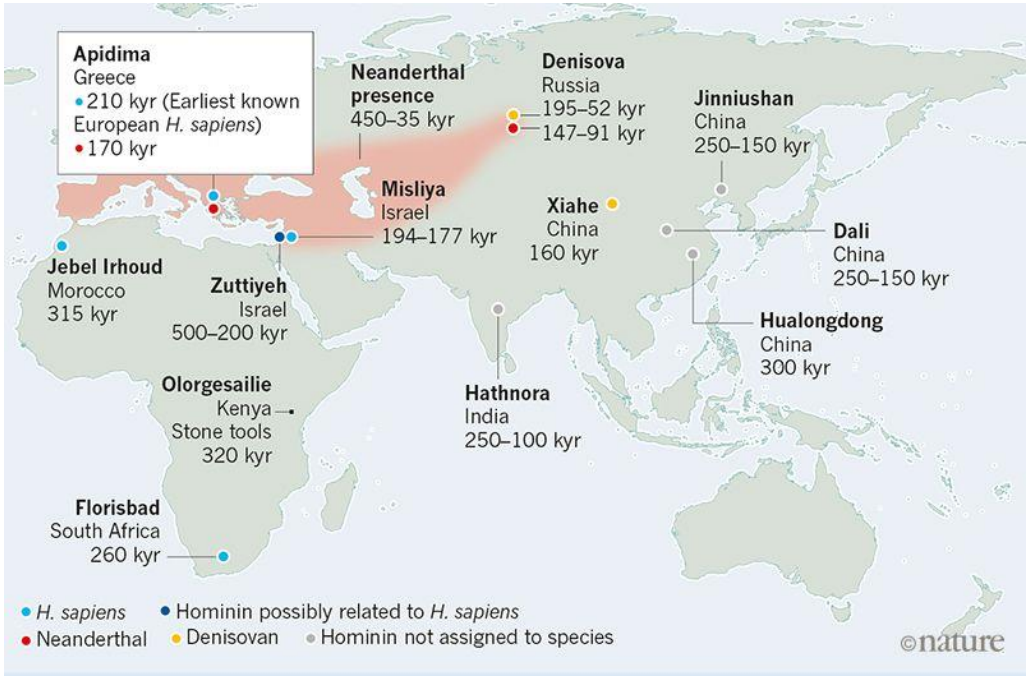
The Apidima Cave complex was excavated in the late 1970s. Two partial crania (skulls without the lower jaw), named Apidima 1 and Apidima 2, were recovered in a single block of a type of rock called breccia. Neither fossil was previously described in detail. Apidima 2 includes the facial region of the skull and had been identified as a Neanderthal[7]. Apidima 1 consists of only the back of the skull and had not been previously allocated definitively to a species. Harvati and colleagues used computed tomography to scan the fossils, and generated a 3D virtual reconstruction of each specimen. They

analysed each fossil to assess aspects of its shape, and thus to determine the fossils' similarity to those of other species.

Apidima 2 is badly damaged owing to previous breakage and distortion. Analyses of all four generated reconstructions of the fossil were consistent with it being an early Neanderthal. Apidima 1 is also damaged, but the specimen is not too badly distorted, so mirroring its right and left sides yielded a good reconstruction. The authors' extensive comparative analysis indicates that this fossil is an early member of *H. sapiens*. The posterior part of the cranium is rounded like that of *H. sapiens*, and it lacks classic Neanderthal features, such as the distinctive occipital 'chignon' — a bulge at the back of the skull that is shaped like hair tied in a bun.

Earlier dating[8] of a fragment of Apidima 2 using a method called uranium-series analysis indicated a minimum age of around 160,000 years. Harvati and colleagues report a more extensive set of uranium-series dating analyses, which surprisingly reveal that Apidima 1 and Apidima 2 are of different ages, even though they were found in close proximity. Apidima 2 is around 170,000 years old — well within the age range of other Neanderthal fossils found across Europe (Fig. 1). Apidima 1 is dated to be at least 210,000 years old, which is much older than any other widely accepted *H. sapiens* fossils found outside Africa.

Harvati *et al*.[5] present their analyses of two fossil skulls from Apidima Cave in Greece. They report that the fossil Apidima 1 is an *H. sapiens* specimen that is at least 210,000 years old, from a time when Neanderthals occupied many European sites. It is the earliest known example of *H. sapiens* in Europe, and is at least 160,000 years older than the next oldest *H. sapiens* fossils found in Europe[6] (not shown). Harvati and colleagues confirm that, as previously reported[7], Apidima 2 is a Neanderthal specimen, and they estimate that it is at least 170,000 years old. The authors' findings, along with other discoveries of which a selection is shown here, shed light on the timing and locations of early successful and failed dispersals out of Africa of hominins (modern humans and other human relatives, such as Neanderthals and Denisovans). kyr, thousand years old.



Some key early fossils of Homo sapiens and related species in Africa and Eurasia.

This finding reveals that at least two species of hominin (humans and human relatives from the branch of the family tree after our split from chimpanzees) inhabited southeastern Europe approximately 200,000 years ago. The discovery of an *H. sapiens* fossil in Apidima raises questions about what happened to this population. Given that this *H. sapiens* existed at a time when there is substantial evidence for a Neanderthal presence at other European sites, was it part of a population that was unable to compete successfully with Neanderthals, especially in the unstable climate of that time? Perhaps one or more times, the two species

replaced each other as the main hominin group present in this region.

Such patterns of replacement characterize the distribution of modern humans and Neanderthals in the Levant region of the Middle East between 250,000 and 40,000 years ago. *Homo sapiens* replaced Neanderthals across Europe between approximately 45,000 and 35,000 years ago[6], eventually giving rise to the ancestral population of Europeans alive today[1]. This evidence from Apidima, along with other discoveries, demonstrates that, on more than one occasion, modern humans kept pushing north and westwards from Africa and the Levant into Europe. Rather than a single exit of hominins from Africa to populate Eurasia, there must have been several dispersals, some of which did not result in permanent occupations by these hominins and their descendants.

There is immense interest in understanding the timing and location of both the successful and failed dispersals of hominins (including modern humans) from Africa. The first hominin dispersal out of Africa is thought to have been when members of the species *Homo erectus* exited some 2 million years ago. The second wave of departures occurred when the ancestral species that eventually gave rise to Neanderthals moved into Europe around 800,000–600,000 years ago.

A third group of migrations out of Africa were those of *H. sapiens*. Many key fossil discoveries from Israel document early examples of these dispersals. A fossil that includes the forehead region of a skull found there, at a site called Zuttiyeh, is dated to between 500,000 and 200,000 years ago, and analysis of the fossil's shape indicates that it is either an early Neanderthal or from a population ancestral to both Neanderthals and *H. sapiens*[9]. The Zuttiyeh fossil shows similarities to the Florisbad and Jebel Irhoud fossils[9], and an earlier study[10] suggested that Zuttiyeh might be an early *H. sapiens*. This is a view that I favour, given its similarity to the shape of the forehead of the Florisbad fossil. Future analysis might reveal that Zuttiyeh is an even older modern human than Apidima 1; nevertheless, it is not from Europe.

A jaw of an early modern human from Misliya Cave in Israel has been dated to approximately 194,000–177,000 years ago[11]. Other early modern human fossils have been found at Skhul and Qafzeh in Israel, dated to around 130,000–90,000 years ago[12]. All of these early Eurasian human fossils seem to represent what might be called 'failed' dispersals from Africa — they reached the Middle East and southeastern Europe, but did not persist in these regions. There is evidence that these populations were replaced at these or neighbouring sites by Neanderthals.

Farther east, fossils of early *H. sapiens* in Asia, dated from between at least 90,000 and 50,000 years ago, have been found in regions ranging from Saudi Arabia to Australia[13]. These Asian fossils, like the European specimens of *H. sapiens* from between 50,000 and 40,000 years ago, might have come from populations that achieved persistent, successful dispersals and contributed to the ancestry of some living humans.

Given that the Apidima 1 fossil and those from Misliya and Zuttiyeh are only partial skulls, some might argue that the specimens are too incomplete for their status as *H. sapiens* to be certain. Could molecular approaches be used to determine the species they are from? It is not always possible to recover DNA from ancient fossils. However, analysing ancient proteins preserved in fossils, a method termed palaeoproteomics, is starting to be used to identify species (see go.nature.com/2xkosom). Compared with analysis of ancient DNA, palaeoproteomics requires less specialized handling of the fossil to prevent contamination. It was recently used[14] to analyse a fossilized jaw found in China that is approximately 160,000 years old, enabling the specimen to be

identified as an enigmatic hominin called a Denisovan, whose scarce fossils have also been found at Denisova Cave in Siberia.

Perhaps palaeoproteomics can be used to verify the identity of the Apidima fossils. It might also be possible to apply this method to contemporaneous fossils from Asia (estimated to be 300,000–150,000 years old) that have not yet been definitively assigned to a species. These fossils are of interest for their potential to reveal how many hominin species might have lived during this time. Perhaps some of them are also *H. sapiens*, although I doubt it. Among the most complete of these specimens are crania from India at a site called Hathnora[15], and from China at Dali[16], Jinniushan[16] and Hualongdong[17]. Until such fossils are studied using palaeoproteomics, analyses such as those of Harvati and colleagues provide our best handle on the complex history of our species and our close relatives as these populations dispersed out of Africa — from the early, unsuccessful dispersals to the migrations that eventually succeeded.

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http://bit.ly/30uNsnW

Opinion: Test Brain-Reviving Technology in Infants First

If a system tested in decapitated pigs ever gets to human clinical trials, neuroscientific and ethical reasons point to testing babies before adults.

John D. Loike, Alan Kadish

A recent *Nature* paper describing an artificial blood perfusion used in an attempt to restore brain function after pigs were decapitated has generated great discussions in the medical, scientific, and bioethical academic arenas. Although the study's results showed marked improvement and restoration in many cellular and molecular functions within the brain, the artificial blood perfusion system, called BrainEx, failed to restore global brain activity associated with awareness, perception, or other higher-order brain functions whose absence are intrinsic to defining death.

Before such a system were to be applied to, say, revive brain activity in stroke patients, there are three scientific questions that remain to be addressed from the researchers' study. First is whether their failure to restore global brain activity was due to the fact that the researchers waited up to four hours after decapitation before hooking up their system to the decapitated pigs. In many cases of stroke, patient recovery is dependent on the fastest method to initiate treatment. Would BrainEx's system be more efficient if the treatment began after one hour?

Second, they only claimed to "treat" the pigs for about 10 hours. As we know, neuronal recovery is slow, and longer treatment times may be more beneficial in applying this system to human stroke victims.

The third question relates to the age of the pigs used in their studies. The medical definition of death has been guided by the Harvard criteria established in 1968. Briefly, these criteria included unreceptivity, unresponsiveness, no movements or breathing, no reflexes, and a flat electroencephalogram (repeated after 24 hours with no change). To date, there has never been a case in which the Harvard criteria of brain death were correctly diagnosed and the adult patient subsequently recovered with any high level neurological function. In other words, the criteria accurately discern alive from dead—at least among adults.

There are cases of infants who had fit the Harvard criteria of death, and yet had awoken from their coma. In Israel, physicians rarely declare an infant under two months of age as brain dead because some of these infants recover from their comas.

These cases suggest that scientists should examine the use of BrainEx on newborn piglets rather than adult pigs as they did in their study. If successful, the first clinical applications should be in

comatose infants—and not adults—to potentially reverse their comas.

There is another benefit to testing this technology in infants: the ethical challenge of getting permission could be minimized. Parents have the autonomous right to approve the clinical testing of this technology on their children. This avoids the issue of how to devise a clear and logical method to obtain patient consent (before they go into a coma) to allow for clinical testing of BrainEX in adult patients.

If clinical testing on infants proves to be efficacious, then it would be logical to expand the clinical testing and examine whether BrainEx improves brain function in adult ischemic stroke victims. From a consent perspective, one could suggest an opt-in type of consent policy as is done with organ donation so that individuals would grant automatic approval for this technology, provided that they did not refuse to participate when they completed their healthcare directives.

If this technology could be developed to enhance brain function in patients who fit the criteria for being brain dead, the medical field will face a new ethical challenge: whether the Harvard criteria's definition of death is more than just "irreversible intraneural functions."

History has taught us that as technologies develop, the definition of death may need to be revised or modified. The traditional criteria of "pulselessness" and apnea (spontaneous respiration) are no longer recognized as defining death because mechanical ventilation and organ transplantation developed in the 1950s changed everything, enabling these patients exhibiting these signs to survive.

The clinical definition of death still remains controversial. Daniel Shewmon of the University of California, Los Angeles, has reported cases showing that the bodies of patients diagnosed as brain dead do not necessarily "disintegrate," as long as they are provided with mechanical ventilation and tube feedings.

Such patients may "retain integrated functioning, including growth and development, wound healing, infection fighting, and gestation of a pregnancy, such that some of these patients may continue to have biological survival for many years."

As new technologies develop, it will be important to define death with an open mind because millions of families rely on physicians to make "dead certain" that their patients have been irreversibly deceased.

http://bit.ly/2XKt6dq

Exoplanet evolution: Astronomers expand cosmic 'cheat sheet'

To understand where exoplanets are in their own evolution, astronomers can use Earth's biological milestones as a Rosetta stone.

By Blaine Friedlander

Cornell astronomers have reached into nature's color palette from early Earth to create a cosmic "cheat sheet" for looking at distant worlds. By correlating tints and hues, researchers aim to understand where discovered exoplanets may reasonably fall along their own evolutionary spectrum.

"In our search to understand exoplanets, we're using the early Earth and its biological milestones in history as a Rosetta stone," said Jack O'Malley-James, a research associate at Cornell's Carl Sagan Institute.

O'Malley-James has co-authored "Expanding the Timeline for Earth's Photosynthetic Red Edge Biosignature" with Lisa Kaltenegger, professor of astronomy and director of the Sagan Institute.

The paper was published July 9 in the Astrophysical Journal Letters.

"If an alien had used color to observe if our Earth had life, that alien

would see very different colors throughout our planet's history – going back billions of years – when different life forms dominated Earth's surface," Kaltenegger said.

"Astronomers had concentrated only on vegetation before, but with a better color palette, researchers can now look beyond a half-billion years and up to 2.5 billion years back on Earth's history to match like periods on exoplanets," she said.

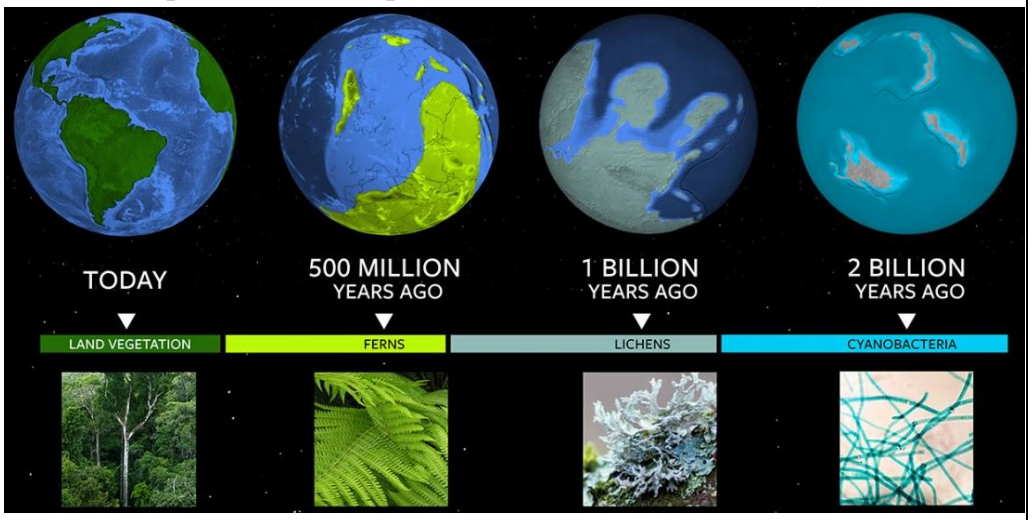


Illustration by Wendy Kenigsberg/Cornell Brand Communications

For the last half-billion years – roughly 10% our planet's lifetime – chlorophyll, present in many familiar forms of plant life such as leaves and lichen, has been the key component in Earth's biosignature.

But other flora, such as cyanobacteria and algae, are much older than land-based vegetation, but their chlorophyll-containing structures leave their own telltale signs on a planet's surface.

"Scientists can observe surface biosignatures beyond vegetation on Earth-like exoplanets by using our own planet as the key for what to look for," O'Malley-James said.

"When we discover an exoplanet, this research gives us a much wider range to look back in time," Kaltenegger said.

"We extend the time that we can find surface biota from 500 million years (widespread land vegetation) to about 1 billion years ago with lichen and up to 2 or 3 billion years ago with cyanobacteria."

O'Malley-James and Kaltenegger modeled spectra of Earth-like exoplanets with different surface organisms that use chlorophyll. Scenarios might include where a few organisms dominate the entire surface of an Earth-like planet, such as the fictional, swampy world of Dagobah, home to Yoda in the "Star Wars" movies.

Lichens (a symbiotic fungal and photosynthetic partnership) may have colonized Earth's land masses some 1.2 billion years ago and would have painted Earth in sage to mint green colors.

This coverage would have generated a "nonvegetative" photosynthetic red-edge signature (the part of the spectrum that helps keep plants from getting burned by the sun) before the biota of today's modern Earth took over.

O'Malley-James and Kaltenegger said that cyanobacteria – like surface algae – may have been widespread between 2 billion and 3 billion years ago, producing a photosynthetic red edge, and could be found on other Earth-like exoplanets.

This research show that lichens, algae and cyanobacteria could have provided a detectable surface red edge feature for a younger Earth, long before land vegetation became widespread 500 million to 750 million years ago, O'Malley-James said.

"This paper expands the use of a photosynthetic red edge surface bio-feature to earlier times in Earth's history," he said, "as well as to a wider range of habitable extrasolar planet scenarios."

Funding for this research came from the Simons Foundation.

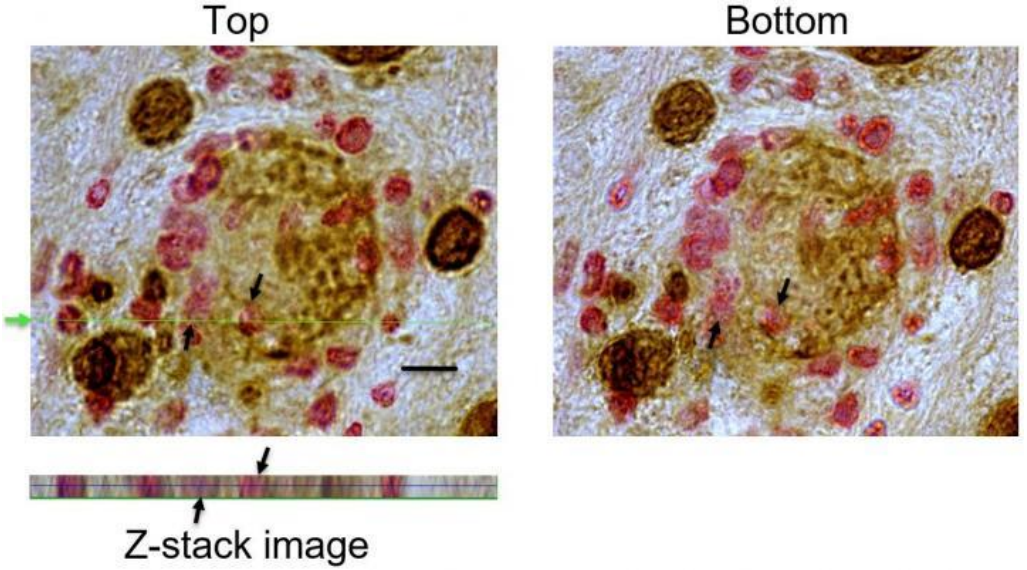
http://bit.ly/30sRQ6M

New evidence shows cytotoxic T cells can identify, invade, and destroy targets of large mass like Toxoplasma gondii tissue cysts

Previously unappreciated capability of CD8+ cytotoxic T cells to penetrate a large target opens avenues to destroy solid cancers, according to a new study in The American Journal of Pathology

Philadelphia - CD8+ cytotoxic T lymphocytes can kill host cells infected with various microorganisms as well as single individual cancer cells through direct cell-to-cell contact, but their ability to destroy a target of large mass remains unexplored. A study in *The American Journal of Pathology*, published by Elsevier, provided novel evidence on the capability of the immune system to eliminate large parasite-filled cysts associated with chronic *Toxoplasma gondii* (*T. gondii*) infection by utilizing the aggressive invader activity of cytotoxic T cells. They may also prove effective for attacking other sizable targets including solid cancers.

"The present study provided clear evidence that the immune system has the capability to attack and eliminate the tissue cysts of *T. gondii*. This sheds light on the possibility of developing a vaccine to activate these invasive cytotoxic T cells to prevent establishment of chronic infection with this parasite. This vaccine may also be applied to individuals chronically infected with *T. gondii* to eradicate existing tissue cysts of the parasite and cure this widespread chronic infection. This study also suggests the possibility of developing a new cancer immunotherapy that can be used to eliminate various types of solid cancers by activating the invasive cytotoxic T cells that specifically attack and penetrate into the target cancers," explained lead investigator Yasuhiro Suzuki, PhD, of the Department of Microbiology, Immunology and Molecular Genetics, University of Kentucky College of Medicine, Lexington, KY, USA.



***Three-dimensional images of* T. gondii *cysts containing CD8+ T cells that had fully invaded into the cysts detected in the brains of infected nude mice that received a transfer of CD8+ immune T cells. Sections (4 um thick) of their brains were applied for immunohistochemical staining for* T. gondii *(brown) and CD3, the T cell marker, (red), and Z-stack images were obtained using light microscopy. Upper panels show the images taken at the top and bottom of the histological section. The presence of the T cells (arrows) can be seen in both images at the top and bottom of the section. The lower panel shows a 3-dimensional image generated from the Z-stack images of the cyst at the cut-line indicated by a green arrow and line. These Z-stack images demonstrate the presence of the T cells (arrows) all the way through the sections. Scale = 10 um. Credit:* The American Journal of Pathology**

One third of the world's human population as well as many other warm-blooded animals are currently infected with *T. gondii*. Although *T. gondii* infection usually produces few, if any obvious symptoms, the latent infection can erupt into a serious and occasionally fatal illness, toxoplasmic encephalitis, particularly in individuals with weakened immunity such as patients with cancer,

HIV/AIDS, or organ transplants. In addition, recent epidemiological studies have reported increased incidence of brain cancers in *T. gondii*-infected individuals. Chronic infection is associated with the formation of cysts that can often grow to the size of more than 50 ?m in diameter filled with hundreds to thousands of the parasites, which are situated most often in the brain, eyes, and striated muscle including the heart. A common cause of *T. gondii* infection is the consumption of tissue cysts in raw or undercooked meat of infected animals, such as pork and mutton.

In this study, scientists investigated the effects of an injection of CD8+ immune T cells purified from the spleens of chronically infected mice, into mice that had ingested multiple *T. gondii* cysts. A few days after the T cell injection, numbers of *T. gondii* cysts fully invaded by the T cells were found in the brains of the mice that received the injection of the immune T cells.

The T-cell-invaded cysts displayed structural signs of deterioration and destruction. Within these deteriorated cysts, granular structures appeared intensely positive for granzyme B, a major cytotoxic protein secreted by cytotoxic T cells. These granular structures were detected in association with *T. gondii* bradyzoites (the slowly-multiplying encysted form of the parasite associated with the dormant stage of infection). Furthermore, the bradyzoites within the destroyed cysts were located within accumulated scavenger cells, including microglia and macrophages. The investigators also showed that perforin (a protein, released by killer cells of the immune system, which destroys targeted cells by creating pore-like lesions in their membranes) was necessary for the CD8+ T cell invasion and cyst elimination process.

In addition to becoming a powerful weapon against *T. gondii* infection, the investigators suggest the same principles can be used to attack solid cancers. "The invasion of the T cells into tumors could induce an infiltration of large numbers of phagocytic cells capable of attacking the cancer cells as was observed against *T. gondii* cysts," noted Dr. Suzuki. "An effective activation of the penetrating capability of cytotoxic T cells, which specifically recognize the target solid cancers, will most likely become a powerful therapeutic approach applicable to various types of solid cancers."

http://bit.ly/2GdPBwJ

Mysterious illness that paralyzes healthy kids prompts plea from CDC

CDC wants more data and faster reporting before the next wave of cases hits.

Beth Mole

After a record number of cases in 2018 of a rare, puzzling illness that causes paralysis in otherwise healthy kids, officials at the Centers for Disease Control and Prevention are urging doctors to hasten reporting and boost data collection before the next big wave of illness hits—which is expected in 2020.

The illness is called acute flaccid myelitis, or AFM, and is marked by the sudden onset of limb weakness (usually upper limb), paralysis, and spinal lesions seen on MRI scans. It most often occurs in children. It’s unclear what causes it and why instances are increasing—though officials suspect that a relative of poliovirus is involved. There is no specific treatment, and doctors can’t predict how affected patients will fare; some regain muscle strength and recover full use of paralyzed limbs over time, some don’t. In rare cases, AFM can cause respiratory failure and death.

AFM first gained attention in 2014, when health officials noted a spike in the polio-like condition nationwide and began carefully documenting cases. Since then, health officials have seen a distinct every-other-year pattern to the illness.

There were 120 recorded cases across 34 states that first year in 2014, followed by just 22 in 2015. Then 149 cases across 39 states and Washington, DC, in 2016, and a drop to 35 cases in 2017. In 2018, the CDC confirmed 233 cases in 41 states, the largest number yet. Of those, nearly all affected people ended up hospitalized, with 60% admitted to intensive care and 27% needing respiratory support. The average age of the patients was 5 years old.

So far, 2019 is looking like a typical off-year, with just 11 cases in eight states halfway through. That said, in each peak year, AFM cases tend to cluster in late summer to fall, generally between August and November.

Viral suspect

The first burst of AFM cases in 2014 coincided with a nationwide outbreak of Enterovirus D68 (EV-D68), which typically causes only respiratory illnesses. Experts immediately suspected a connection between AFM and EV-D68. For one thing, enteroviruses were already linked to paralytic illnesses—poliovirus is a type of enterovirus. Enterovirus type 71 (EV-A71), which is a main cause of hand-foot-and-mouth disease, has also been linked to a polio-like illness.

Moreover, researchers in California found evidence of EV-D68 infections in some of the 2014 AFM cases they closely examined. And they reported that the damage they saw in some AFM patients' spinal cords was "consistent with spinal motor neuron injury from direct viral invasion of tissue, which is characteristic of poliovirus and enterovirus A71 infections."

To date, more than 90% of those with AFM report having a mild respiratory infection or fever right before the onset of limb weakness. In the 2018 cases, limb weakness first appeared an average of just five days after the start of a mild viral illness. And enteroviruses—like some other viral respiratory infections—often peak when AFM does, in late summer to fall.

Collectively, the circumstantial evidence points to the idea that in some children, respiratory infections from enteroviruses spill over into motor neurons in the spinal cord and cause devastating damage.

Feeble data

But while that hypothesis seems like a slam-dunk, the evidence to back up the connection between EV-D68 and AFM has been maddeningly hard to get. From the 233 confirmed AFM cases in 2018, health officials were able to collect just 123 respiratory samples. Of those, only 30 tested positive for EV-D68, while ten others were positive for EV-A71 and 14 were positive for other enterovirus infections. Likewise, officials collected 74 samples of cerebrospinal fluid from the 233 cases, and only one tested positive for EV-D68. One other sample tested positive for EV-A71.

Researchers at the CDC suspect that the problem is either that the viruses simply aren't shedding into spinal fluid or that doctors are collecting spinal fluid samples too late, days after the viral culprit is gone and the damage is done. That's in part why the CDC is calling on doctors to notify health departments of suspected cases as soon as they can. The main purpose of the call to action is to prompt doctors to speed up their reporting, Dr. Tom Clark tells Ars. Clark is the deputy director of the CDC's Division of Viral Diseases. Faster reporting could help officials collect more samples faster, as well as try out additional tests.

Beyond fingering a specific virus behind AFM cases, there are still plenty of other questions to answer. Namely, why are cases suddenly popping up now, or in these two-year cycles, or in certain, otherwise healthy children, and how is AFM best treated? Investigators have found evidence of EV-D68 infections in sets of siblings, while only one sibling develops AFM, hinting at some unknown, individual-specific risk factors. Doctors have come up with interim treatment recommendations, including physical

therapy, steroids, and antiviral medications, but it's unclear if they work.

Remaining riddles

Answers to these questions are far more speculative. For instance, though Clark tells Ars that the current thinking is that AFM is caused by a virus directly infecting and damaging spinal cord tissue—in part because it seems that damage occurs so quickly after the onset of a viral infection—there's also the possibility that the damage is caused by a berserk immune response.

This is thought to be the cause of other paralytic conditions linked to viral infections, namely Guillain-Barré Syndrome (GBS). As in AFM, GBS usually strikes after a viral infection, either a respiratory or gastrointestinal illness. Upticks in GBS cases were noted in the wake of recent Zika outbreaks, for instance. Unlike AFM, GBS tends to start with weakness in the legs and back and progress toward paralysis relatively slowly, over weeks rather than days.

Intriguingly, a report from 2006 suggested that a single virus—West Nile virus—was associated with both AFM cases and a GBS-like syndrome in a cluster of 32 patients in Colorado. (West Nile virus infects birds in the US and spreads to humans via mosquito bites, typically causing asymptomatic infections or ones with vague viral symptoms, such as fever and body aches.)

Another odd ripple comes from a 2003 report from an international team of researchers who noted that a cluster of eight cases of AFM during an outbreak of hand-foot-and-mouth disease (caused by EV-A71) in Malaysia also seemed to be associated with a second virus, an unusual adenovirus. This led them to wonder if the overlap or interactions of the viruses had something to do with the severe illness. "Whether the epidemic of EV71-associated HFMD was coincidental or whether the severe presentation was due to an interaction between the 2 viruses is not certain… Clearly, more detailed prospective clinical, virological, and pathophysiological studies are needed to investigate the possible interaction between enteroviruses and adenoviruses and the patterns of disease that they cause," they concluded.

For now, Clark tells Ars that it's too early to speculate on all the factors that may be behind the current trend in AFM cases in the US. Cases are simply too few, with too little data to say much for certain. He and others at the CDC are hopeful that speedier reporting and closer surveillance from doctors will yield insight soon.

In the meantime, Clark recommends that parents be vigilant as well. "Colds are common and AFM is rare," he says. But if a child suddenly develops weakness in a limb, take it seriously and get it checked by a doctor, he says.

http://bit.ly/2XLTnmH

Open data linked to higher citations for journal articles

Studies that provide access to underlying data are cited 25% more often than those that don't

By Rebecca Trager

Research papers that make their underlying data openly available are significantly more likely to be cited in future work, according to an analysis led by researchers at the Alan Turing Institute in London that has been published as a preprint. The study, which is currently under peer review, examined nearly 532,000 articles in over 350 open access journals published by Public Library of Science (PLoS) and BioMed Central (BMC) between 1997 and 2018, and found those that linked directly to source data sets received 25% more citations on average.

'We found half a million papers were published by these open access journals over the study period, and one-third included data availability statements, and those papers were then examined to see if there was a citation benefit,' explains Iain Hrynaszkiewicz, head

of data publishing at the publisher Springer Nature. The results clearly point to a citation advantage, of up to 25.36%, for articles that include a link to a repository via a URL or other permanent identifier. This is consistent with the results of previous smaller studies that focussed specifically on gene expression microarray or oceanographic data.

This new evidence can better justify the increased costs associated with the introduction of stronger research data policies, Hrynaszkiewicz and colleagues say. They controlled for several factors known to affect citations, such as the number of authors and references, as well as author reputation.

'By making both the research papers and the underlying data publicly available, the authors are increasing their visibility, and that leads to data reuse and then more citations,' says Hrynaszkiewicz. He also points out that more successful, visible research groups might have more resources at their disposal to share underlying data and code.

New incentives for open data

Peter Suber, who directs Harvard University library's office for scholarly communication and was not involved with the study, says the conclusions are significant because they could prompt journals to create new incentives for authors to open their datasets and link to them from within articles.

'Many journals have open data policies, but some have trouble getting authors to comply,' Suber says. 'The trick is to get the data open a little before publication so that the link can be included in the text. Journals might now be motivated to increase the pressure on authors to make their data open on a specific timetable.'

Peter Murray-Rust, a chemist at Cambridge University in the UK who champions open access publishing, calls the preprint study 'well done' and 'a good piece of work'. However, he says it is important to determine whether those links to data that the researchers identified actually retrieve real files that are useful. 'A responsible scientific publisher would say you should have *InChIs* and MOL files, but we often have PDFs or JPEGs – these files are largely a graveyard of destroyed information,' Murray-Rust explains. He is currently writing software to turn PDFs back into spectra in order to make them more useable.

He also argues that citations have limited use when trying to assess whether research is of high quality or seminal. 'What we should be measuring is not the citations, but reuse of the data,' he states. This can only happen, Murray-Rust notes, if researchers put their data in a repository and thereby create a public record that enables citation information to be measured and tracked, as well as views and downloads.

***References** G Colavizza et al, 2019, arXiv: 1907.02565*

http://bit.ly/2YbqB3u

An 'EpiPen' for spinal cord injuries

An injection of nanoparticles can prevent the body's immune system from overreacting to trauma, potentially preventing some spinal cord injuries from resulting in paralysis.

ANN ARBOR--The approach was demonstrated in mice at the University of Michigan, with the nanoparticles enhancing healing by reprogramming the aggressive immune cells--call it an "EpiPen" for trauma to the central nervous system, which includes the brain and spinal cord.

"In this work, we demonstrate that instead of overcoming an immune response, we can co-opt the immune response to work for us to promote the therapeutic response," said Lonnie Shea, the Steven A. Goldstein Collegiate Professor of Biomedical Engineering.

Trauma of any kind kicks the body's immune response into gear. In a normal injury, immune cells infiltrate the damaged area and clear debris to initiate the regenerative process.

The central nervous system, however, is usually walled off from the rough-and-tumble of immune activity by the blood-brain barrier. A spinal cord injury breaks that barrier, letting in overzealous immune cells that create too much inflammation for the delicate neural tissues. That leads to the rapid death of neurons, damage to the insulating sheaths around nerve fibers that allow them to send signals, and the formation of a scar that blocks the regeneration of the spinal cord's nerve cells.

All of this contributes to the loss of function below the level of the injury. That spectrum includes everything from paralysis to a loss of sensation for many of the 12,000 new spinal injury patients each year in the United States.

Previous attempts to offset complications from this immune response included injecting steroids like methylprednisolone. That practice has largely been discarded since it comes with side effects that include sepsis, gastrointestinal bleeding and blood clots. The risks outweigh the benefits.

But now, U-M researchers have designed nanoparticles that intercept immune cells on their way to the spinal cord, redirecting them away from the injury. Those that reach the spinal cord have been altered to be more pro-regenerative.

With no drugs attached, the nanoparticles reprogram the immune cells with their physical characteristics: a size similar to cell debris and a negative charge that facilitates binding to immune cells. In theory, their nonpharmaceutical nature avoids unwanted side effects. With fewer immune cells at the trauma location, there is less inflammation and tissue deterioration. Second, immune cells that do make it to the injury are less inflammatory and more suited to supporting tissues that are trying to grow back together.

"Hopefully, this technology could lead to new therapeutic strategies not only for patients with spinal cord injury but for those with various inflammatory diseases," said Jonghyuck Park, a U-M research fellow working with Shea. Previous research has shown success for nanoparticles mitigating trauma caused by the West Nile virus and multiple sclerosis, for example.

"The immune system underlies autoimmune disease, cancer, trauma, regeneration--nearly every major disease," Shea said. "Tools that can target immune cells and reprogram them to a desired response have numerous opportunities for treating or managing disease."

The research, published in the current issue of Proceedings of the National Academy of Sciences, *was supported by The National Institutes of Health. Shea is also the William and Valerie Hall Chair of Biomedical Engineering and a professor of chemical engineering.*

Study abstract: https://www.pnas.org/content/early/2019/07/02/1820276116

http://bit.ly/30xBFVQ

New virus found in one-third of all countries may have coevolved with human lineage

Study investigates the origin and evolution of crAssphage, which may have coevolved with human lineage

In 2014, a virus called crAssphage that infects bacteria was discovered as part of the body's intestinal environment. Now, a new study has investigated the origin and evolution of this virus, which may have coevolved with human lineage.

Published in Nature Microbiology, a recent study shows that the virus was found in the sewage of more than one-third of the world's countries. Additionally, the makeup of the virus can vary depending on in which country and city someone resides.

"The virus is both highly abundant in the human gut and represents an entirely new viral family. With this study, we were able to expand our understanding of the diversity and evolutionary history of the human microbiome globally," said Kyle Bibby, co-author of the study and associate professor and Wanzek Collegiate Chair in the Department of Civil and Environmental Engineering and Earth Sciences. "Our team at Notre Dame has been evaluating the potential uses of this newly identified virus and is developing it as

an alternative to E. coli or other fecal indicator bacteria that are not specific to humans, as an indicator of fecal pollution."

The research was completed through a global collaboration of more than 115 scientists from 65 countries, allowing for the collection of a significant amount of sequencing data. This information was sampled from a variety of volunteers and from sewage samplings around the world. Genetic material data were also collected from primates as well as three pre-Columbian Andean mummies and a Tyrollean glacier mummy, which had 5,300-year-old intestinal content.

"We are in debt to all the amazing colleagues around the world who helped us explore the global diversity of this unique virus," said Robert Edwards, project lead and professor of computer science and biology from San Diego State University. "This is truly a world first in the global scope and nature of the project."

Bibby's research on the virus was funded by the National Science Foundation.

Bibby is an affiliated member of Advanced Diagnostics and Therapeutics, the Eck Institute for Global Health and the Environmental Change Initiative at Notre Dame.

https://go.nature.com/2XRHPi9

Versatile virus hops between three primate species — including humans

No other emerging pathogen is known to have jumped so frequently from species to species.

A virus that killed a six-year-old boy in 1965 has also infected bonobos and chimpanzees in an unprecedented case of viral 'ping-pong' between species.

James Chodosh at Harvard Medical School in Boston, Massachusetts, Donald Seto at George Mason University in Manassas, Virginia, and their colleagues reconstructed the history of a long-stored sample of adenovirus, a type of virus that causes colds and other illnesses. By tracking the small changes that accumulated in the virus's genome when it infected new species, the researchers found that it had previously lived in bonobos (*Pan paniscus*), chimpanzees (*Pan troglodytes*) and humans.

The analysis also showed that the pathogen was remarkably similar to an adenovirus recently identified in two groups of primates that had never come into contact with each other: bonobos in the San Diego Zoo in California and chimpanzees in a primate research facility in Louisiana.

The results suggest that the transmission of adenoviruses to humans from other animals might have an important role in the emergence of pathogens that could harm human health. *J. Virol.* (2019)

http://bit.ly/2XLVcjx

This Common Sugar Substitute Can Be Deadly for Dogs, FDA Warns

Although xylitol is safe for humans, it can be poisonous for dogs

By Rachael Rettner, Senior Writer

You should always be careful about what you let your dog eat — case in point, a common sugar substitute found in everything from chewing gum to peanut butter can be deadly for man's best friend, according to the U.S. Food and Drug Administration (FDA).

This week, the FDA warned pet owners about the dangers of xylitol, a type of sugar alcohol that is sometimes found in sugar-free foods. Although the substance is safe for humans, it can be poisonous for dogs. Over the last several years, the agency has received reports of dogs being poisoned by eating foods that contain xylitol.

Many of the poisonings occurred when dogs ate sugar-free gum, the FDA said. But xylitol can also be found in other food or consumer products, including sugar-free candy, breath mints, baked goods, sugar-free (or "skinny") ice cream, toothpaste, cough syrup, and some peanut and nut butters.

When dogs eat xylitol, it is quickly absorbed into the bloodstream and causes a rapid release of insulin, the hormone that helps sugar enter cells. This insulin spike may cause dogs' blood sugar levels to

plummet to life-threatening levels, a condition known as hypoglycemia, the FDA said. In humans, xylitol isn't dangerous, because it does not stimulate the release of insulin.

Signs of xylitol poisoning in dogs — including vomiting, weakness, difficulty walking or standing, seizures, and coma — typically occur within 15 to 30 minutes of consumption, and deaths have occurred in as little as 1 hour, the FDA said.

To protect your dog, the FDA recommends checking food labels for xylitol, particularly if the product is advertised as sugar-free or low sugar, said Martine Hartogensis, a veterinarian at the FDA. "If a product does contain xylitol, make sure your pet can't get to it," Hartogensis said in a statement.

This also applies to products you might not think of as food, such as toothpaste, which your dog might still attempt to eat.

And if you give your dog peanut or nut butters as a treat or vehicle for pills, you should also check the label to make sure the product doesn't contain xylitol, the agency said.

http://bit.ly/2XJqB1N

Meet the Ploonets! Runaway Moons with Delusions of Planethood Get Astronomy's Cutest Name Ever

What do you call a runaway exomoon with delusions of planethood? You call it a "ploonet," of course.

Scientists had previously proposed the endearing term "moonmoons" to describe moons that may orbit other moons in distant solar systems.

Now, another team of researchers has coined the melodious nickname "ploonet" for moons of giant planets orbiting hot stars; under certain circumstances, these moons abandon those orbits, becoming satellites of the host star.

The former moon is then "unbound" and has an orbit like a planet's — ergo, a ploonet.

Ploonets — and all exomoons, for that matter — have yet to be detected. But ploonets may produce light signatures that planet-hunting telescopes could identify, researchers reported in a new study.

Their findings were published June 27 in the preprint journal arXiv and have not been peer-reviewed.

For the study, the scientists created computer models to test scenarios that might transform a planet-orbiting moon into a star-orbiting ploonet.

The researchers found that if a moon is circling a type of exoplanet known as a "hot Jupiter" — a massive gas giant close to a star — the gravitational tug of war between star and planet could be powerful enough to wrest the moon from its planetary orbit and send the object circling around the star instead.

Orbiting a nearby star would be stressful for a tiny ploonet; during its transit, the ploonet's atmosphere could evaporate and the world would lose some of its mass, creating a distinctive signature in the light emitted from the star's vicinity, the study said.

That's the signature that telescopes might be able to detect.

In fact, recent observations of mysterious light emissions around faraway hot stars could be explained by the appearance, and drawn-out deaths, of wayward ploonets, the study said.

Some ploonets could sustain their orbits for hundreds of millions of years. By accreting material from the disk of dust and gas around its star, a ploonet could even build up its body until it eventually became a small planet, the study authors wrote.

However, most ploonets would likely be relatively short-lived, the simulations showed. The majority of the endearingly named objects disappeared within a million years and never became planets; instead, they disintegrated during collisions with their former host planets, were gobbled up by stars in acts of "planetary cannibalism" or were ejected from orbit into space, the researchers reported.

http://bit.ly/2XJJz1m

Sounds of intense emotion may be universal language across species, study shows

People can tell how other people are feeling by the sounds they make and now, new research from the University of Alberta shows that may also apply to different animals.

by Katie Willis

"The idea is that some species (those that are vocal learners) can understand other species' vocalizations," explained psychology Ph.D. student Jenna Congdon, who led a new study that showed both humans and black-capped chickadees can detect intense emotions such as fear or excitement in other species

Black-capped chickadees and humans share an ability to understand other species' vocalizations indicating intense feelings such as fear and excitement, according to new U of A research. **_CC0 Public Domain**

"For instance, a songbird is able to understand the call of distress of a different type of songbird when they are in the presence of a predator, like an owl or a hawk. Or, for example, if your friend scared you and you screamed. Both of these are high-arousal vocalizations, and being able to understand what that sounds like in a different species can be very useful."

Under the supervision of neuropsychologist Chris Sturdy, Congdon conducted two experiments, one examining chickadees and another examining humans. In the experiments, participants distinguished between high- and low-arousal vocalizations produced by other species, including alligators, chickadees, elephants, humans, pandas, piglets, ravens, macaques and tree frogs. Human subjects were able to identify high arousal in different species.

"Black-capped chickadees were also able to identify high arousal in other chickadees, humans and giant pandas," said Congdon. "This is fascinating, because a chickadee that has never come across a giant panda before is able to categorize high—and low—arousal vocalizations." She said only a small group of species are able to do this—humans, songbirds, hummingbirds, parrots, bats, whales and dolphins, and elephants.

The scientists suspect other vocal learners, or species that learn their vocalizations from parents and models to survive, have this ability as well. "If humans and songbirds show an innate ability to understand the vocalizations of other species, would other vocal learners show this same propensity?" she asked.

The study, "Hear Them Roar: A Comparison of Black-Capped Chickadee (*Poecile atricapillus*) and Human (*Homo sapiens*) Perception of Arousal in Vocalizations Across All Classes of Terrestrial Vertebrates," was published in the *Journal of Comparative Psychology*.

More information: *Jenna V. Congdon et al. Hear them roar: A comparison of black-capped chickadee (Poecile atricapillus) and human (Homo sapiens) perception of arousal in vocalizations across all classes of terrestrial vertebrates., Journal of Comparative Psychology (2019). DOI: 10.1037/com0000187*

http://bit.ly/2JxEQas

In a first, a Japanese spacecraft appears to have collected samples from inside an asteroid

First collection of subsurface materials from a solar system body other than the moon

By Dennis Normile

Japan's Hayabusa2 successfully completed its second touchdown on the asteroid Ryugu and probably captured material from its interior that was exposed by firing a projectile into the asteroid earlier this year. It is the first collection of subsurface materials from a solar system body other than the moon.

Engineers and technicians in the spacecraft's control room near Tokyo could be seen erupting into cheers and applause on a

YouTube live stream when Project Manager Yuichi Tsuda proclaimed the operation a success just before 11 a.m. local time.

At an afternoon press briefing, Tsuda said, “Everything went perfectly.” He joked that if a score of 100 indicated perfection, “I would give this a score of 1000.”

Hayabusa2 was launched by the Japan Aerospace Exploration Agency’s Institute of Space and Astronautical Science in Sagamihara, near Tokyo, in December 2014 and reached Ryugu in June 2018.

Engineers and technicians in Sagamihara, Japan, cheer for Hayabusa2’s successful second touchdown on the asteroid Ryugu. **ISAS/JAXA**

Since then it has conducted remote observations, released several rovers that hopped around on the asteroid, and made a February touchdown to retrieve surface samples. To get interior material, Hayabusa2 in April released a tiny spacecraft that exploded and sent a nonexplosive, 2-kilogram copper projectile into Ryugu, creating a crater. Subsequent remote examination of the site indicated material ejected from the crater had accumulated about 20 meters to one side.

That area became the target for the second touchdown, which occurred this morning. Engineers moved the spacecraft into position above the target site over the previous day and then placed it into autonomous mode. As the craft touched down, it fired a tantalum bullet into the surface, likely kicking dust and rock fragments into a collection horn. The craft then ascended.

The team won’t know for certain what is in the sample return capsule until it returns to Earth in December 2020. “But we expect that we obtained some subsurface samples,” said project scientist Seiichiro Watanabe, a planetary scientist at Nagoya University in Japan. They will be able to compare these subsurface samples with those collected from the surface. The team believes comparing the surface samples subjected to eons of space weathering and the more pristine material from the interior will provide clues to the origins and evolution of the solar system.

Watanabe noted that NASA’s in-progress Origins, Spectral Interpretation, Resource Identification, Security, Regolith Explorer mission also plans to bring samples from an asteroid, named Bennu, back to Earth in 2023. But at least for the near future, Japan is the only nation that will have acquired samples from both the surface and interior of an asteroid, Watanabe said. The samples “will have great significance scientifically,” he said.

Hayabusa2 will continue remote observations until December 2020. “We shouldn’t waste even a single day,” Tsuda said.

https://wb.md/32pAARO

Doubled Risk of Death After MIS for Cervical Cancer: 'Disturbing'

Another blow has been dealt for minimally invasive surgery (MIS) in patients with cervical cancer — this time by Canadian researchers.

Pam Harrison

They report a population cohort study, which they say better reflects 'the real world impact' of such surgery. Their review of nearly 1000 patients with early stage cervical cancer found a twofold higher risk of death and cancer recurrence in those who underwent minimally invasive surgery (MIS) compared with those who had an open radical hysterectomy. The finding held even after controlling for surgeon volume. The study was published online July 6 in the *American Journal of Obstetrics and Gynecology*.

The new findings echo those reported last year from two studies published in the *New England Journal of Medicine*.

"Rather surprisingly, and some would say shockingly, both studies showed a significant inferior survival associated with the use of the

minimally invasive procedures," Maurie Markman, MD, from Cancer Treatment Centers of America in Philadelphia, commented at the time. The data from the two studies "have shown rather convincingly — and I would say definitively — that these minimally invasive procedures should not be performed, except under perhaps extraordinary circumstances where there is a serious risk for the patient associated with the standard approach," he said.

Now, with the newly published Canadian findings, Markman is even more convinced that there are real dangers in using a minimally invasive approach in the treatment of cervical cancer.

"These disturbing data…again emphasize the critical need for well-designed and well-controlled clinical trials before a 'novel surgical approach' should be accepted as standard-of-care in cancer management," he told *Medscape Medical News* in an email.

Monica Bertagnolli, MD, chief of surgical oncology at the Dana-Farber Cancer Institute in Boston, Massachusetts, and president of the American Society of Clinical Oncology, told *Medscape Medical News* recently that the results showing inferior oncologic outcomes after minimally invasive surgery in cervical cancer are "very very sobering." In general, more rigorous studies of minimally invasive cancer surgery are needed. What is most important, said Bertagnolli emphatically, is cancer outcomes — and not short-term benefits.

The Food and Drug Administration (FDA) has also expressed concern. In February, the agency issued a 'caution' about the use of robotically-assisted surgical devices in women's health, and this included minimally invasive surgery for cervical and breast cancer. The agency urged caution about any such use, noting that robotic devices are approved for use in prostate cancer but not in most cancers.

Advantages of Minimally Invasive Approach?

Arguments in favor of the minimally invasive approach include a shorter postoperative hospital stay, fewer complications, and smaller incisions, resulting in quicker recovery time and improved patient satisfaction compared with open surgery.

However, as one *Medscape* reader working in Ob/Gyn and women's health commented: "I would suggest that the protocol of minimally invasive radical hysterectomy has benefited the bottom line of hospitals and insurance providers.

"I challenge all gynecologists to search for any protocol change that financially benefits hospitals and insurance companies that has truly benefited the patient," the reader wrote in the comment section of the Markman article.

Another clinician in women's health commented in agreement: "Well, finally, someone who has the good sense to state the obvious. Minimally invasive surgery for cancer has as its main beneficiaries the health insurance industry (reduced length of stay) and the companies that manufacture all that wonderfully expensive equipment used for the procedure, not the patient whose survival time is not a factor in revenue to the medical system."

New Data From Canada

The new data from Canada come from a population-based retrospective cohort study of patients with cervical cancer who underwent a primary radical hysterectomy by a gynecologic oncologist from 2006–2017 in Ontario.

The team identified 958 women,958 women (mean age, 45.9 years) with predominantly stage 1B cervical cancer who underwent radical hysterectomy within 9 months of their diagnosis.

Open radical hysterectomy was done in half of the cohort; in the other half, 90% of the minimally invasive procedures were performed laparoscopically.

Patients undergoing minimally invasive radical hysterectomy were less likely to have high-risk features and fewer comorbidities than women who underwent open radical hysterectomy, the researchers note.

At a median follow-up of 6 years, "minimally invasive radical hysterectomy was associated with a two-fold higher rate of all-cause death and recurrence compared to open radical hysterectomy in patients with stage 1B disease, but not 1A or 2+ disease," Maria Cusimano, MD, from the University of Toronto, and colleagues report.

This relationship held even after adjusting for patient factors as well as surgeon volume, they add.

The researchers note that, in contrast to the previously reported studies, "this population-based patient-level analysis reflects the real-world impact of minimally invasive radical hysterectomy, as performed by unselected surgeons on unselected early-stage cervical cancer patients," the investigators write.

"Open hysterectomy should be the recommended approach in this population," they conclude.

MIS Now Used in at Least Half of Cases

The new Canadian findings will undoubtedly fuel the argument that minimally invasive surgery is not as favorable as open radical hysterectomy in early cervical cancer — and this at a time when the proportion of early cervical cancer being treated with less invasive surgery is exploding.

For example, minimally invasive procedures accounted for more than half of all radical hysterectomies done for the treatment of cervical cancer in 2013, according to the authors of the National Cancer Database analysis that was published in the *New England Journal of Medicine* last year.

In the new Canadian cohort study, the proportion of cervical cancers treated using minimally invasive techniques — at least in the province of Ontario — climbed from 4.8% of all hysterectomies in 2006 to 65% in 2017.

Experts Caution Against It

Commenting on the National Cancer Database results last year in an accompanying *NEJM* editorial, Amanda Fader, MD, Johns Hopkins School of Medicine, Baltimore, Maryland suggested that select patient subgroups may still benefit from the less invasive approach. One example would be patients with tumors measuring less than 2 cm prior to surgery — for these types of patients, the outcomes were not worse with MIS in either of the two studies.

However, until it's clear that the less invasive approach is equivalent to open hysterectomy in specific subgroups of patients, Fader urged surgeons to proceed with caution and to counsel their patients about these findings so that women are aware that there is a higher risk of recurrence with minimally invasive surgery than with open radical hysterectomy.

However, Markman in his *Medscape* commentary went a step further, and said that, at least from his perspective, minimally invasive radical hysterectomy should no longer be considered a standard-of-care for the treatment of early-stage cervical cancer.

In another commentary about the two studies, published earlier this year in the *Journal of the National Comprehensive Cancer Network*, Kathryn Pennington, MD, from the University of Washington Medicine in Seattle, and colleagues say that open radical hysterectomy and not a less invasive approach should now be considered standard-of-care for stage 1A2-1B1 cervical cancer.

Patients who still want to undergo less invasive surgery should be "guided appropriately", they suggest, in order to make a more informed decision about which approach they would prefer their surgeon to take.

The Canadian authors have disclosed no relevant financial relationships. Markman has received grants from Genentech, AstraZeneca, Celgene, Clovis, and Amgen. Fader has received personal fees from Ethicon outside the submitted work. Pennington and Bertagnolli have disclosed no relevant financial relationships.

Am J Obstet Gynecol. Published online July 6, 2019. Full text

http://bit.ly/2GfvhuN

Shortening trainee doctor hours hasn't harmed patients: U.S. study

No difference in hospital deaths, readmissions or costs for doctors trained before and after 80 hour per week duty caps took effect

NEW YORK - When reforms shortened working hours for U.S. doctors-in-training, some worried: Was that enough time to learn the art of medicine? Would future patients suffer?

Now a study has answers, finding no difference in hospital deaths, readmissions or costs when comparing results from doctors trained before and after caps limiting duties to 80 hours per week took effect.

“Some still long for the old days of 100-hour work weeks, but most of the world has moved on and realized there are better ways to train residents,” said Dr. Karl Bilimoria of Northwestern University Feinberg School of Medicine, who was not involved in the research published Thursday in the journal BMJ.

Eliminating extra paperwork and some academic conferences for residents, while adding nurse practitioners to the workforce help make training more efficient, Bilimoria said.

Prior studies suggested the reforms didn’t harm residents’ patients. The new study is the first to find similar reassuring results for doctors once they hit the real world, said Dr. Mitesh Patel of University of Pennsylvania who wasn’t involved with the study.

Dr. Isaiah Cochran, 26, worked 75 hours a week, including some 16-hour shifts, at Dayton Children’s Hospital in Ohio for a stretch during his last year of medical school. He plans to apply for a family medicine residency next year.

“It’s doable. It’s not insane,” said Cochran, president of the American Medical Student Association, which supports keeping the 80-hour cap and other measures aimed at adequate sleep for doctors.

For the study, researchers analyzed data from more than 400,000 hospitalizations of Medicare patients. Using billing codes, they assigned each case to a key doctor who dealt most with each patient.

Then researchers compared cases from two six-year time periods: before and after 2006, when the first new doctors who were fully affected by the reforms had finished their residencies.

This was an era of improvements in patient safety. So researchers compared the new doctors — some affected by reforms and some not — to trends among veteran doctors with 10 years’ experience and all trained under the old rules.

They found no difference in patient deaths, readmissions or costs.

Patients depend on hospital teams, not just one doctor, and that may explain why doctor training time seemed to have no effect on care.

Teamwork and technology have changed hospital care so much that the impact of any one doctor is muted, said lead author Dr. Anupam Jena of Harvard Medical School.

And more change is ahead with artificial intelligence. With computers assuming a larger role in diagnosis and treatment, Jena said, “it should be an open question whether 80 hours a week is the right number” for training. Maybe it could be less.

The results apply to internal medicine doctors, not surgeons. More research is needed on whether surgeons are getting enough experience during training, Jena said.

http://bit.ly/30zqPyU

Bone and the Microbiome Have a Brittle Relationship

Animal studies and a few small clinical trials show it’s possible to get commensal microbes to protect against bone loss, rather than contribute to it.

Kerry Grens

Laura McCabe had been living a dual professional life at Michigan State University for more than a decade, studying bone in her lab while teaching medical students gastrointestinal physiology in the

classroom, when she came across a call for proposals from the Crohn's and Colitis Foundation. Could researchers look into how inflammatory bowel diseases affect bone? "I thought, 'This is me!'" McCabe says. In 2007, with grant funding in hand, her two disciplines had collided.

Researchers already knew that patients with inflammatory bowel disease have bone loss; the question was why. In mouse experiments, McCabe found that exposing the animals to bacterial infections of the intestine or to a detergent that causes breaks in the gut's epithelial barrier could lead to bone erosion.

"It became clear [that] we could do all these bad things to the gut and make it inflamed and cause bone loss," McCabe says. "So the natural question was, What can we do that's good for bone?"

She spoke with her Michigan State colleague Rob Britton, who suggested trying a probiotic he had been studying in his microbiology lab. He had found that the bacterium *Lactobacillus reuteri* promoted gut health, so perhaps it could help bones too, he reasoned.

I was just blown away. It was one of those times you find something very plausible that you never thought about before.

—Roberto Pacifici, Emory University

The two researchers tried it out in healthy male mice "just to see how it would go," says McCabe. When the results came in, "we were flabbergasted actually." Not only did the bacterium reduce intestinal inflammation, it also caused the mice to gain bone mass. The study, published in 2013, suggested that even among healthy mice, bone density was compromised by inflammation in the gut, and quelling that inflammation could provide a means to boost bone strength.

This gave them the idea that the microbiome had some role in regulating bone density. They then tested *L. reuteri* in estrogen-deficient mice, a model of the post-menopausal period during which women often lose bone density, and found that the treatment again prevented mice from losing bone mass.

In the years since, McCabe has been unraveling the threads linking gut bugs to inflammatory signaling to bone turnover. And she's joined by a number of other investigators similarly following these connections and testing out various means of adjusting them to intervene against age-related bone loss.

The bone loss signal

Emory University's Roberto Pacifici is a leader in the field of osteoimmunology, the relationship between the immune system and bone.

For years, he had been working on the hypothesis that estrogen deficiency in menopause causes bone loss by activating T cells in the bone marrow, leading to the production of tumor necrosis factor (TNF) and other inflammatory cytokines, which promote the breakdown of bone tissue to release calcium, a process known as bone resorption.

Pacifici knew there must be an antigen that was kicking the T cells into gear, but he hadn't pinned it down. Then in 2012, he read a paper showing that mice raised in a germ-free environment had higher bone density. "When I saw that article, I said, 'Ah ha! The antigen must be something provided by the microbiota," Pacifici says.

To find out if in fact the microbiota was the missing link, Pacifici's group developed a germ-free mouse model that was also estrogen deficient. In line with his suspicions, the mice didn't lose bone like estrogen-deficient animals with intact microbiomes did.

In that same study, reported in 2016, the researchers also discovered that estrogen deficiency causes the gut to become more permeable to gut bacteria and their products. These leaked materials appear to be the stimulants that activate immune cells, which travel

to the bone marrow, overproduce cytokines, and ultimately cause bone loss.

"I was just blown away," Pacifici says. "It was one of those times you find something very plausible that you never thought about before."

McCabe's work has also shown that a strong gut barrier is critical to staving off bone loss. Breaches in the gut lumen can allow for bacterial endotoxins, metabolites, or vitamins to spill out and trigger inflammatory signaling that can lead to bone erosion. Resident immune cells of the gut are also surveilling for intestinal damage and then relaying the alarm to the bone marrow, revving up the bone-damaging immune response. "I think we're going to find there are multiple things going on," McCabe says.

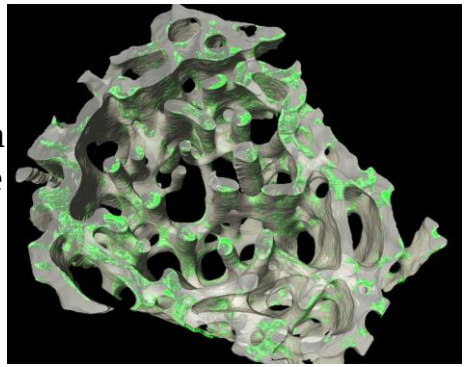
Chad Novince, who is studying the microbiome's role in skeletal maturation at the Medical University of South Carolina, has identified yet another means of communication between the microbiome and the skeleton: the "gut-liver-bone axis." In 2017, he and his group described a study in which healthy, young adult mice with specific pathogens removed from their microbiomes had less bone than germ-free mice and also enhanced immune activity in the liver.

From a suite of experiments looking at the differences between these two mouse types, Novince and his team concluded that gut microbes or metabolites they produce pass through the intestines' mucosal barrier into circulation, where they travel to the liver and fire up innate and adaptive immune responses that suppress bone formation while enhancing bone resorption.

The molecular triggers within bone that cause the loss of tissue aren't perfectly nailed down, but McCabe and Pacifici have independently found that the signaling molecule Wnt10b, critical to bone formation and delivered to bone by immune cells, is an important factor. Meanwhile, McCabe and her colleague Narayanan Parameswaran and, separately, Novince have homed in on RANKL, a molecule important in regulating bone resorption.

Christopher Hernandez, a biomechanics researcher at Cornell University, and colleagues have discovered signs that vitamin K produced by microbes might be influencing bone formation directly. In results published in 2017, they found that mice with an altered gut microbiome during their early lives end up with weaker bones than control animals. A follow up metagenomics study of the animals' gut bacteria published this year found differences in genes for the production of vitamin K.

ernandez hypothesizes that the vitamin makes it to the bone where vitamin K–dependent molecules such as osteocalcin use it to build the bone matrix. "I think we're right now at the very beginnings which of these mechanisms are influencing the bone," he says.



Rat tail bone. The green indicates regions where new bone is forming.
Christopher Hernandez

Probiotics to prevent bone loss

After Pacifici's team had generated evidence of the link between microbiota and bone loss in estrogen-deficient mice, the researchers took the next step to see if manipulating the microbiome could help protect bones.

They fed mice either the widely used probiotic strain *Lactobacillus rhamnosus* GG or a combination of seven bacteria, and in both cases the probiotics stimulated bone improvement among estrogen-deficient animals.

He says there wasn't much scientific rationale behind the choice of bacteria, they just happened to be popular. "I think the number of

cells in dose is very, very important, perhaps more important than the type," he says.

Some small clinical studies have looked at whether the results in mice translate to women. A group in Sweden, for example, published findings last year after giving older women with low bone density *L. reuteri*, the microbe McCabe and Britton have studied, or a placebo daily for a year. The loss of bone mineral density was lower among the women who took the probiotic.

A few years earlier, Purdue University's Connie Weaver and colleagues reported that soluble corn fiber, a prebiotic considered a food for commensal microbes, is able to essentially stave off the usual rate of bone loss in postmenopausal women.

"Once they lost the bone already, I didn't think we could further protect them," says Weaver. "I was pretty surprised." Likewise in young people, Weaver found corn fiber supplements led to an increase in bone calcium, an indicator of bone density.

Weaver says the thinking is that pro- or prebiotics stimulate the production of short chain fatty acids, which trigger a pathway that ends up in the production of bone.

Pacifici's team recently produced supporting evidence for this mechanism in healthy mice, whose bone density benefited from probiotics. The model is that *Lactobacillus* produces lactate, which feeds the commensal bacteria *Clostridia* and *Bacteroides*. They then go on to produce the short chain fatty acid butyrate, which, when fed to mice on its own, stimulates bone growth just as well as the probiotic does.

McCabe says more clinical studies are needed to determine if the dietary interventions will be able to either treat disease or protect against normal bone loss. But she is optimistic that the field is moving forward. "I'm so happy when we're all finding the same results in different places. . . . It strengthens it for translation."

http://bit.ly/2JAHgFn

Surveillance Cameras Debunk the Bystander Effect

A new study uses camera footage to track the frequency of bystander intervention in heated incidents in Amsterdam; Cape Town; and Lancaster, England.

Richard Florida

It's one of the most enduring urban myths of all: If you get in trouble, don't count on anyone nearby to help. Research dating back to the late 1960s documents how the great majority of people who witness crimes or violent behavior refuse to intervene.

Psychologists dubbed this non-response as the "bystander effect"—a phenomenon which has been replicated in scores of subsequent psychological studies. The "bystander effect" holds that the reason people don't intervene is because we look to one another. The presence of many bystanders diffuses our own sense of personal responsibility, leading people to essentially do nothing and wait for someone else to jump in.

Past studies have used police reports to estimate the effect, but results ranged from 11 percent to 74 percent of incidents being interventions. Now, widespread surveillance cameras allow for a new method to assess real-life human interactions. A new study published this year in the *American Psychologist* finds that this well-established bystander effect may largely be a myth. The study uses footage of more than 200 incidents from surveillance cameras in Amsterdam; Cape Town; and Lancaster, England.

Researchers watched footage and coded the nature of the conflict, the number of direct participants in it, and the number of bystanders. Bystanders were defined as intervening if they attempted a variety of acts, including pacifying gestures, calming touches, blocking contact between parties, consoling victims of aggression, providing practical help to a physical harmed victim, or holding, pushing, or

pulling an aggressor away. Each event had an average of 16 bystanders and lasted slightly more than three minutes.

The study finds that in nine out of 10 incidents, at least one bystander intervened, with an average of 3.8 interveners. There was also no significant difference across the three countries and cities, even though they differ greatly in levels of crime and violence.

Instead of more bystanders creating an immobilizing "bystander effect," the study actually found the more bystanders there were, the more likely it was that at least someone would intervene to help. This is a powerful corrective to the common perception of "stranger danger" and the "unknown other." It suggests that people are willing to self-police to protect their communities and others. That's in line with the research of urban criminologist Patrick Sharkey, who finds that stronger neighborhood organizations, not a higher quantity of policing, have fueled the Great Crime Decline.

But how does this study generate findings that are so at odds with such widely held norms? The researchers point out that the bystander effect was reinforced by research that took place in laboratory-like experiments, which put bystanders in situations that do not approximate real life. Surveillance footage shows not what people guess they'd do in an experimental setting, but what they actually do in the real world.

This high rate that bystanders intervene may seem somewhat surprising given the high personal risks they take. But, such a willingness to intervene is actually more in line with the "better angels of our nature." Human beings are social animals and cooperative creatures: We empathize, forge bonds, and build communities. Instead of putting our heads down and looking away, we are much more likely to intervene when necessary, even at risk to ourselves—to deter bad behavior and protect others.

CityLab editorial fellow Claire Tran contributed research and editorial assistance to this article.

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1 in 10 patients are infected in hospital, and it's not always with what you think

One in ten adult patients in hospital with an acute (short-term) condition had a health care associated infection

Philip Russo* **Brett Mitchell****

Most people expect hospital treatment to make them better. But for some, a stay in hospital can actually make them sicker. Their wound might get infected after an operation or they might get a blood infection as a result of a medical procedure.

Our study, published today in the international journal Antimicrobial Resistance and Infection Control, found one in ten adult patients in hospital with an acute (short-term) condition had a health care associated infection.

In the first study of its kind in Australia for over 30 years, we also uncovered unexpected infections, like pneumonia and urinary tract infections, as well as high numbers of patients with multi-drug resistant organisms (superbugs).

Why do we need to keep track of infections?

Most of these infections can be prevented. So it is important to know what type of infections they are, how common they are and which patients get them. Once we have this information, we can work out a way to prevent them.

Left unchecked, these infections can make already sick patients sicker, can divert hospital resources unnecessarily, and can kill.

Most hospitals in Australia have ongoing surveillance for specific infections, such as wound and bloodstream infections.

Some states have well coordinated programs like the Victorian program VICNISS, leading to detailed data on health care associated infections. This data is then used to inform hospital strategies on how to prevent infections. However, this type of surveillance method requires extensive resources and does not capture all infections that occur in a hospital.

Instead, we conducted a "point prevalence" survey, which takes a snapshot of the current situation on any given day. This is less resource intensive than ongoing surveillance and it provides valuable information on the distribution and occurrence of *all* infections in a hospital.

In Europe, the European Centre for Disease Prevention and Control co-ordinates national point prevalence studies every four years. These have provided valuable insight into the burden of health care associated infections.

They have also been used to track the emergence of multi-drug resistant organisms in Europe. The US, Singapore and many other countries also run them.

Most hospital infections can be prevented. Santypan/Shutterstock

Unlike most OECD countries, Australia does not have a national health care associated infection surveillance program and does not undertake national point prevalence studies.

The only national data routinely collected relates to bloodstream infections caused by the microorganism *Staphylococcus aureus*. These infections are serious but rare and only represent a tiny fraction of all infections in hospitals.

To improve our understanding of health care associated infections across Australia, we used the same study method as the Europeans. Over a four month period in 2018, we visited 19 large hospitals across Australia and collected information on all infections in adult acute inpatients.

Four of the hospitals were regional, the others major city hospitals.

What infections did we find?

Of the 2,767 patients we surveyed, we found 363 infections in 273 patients, meaning some patients had more than one infection. The most common infections were wound infections after surgery (surgical site infections), pneumonia and urinary tract infections. These accounted for 64% of all the infections we found.

This is important as most hospitals do not normally look for pneumonia or urinary tract infections and there is no routine statewide or national surveillance for these.

Our findings mean these infections are commonly occurring but undetected. A potential source of information on these types of infections is hospital administrative coding data. However, these codes were mainly designed for billing purposes and have been shown to be unreliable when it comes to identifying infections.

We also found patients with a medical device, such as a large intravenous drip, or urinary catheter (a flexible tube inserted into the bladder to empty it of urine), were more likely to have an infection than those who did not.

Intensive care units treat patients who are gravely unwell and at greater risk of infection. So it was unsurprising to find that 25% of patients in intensive care units had a health care associated infection.

The emergence of multi-drug resistant organisms (superbugs) is a concern worldwide. Previously unknown, our study revealed that 10% of the adult acute inpatients in our study had a multi-drug resistant organism.

What have other studies found?

For the first time in 34 years we have a glimpse of how common health care associated infections are in Australian hospitals. Although the only other previous study was larger, a major strength of our study is that we used the same two trained data collectors to collect the data from all hospitals.

This reduced the potential inconsistency in finding infections that might occur if hospital staff collected their own data. It also minimised the use of hospital resources to undertake the survey.

Importantly though, we did not survey all types of hospitals. It is possible that if the same survey was extended to include children, babies and cancer hospitals, higher rates of infection may be found given the vulnerability of these patients.

What can we do better?

As one of the authors has previously noted, a major gap in Australia's effort to combat health care associated infections, and the emergence of multi-drug resistance organisms, is the lack of robust national data.

This means we cannot measure the effect of national policy or guidelines despite significant investment.

In the absence of a national surveillance program, we recommend that large-scale point prevalence surveys, including smaller hospitals, specialist hospitals and the private sector be undertaken regularly. Data generated from these studies could then be used to inform and drive national infection prevention initiatives.

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**Professor of Nursing, University of Newcastle

Disclosure statement

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http://bit.ly/2YRFzZi

Southeast Asia was crowded with archaic human groups long before we turned up

Remarkable journey of how the ancestors of modern humans met and genetically mixed with a number of archaic human groups

João Teixeira*

Around 55,000-50,000 years ago, a population of modern humans left Africa and started on the long trek that would lead them around the world. After rapidly crossing Eurasia and Southeast Asia, they travelled through the islands of Indonesia, and eventually as far as the continent of Sahul – modern-day Australia and New Guinea.

Their descendants are the modern human populations found right across this enormous region today.

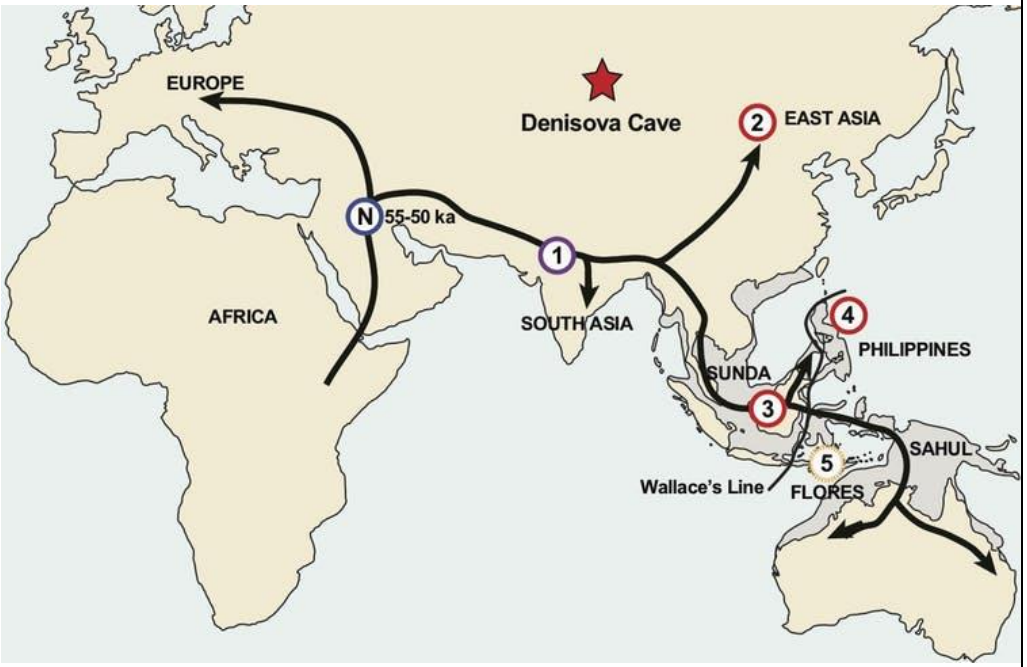
In new research published in Proceedings of the National Academy of Sciences, we detail how during this remarkable journey the ancestors of modern humans met and genetically mixed with a number of archaic human groups, including Neandertals and Denisovans, and several others for which we currently have no name. The traces of these interactions are still preserved in our genomes.

For example, all modern non-African populations contain about 2% Neandertal ancestry. This strong universal signal shows that the original Neandertal mixing event must have happened just after the small founding population left Africa.

We can even use the Neandertal genetic signal to date when they left Africa. The large size of Neandertal DNA fragments in the genome of an ancient skeleton from southern Russia, which is

45,000 years old, shows that at most 230-430 generations could have passed since the initial mixing event (dating it around 50-55,000 years ago).

By analysing where the archaic genetic traces are found today (from previous genetic studies) and using paleovegetation maps that identify favourable savannah-like habitat along the route 55,000 years ago, we have reconstructed the likely geographic locations and number of the archaic hominin mixing events.



A map showing where the ancestors of modern humans appear to have met and mixed with archaic hominins. **Author provided**

Leaving Africa

One of the first mixing events after the Neandertals appears to have taken place during the movement across southern Asia. The archaic human group involved was neither the Neandertals or Denisovans, but something similar – which currently has no name.

The genetic traces of this archaic group can be found from modern Punjabi and Bengal populations all the way through to New Guinea and Australia. As a result, we think this mixing event (marked 1 on the map) likely took place somewhere around northern India, which is the most "upstream" or westerly position it is first observed.

The ancestral population of modern humans then appears to have split as it moved across Asia with one pulse dispersing north into mainland Asia, where it met and mixed with a Denisovan group (marked 2 on the map). These Denisovans were genetically close to those we already know about from the Altai mountains. The traces of this event can be seen in East Asia today, and also in North and South America populations, who stem from northeastern Asia.

Island Southeast Asia was already crowded

The other pulse of modern humans headed south down the Malaysian Peninsula and into Island Southeast Asia (ISEA) where a big surprise awaited. They found the area was already crowded with different archaic human groups, including completely different species.

Recent fossil finds of small skeletons have shown that apparent relatives of *Homo erectus* (whose early fossils are common on Java) had survived on the Philippines and Flores (where they are known as "hobbits") until around 52,000 years ago. Effectively right up until the modern humans arrived.

The incoming modern human population apparently first met and mixed with a distant relative of the Denisovans in the area, leaving a signal in the genomes of Australo-Papuans and several ISEA populations. These signals are very different from the above East Asian mixing event, and instead come from a Denisovan relative that had separated genetically from the Altai/East Asian Denisovans around 280,000 years ago. This mixing event appears to have been somewhere around southern Malaysia/Borneo (marked 3 on the map).

Landfall in Australia

The wave of modern humans does not appear to have waited long to cross Wallace's Line – the famous biogeographic barrier that effectively marks the edge of the ISEA landmasses joined together during past glacial periods, when sea levels were up to 120 metres lower.

We know this because a sudden appearance of archaeological sites right across Australia around 50,000 years ago indicates that modern humans had quickly crossed the marine gaps through ISEA. While there is one much earlier Australian site, the 65-80,000 year old Madjedbebe rock shelter in Arnhem Land, it is a complete outlier to the rest of the Australian record and the age of the site has been queried.

While moving through ISEA, the modern human population appears to have met – and mixed with – two more archaic human groups. Hunter-gatherer populations in the Philippines preserve signals of yet another Denisovan-mixing event (marked 4 on the map), after they had diverged from the main wave of modern humans moving through ISEA.

Similarly, a genetic study of the short-statured modern day population that lives around the Flores cave where the tiny skeletons of the "hobbits" were found identified signals of DNA not from *Homo erectus*, the target of the study, but an enigmatic signal from something else. The source was neither Neandertal nor Denisovan but something of similar age – yet another currently unknown archaic group (marked 5 on the map).

The last survivors

What the different genetic studies across this region tell us is that the ancestors of modern humans appear to have met and mixed with four different archaic hominins, in at least six events. And this all happened in the very short window of time between leaving Africa 50-55,000 years ago, and arriving in Australia and New Guinea at most 5,000 years later.

Remarkably, none of these genetic mixing events appears to have involved fossil species in ISEA that we know were still around when modern humans arrived, such as *Homo luzonensis* (Philippines) and the Flores hobbits.

ISEA was clearly a very crowded place around 50,000 years ago, occupied by many different archaic human groups on many different islands. But shortly thereafter there was only one survivor: us.

**Research associate, University of Adelaide*

Disclosure statement

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http://bit.ly/2SklQyX

Meet the six-legged superfoods: grasshoppers top insect antioxidant-rich list

Grasshoppers and silkworms have antioxidant capacity similar to fresh orange juice, says study

— by Matthew Prior, Frontiers science writer

For the first time, a study has measured antioxidant levels in commercially available edible insects.

Vegetarians like grasshoppers have higher antioxidant activity than carnivores, like spiders and scorpions. **Image: Shutterstock.**

Sure, most of them don't have six legs – and scorpions, spiders, and centipedes aren't even insects. But for open-minded health freaks, it's good news: crickets pack 75% the antioxidant power of fresh OJ, and silkworm fat twice that of olive oil.

And while even ladybirds fart, insects have a tiny land, water and carbon footprint compared with livestock – so anything that encourages insect eating is good news for the planet, too.

Antioxidant Activities* in vitro *of Water and Liposoluble Extracts Obtained by Different Species of Edible Insects and Invertebrates

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Look who's come crawling back

Faced with eating ourselves and the planet to death, the West has begun reluctantly to consider creepy crawlies as a more sustainable alternative to meat and animal products.

"At least 2 billion people – a quarter of the world's population – regularly eat insects," says senior study author Prof. Mauro Serafini, of the University of Teramo. "The rest of us will need a bit more encouragement."

Providing selfish and immediate incentives could help consumers to make the environmentally friendly choice, says Serafini. Taste and image are key – but for many, health is also an incentive.

"Edible insects are an excellent source of protein, polyunsaturated fatty acids, minerals, vitamins and fiber. But until now, nobody had compared them with classical functional foods such as olive oil or orange juice in terms of antioxidant activity."

Antioxidant activity is that free-radical scavenging ability that typically designates a 'superfood' – although this poorly defined term is eschewed by researchers, says Serafini.

The study

The researchers tested a range of commercially available edible insects and invertebrates, using various measures of antioxidant activity.

Inedible parts like wings and stings were removed, then the insects were ground and two parts extracted for each species: the fat, and whatever would dissolve in water.

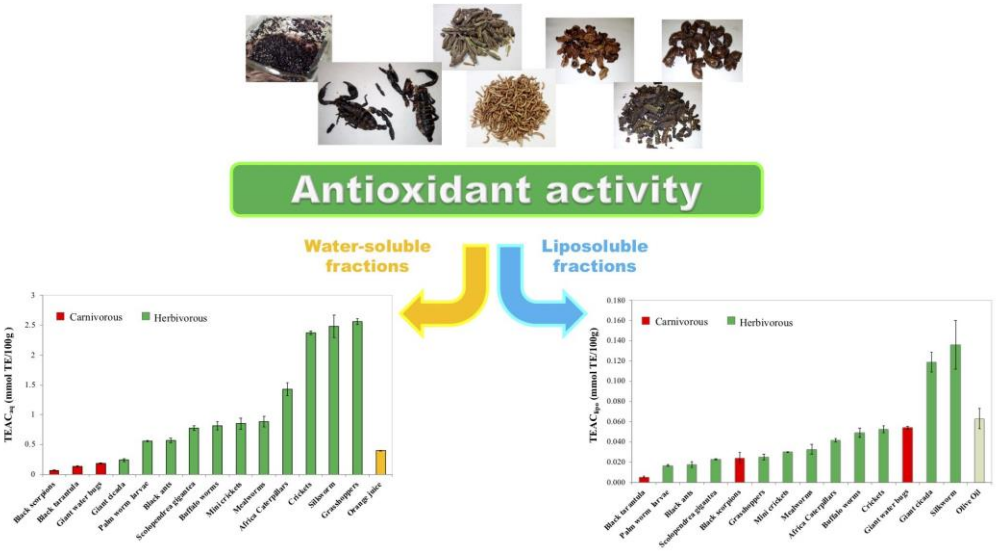
Each extract was then tested for its antioxidant content and activity.

"For perspective, using the same setup we tested the antioxidant capacity of fresh orange juice and olive oil – functional foods that are known to exert antioxidant effects in humans," Serafini explains.

The first insect antioxidant rankings

Water-soluble extracts of grasshoppers, silkworms and crickets displayed the highest values of antioxidant capacity – fivefold higher than fresh orange juice – while giant cicada, giant water bugs, black tarantula and black scorpions showed negligible values.

"There's a clear trend: the vegetarians have markedly higher antioxidant capacity," notes Serafini.



Tables comparing antioxidant capacity (TEAC) of commercially available edible insects and arthropods, with: fresh orange juice (left, for water-soluble extracts) and olive oil (right, for lipid-soluble extracts). Note that the water-soluble extract figures are for the dry extract. Even so, some quick math shows that at the same dilution (88% water), grasshoppers and silkworms would have about 75% the antioxidant activity of OJ. **Credit: Professor Mauro Serafini**

Note that these comparisons are for the dry, fat-free insect dust – a tad tougher to swallow than fresh OJ. Even so, some quick math shows that at the same dilution (88% water), grasshoppers and silkworms would have about 75% the antioxidant activity of OJ.

Interestingly, the total content of polyphenols – the major source of plant-derived antioxidant activity – followed a similar pattern across species, but was far lower in all insects compared to OJ.

“These results suggest that besides polyphenols, the antioxidant capacity of insects also depends on other, as yet unknown compounds,” Serafini adds.

The results for the insect fat were similarly impressive.

“Fat from giant cicadas and silkworms showed twice the antioxidant activity of olive oil, while black tarantula, palm worm and black ants are placed in the bottom of the ranking.”

Bioavailability

The group’s key message is: edible insects like grasshoppers and silkworms are a rich source of antioxidants.

“A high content of antioxidant in the food matrix is a primary requisite for a first screening of antioxidant potentiality of novel foods, so these are promising results.”

But the questions remains: what are these antioxidants, and do they work in humans?

“The in vivo efficiency of antioxidant-rich food is highly dependent on bioavailability and the presence of an ongoing oxidative stress. So as well as identifying other antioxidant compounds in insects, we need tailored intervention studies to clarify their antioxidant effects in humans.

“In the future, we might also adapt dietary regimens for insect rearing in order to increase their antioxidant content for animal or human consumption.”

Original article: *Antioxidant Activities* in vitro *of Water and Liposoluble Extracts Obtained by Different Species of Edible Insects and Invertebrates*