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How ancient microbes created massive ore deposits, set the stage for early life on Earth

The research provides a possible explanation to the 'faint-young-sun' paradox, originated by astronomer Carl Sagan.

New research in Science Advances is uncovering the vital role that Precambrian-eon microbes may have played in two of the early Earth's biggest mysteries.

University of British Columbia (UBC) researchers, and collaborators from the universities of Alberta, Tübingen, Autònoma de Barcelona and the Georgia Institute of Technology, found that ancestors of modern bacteria cultured from an iron-rich lake in Democratic Republic of Congo could have been key to keeping Earth's dimly lit early climate warm, and in forming the world's largest iron ore deposits billions of years ago.

The bacteria have special chemical and physical features that in the complete absence of oxygen allow them to convert energy from sunlight into rusty iron minerals and into cellular biomass. The biomass ultimately causes the production of the potent greenhouse gas methane by other microbes.

"Using modern geomicrobiological techniques, we found that certain bacteria have surfaces which allow them to expel iron minerals, making it possible for them to export these minerals to the seafloor to make ore deposits," said Katharine Thompson, lead author of the study and PhD student in the department of microbiology and immunology.

"Separated from their rusty mineral products, these bacteria then go on to feed other microbes that make methane. That methane is what likely kept Earth's early atmosphere warm, even though the sun was much less bright than today."

This is a possible explanation to the 'faint-young-sun' paradox, originated by astronomer Carl Sagan. The paradox is that there were liquid oceans on early Earth, yet heat budgets calculated from the early Sun's luminosity and modern atmospheric chemistry imply Earth should have been entirely frozen. A frozen Earth would not have supported very much life. A methane-rich atmosphere formed in connection to large-scale iron ore deposits and life was initially proposed by University of Michigan atmospheric scientist James Walker in 1987. The new study provides strong physical evidence to support the theory and finds that microscale bacterial-mineral interactions were likely responsible.

"The fundamental knowledge we're gaining from studies using modern geomicrobiological tools and techniques is transforming our view of Earth's early history and the processes that led to a planet habitable by complex life including humans," said senior author of the paper, Sean Crowe, Canada Research Chair in Geomicrobiology and associate professor at UBC.

"This knowledge of the chemical and physical processes through which bacteria interact with their surroundings can also be used to develop and design new processes for resource recovery, novel building and construction materials, and new approaches to treating disease."

In the future, such geo-microbiological information will likely be invaluable to large-scale geoengineering efforts that might be used to remove from CO2 from the atmosphere for carbon capture and storage, and again influence climate through bacterial mineral interactions.

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Study finds common cold virus can infect the placenta

Suggests it may be possible for the infection to pass from expectant mothers to their unborn children

Researchers have shown that a common cold virus can infect cells derived from human placentas, suggesting that it may be possible for the infection to pass from expectant mothers to their unborn

children. The study, published in the journal *PLOS ONE*, was led by Dr. Giovanni Piedimonte, professor of pediatrics and vice president of research at Tulane University.

"This is the first evidence that a common cold virus can infect the human placenta," Piedimonte said. "It supports our theory that when a woman develops a cold during pregnancy, the virus causing the maternal infection can spread to the fetus and cause a pulmonary infection even before birth."

During pregnancy, the placenta acts as a gatekeeper to provide essential nourishment from a mother to a developing fetus while filtering out potential pathogens. Scientists are discovering that the barrier isn't as impenetrable as once believed with recent studies showing how viruses such as Zika can slip through its defenses.

Using donated placentas, researchers isolated the three major cells types found in placentas -- cytotrophoblast, stroma fibroblasts and Hofbauer cells -- and exposed them in vitro to the respiratory syncytial virus (RSV), which causes the common cold. While the cytotrophoblast cells supported limited viral replication, the other two types were significantly more susceptible to infection.

For example, the Hofbauer cells survived and allowed the virus to replicate inside the cell walls. As Hofbauer cells travel within the placenta, researchers suspect they could act as a Trojan horse and transmit the virus into the fetus.

"These cells don't die when they're infected by the virus, which is the problem," Piedimonte said. "When they move into the fetus, they are like bombs packed with virus. They don't disseminate the virus around by exploding, which is the typical way, but rather transfer the virus through intercellular channels."

Researchers suspect RSV could attack lung tissue within the fetus, causing an infection that may predispose offspring to developing asthma in childhood. Piedimonte plans to launch a clinical study at Tulane to further test the theory.

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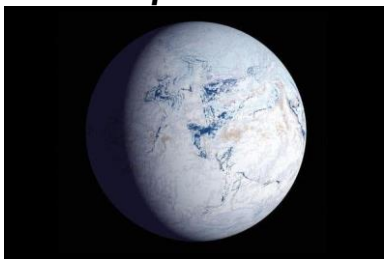
How Life on Our Planet Made It Through Snowball Earth

Rusty rocks left over from some of our planet's most extreme ice ages hint at oases for survival beneath the freeze.

By Lucas Joel



Today, the world is warming. But from about 720 to 635 million years ago, temperatures swerved the other way as the planet became encased in ice during the two ice ages known as Snowball Earth.

An artist's concept of the Earth frozen in snow, during one of the planet's most severe ice ages. **Chris Butler/Science Source**

It happened fast, and within just a few thousand years or so, ice stretched over both land and sea, from the poles to the tropics. Life lived in the oceans at the time, and the encroaching ice entombed that life, cutting it off from both the sun and the atmosphere.

"This is the one time when Earth's natural thermostat broke," said Noah Planavsky, a biogeochemist at Yale University. "The question on everyone's minds was: How did life actually make it through this?"

Glaciations can drive mass extinctions of life. Yet life, including perhaps our distant animal ancestors, somehow survived these deep freezes. In research published Monday in Proceedings of the National Academy of Sciences, Dr. Planavsky and his colleagues report the discovery of oases just beneath the ancient ice sheets that likely helped life persevere.

Snowball Earth came to an abrupt end over a half-billion years ago, but its marks still exist in remote corners of the planet. In 2015, to reach one of those corners, Max Lechte and his graduate adviser at the time, Malcolm Wallace, both sedimentologists at the University of Melbourne, drove 15 hours into the South Australian outback.

They trekked over hills made of red-colored rock, and it was so hot out — about 122 degrees Fahrenheit — that the soles of Dr. Wallace's boots melted. "A bit of duct tape fixed that up," said Dr. Lechte, who led the new research.

These red-hot rocks formed in the oceans during the snowball glaciations, and their color caught Dr. Lechte's eye, so he took a few samples. Then, in 2015 and 2016, he traveled to Namibia and Death Valley in California and found more rocks — also red — that formed at the same time.

The rocks' color signaled to Dr. Lechte that they are rich in iron, which means they turned red for the same reason that old cars with iron exteriors turn red: They rusted.

Oxygen needs to be present for iron to rust. It also needs to be present for animals and many other organisms to survive. If the iron rocks below the ancient oceans rusted, then there was also oxygen in those oceans. And if there was oxygen, then oxygen-breathing life-forms had a lifeline they could cling to.

"This is the first direct evidence for oxygen-rich marine environments during Snowball Earth," said Dr. Lechte, now a postdoctoral researcher at McGill University in Canada.

But how that oxygen got into the oceans in the first place was a mystery. The atmosphere is a major source of oxygen for the oceans, and with the ice sheets of Snowball Earth acting as giant air-blocking shields, oxygen in seawater should've been nonexistent.

"This could've led to anoxic oceans, which could've killed off life-forms that need oxygen to survive." Dr. Lechte said. "It presents a bit of an unsolved problem."

In labs at Yale as well as Nanjing University in China, Dr. Lechte and his team crushed the iron-rich rocks, dissolved them in acid and measured the abundances of different iron isotopes. They found that the iron in rocks that formed far out in the open oceans rusted much less than the iron in rocks that formed closer to land, right where ice sheets dove from continents and into the oceans.

Today, beneath ice sheets in Antarctica, glacial meltwater streams flow into the Southern Ocean. That water melts from ice that can have air bubbles trapped inside it, and those bubbles can seed the meltwater streams with oxygen. On Snowball Earth, Dr. Planavsky explained, such oxygen-laden streams flowed into the oceans around the edges of continents and sustained life.

Paul Hoffman, a geologist at Harvard University who pioneered the Snowball Earth hypothesis, thinks this idea for how oxygen made it into the oceans is solid. "I'm attracted to the idea, and I think it's consistent with my own observations," he said.

But, Dr. Hoffman added, whether or not this oxygen pump was the main thing that helped many living things survive those ice ages is still an open question. "We just don't know enough from a theoretical standpoint about how life would have responded to the challenge of a Snowball Earth," he said.

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1940s blood samples reveal historical spread of malaria

Uncovers the spread of malaria from Europe to the Americas during the colonial period

DNA from 75-year old eradicated European malaria parasites uncovers the historical spread of one of the two most common forms of the disease, Plasmodium vivax, from Europe to the Americas during the colonial period, finds a new study co-led by UCL.

The research published in Molecular Biology and Evolution reports the genome sequence of a malaria parasite sourced from blood-stained medical microscope slides used in 1944 in Spain, one of the last footholds of malaria in Europe.

Malaria was a major disease throughout Europe since antiquity and was only eradicated in the region in the 20th century.

The international team, led by UCL, the Institute of Evolutionary Biology (IBE), Barcelona, and the University of Copenhagen, analysed microscopy slides from the 1940s that were obtained with permission from the medical collection of Dr Ildefonso Canicio, a Spanish malaria researcher from the early 1900s. The slides were used to diagnose patients suffering from malaria in Spain's Ebro Delta, where malaria was common until the 1960s.

By comparing the genetic data from the slides to a global dataset of modern P. vivax genomes, the researchers found that the eradicated European malaria parasites were genetically most similar to tertian (P. vivax) malaria strains currently found in the Americas, including Mexico, Brazil and Peru.

"Being able to obtain a full genome of extinct European Plasmodium vivax from these decades old slides allowed us to ask questions as to how malaria may have been affecting us centuries ago," said co-lead author Dr Lucy van Dorp (UCL Genetics Institute).

"We found a clear relationship with modern Central and South American strains, establishing historic links spreading disease between these continents."

Analysing a historical sample also enabled the researchers to estimate mutation rates, helping them to infer when the different regional strains of P. vivax malaria diverged from each other. They estimated the last common ancestor between the eradicated European strain and the ones still present in the Americas to the 15th century.

This divergence is in line with European colonists introducing tertian malaria into the Americas and suggests indigenous peoples of the Americas were not infected before their contact with Europeans. There is no reliable evidence of malaria in the Americas before colonial times, but there are historical accounts of tertian malaria in Europe as far back as classical Greece.

"We could date the age of the spread to the Americas to around the 15th century, which clearly points to an introduction of the disease following European contact," explained co-author Professor Francois Balloux (UCL Genetics Institute).

The researchers were also able to gain new insights into how infectious disease agents can develop resistance to treatments. The team found that the 1940s malaria sample already had some genetic mutations which are known to confer resistance to modern anti-malarial drugs, despite them not having been in use at the time.

The findings suggest drug resistance potential may have already existed in some past malaria strains, possibly due to the historical use of quinine (which has been used to treat malaria as well as other ailments), allowing the parasite to evade modern medications soon after their introduction.

Professor Carles Lalueza-Fox, paleogeneticist at the Institute of Evolutionary Biology (IBE, CSIC-UPF) in Barcelona who co-led the study, said he is excited by the prospect of historical genomes to help us understand malaria: "My initial motivation to study this ancient malaria strain is the fact that my father contracted malaria in 1938, while crossing the Ebro region with the Republican army during the Spanish Civil War."

"After realising the potential of old medical material to understand modern infectious diseases, I got hooked and we're currently sourcing more slides from medical and museum collections to understand where malaria emerged first and then spread to other regions of the world."

The research was supported by the "la Caixa" Foundation, FEDER-Ministry of Science, Innovation and Universities (Spain), the European Research Council, the Medical Research Council (MRC, UK), and the Biotechnology and Biological Sciences Research Council (BBSRC, UK).

http://bit.ly/2OSVap4

Micro implants could restore standing and walking

University of Alberta research has a proven concept to restore spinal function

When Vivian Mushahwar first applied to grad school, she wrote about her idea to fix paralysis by rewiring the spinal cord.

It was only after she was accepted into a bioengineering program that the young electrical engineer learned her idea had actually prompted laughter. "I figured, hey I can fix it, it's just wires," Mushahwar said. "Yeah, well, it's not just wires. So I had to learn the biology along the way."

It's taken Mushahwar a lot of work over two decades at the University of Alberta, but the Canada Research Chair in Functional Restoration is still fixated on the dream of helping people walk again. And thanks to an electrical spinal implant pioneered in her laboratory and work in mapping the spinal cord, that dream could become a reality in the next decade.

Because an injured spinal cord dies back, it's not simply a matter of reconnecting a cable. Three herculean feats are needed. You have to translate brain signals. You have to figure out and control the spinal cord. And you have got to get the two sides talking again.

People tend to think the brain does all the thinking, but Mushahwar says the spinal cord has built-in intelligence. A complex chain of motor and sensory networks regulate everything from breathing to bowels, while the brain stem's contribution is basically "go!" and "faster!" Your spinal cord isn't just moving muscles, it's giving you your natural gait.

Other researchers have tried different avenues to restore movement. By sending electrical impulses into leg muscles, it's possible to get people standing or walking again. But the effect is strictly mechanical and not particularly effective. Mushahwar's research has focused on restoring lower-body function after severe injuries using a tiny spinal implant. Hair-like electrical wires plunge deep into the spinal grey matter, sending electrical signals to trigger the networks that already know how to do the hard work.

In a new paper in Scientific Reports, the team showcases a map to identify which parts of the spinal cord trigger the hip, knees, ankles and toes, and the areas that put movements together. The work has shown that the spinal maps have been remarkably consistent across the animal spectrum, but further work is required before moving to human trials.

The implications of moving to a human clinical setting would be massive, but must follow further work that needs to be done in animals. Being able to control standing and walking would improve bone health, improve bowel and bladder function, and reduce pressure ulcers. It could help treat cardiovascular disease--the main cause of death for spinal cord patients--while bolstering mental health and quality of life. For those with less severe spinal injuries, an implant could be therapeutic, removing the need for months of gruelling physical therapy regimes that have limited success.

"We think that intraspinal stimulation itself will get people to start walking longer and longer, and maybe even faster," said Mushahwar. "That in itself becomes their therapy."

Progress can move at a remarkable pace, yet it's often maddeningly slow. "There's been an explosion of knowledge in neuroscience over the last 20 years," Mushahwar said. "We're at the edge of merging the human and the machine."

Given the nature of incremental funding and research, a realistic timeline for this type of progress might be close to a decade.

Mushahwar is the director of the SMART Network, a collaboration of more than 100 U of A scientists and learners who intentionally break disciplinary silos to think of unique ways to tackle neural injuries and diseases. That has meant working with researchers like neuroscientist Kathryn Todd and biochemist Matthew Churchward,

both in the psychiatry department, to create three-dimensional cell cultures that simulate the testing of electrodes.

The next steps are fine-tuning the hardware--miniaturizing an implantable stimulator--and securing Health Canada and FDA approvals for clinical trials. Previous research has tackled the problem of translating brain signals and intent into commands to the intraspinal implant; however, the first generation of the intraspinal implants will require a patient to control walking and movement. Future implants could include a connection to the brain.

It's the same goal Mushahwar had decades ago. Except now it's no longer a laughable idea.

"Imagine the future," Mushahwar said. "A person just thinks and commands are transmitted to the spinal cord. People stand up and walk. This is the dream."

http://bit.ly/2Rrct20

Healing power of honey

How a Manuka honey 'sandwich' could be the key to fighting infections

Layering minute amounts of Manuka honey between layers of surgical mesh acts as a natural antibiotic that could prevent infection following an operation, new research has shown.

Meshes are used to help promote soft tissue healing inside the body following surgery and are common in operations such as hernia repair.

However, they carry with them an increased risk of infection as the bacteria are able to get a hold inside the body by forming a biofilm on the surface of the mesh.

Skin and soft tissue infections are the most common bacterial infections, accounting for around 10% of hospital admissions, and a significant proportion of these are secondary infections following surgery.

Currently, any infection is treated with antibiotics, but the emergence of antibiotic resistant strains - or 'superbugs' - means scientists are on the hunt for alternatives.

Sandwiching eight nano-layers of Manuka honey (with a negative charge) between eight layers of a polymer (with a positive charge), the international team of scientists and engineers led by Dr Piergiorgio Gentile at Newcastle University, UK, and Dr Elena Mancuso, at Ulster University, showed it is possible to create an electrostatic nanocoating on the mesh which in the lab inhibits bacteria for up to three weeks as the honey is slowly released.

Publishing their findings today in the academic journal Frontiers, the team says the study highlights the potential benefits of infusing medical implants with honey.

Dr Piergiorgio Gentile, lead author and a Biomedical Engineer at Newcastle University, explains:

"Mesh is implanted inside the body to provide stability while the internal tissues heal but, unfortunately, it also provides the perfect surface for bacteria to grow on. Once the bacteria form a biofilm on the surface, it's very difficult to treat the infection. By sandwiching the honey in a multilayer coating on the mesh surface and slowly releasing it, the aim is to inhibit the growth of the bacteria and stop the infection before it even starts.

"These results are really very exciting. Honey has been used to treat infected wounds for thousands of years but this is the first time it has been shown to be effective at fighting infection in cells from inside the body."

Dr Mancuso, a lecturer within the Nanotechnology and Integrated Bioengineering Centre (NIBEC) at Ulster University, adds:

"Although numerous antibiotic-based coatings, constructed through layered approaches, and intended for the development of antibacterial implants, have been investigated so far, it has been

found that the effect of antibiotics may decrease with time, since antibiotic resistant bacteria may potentially develop."

Ancient remedy

Honey has been used to treat infected wounds since ancient times, and thousands of years before the discovery of bacteria.

Most honey is believed to have some bacteria killing properties because it contains chemicals that produce hydrogen peroxide.

However, in 1991 a New Zealand study showed that when you remove the hydrogen peroxide from a range of honeys, Manuka - made from nectar collected by bees that forage on the wild Manuka tree - was the only type that kept its ability to kill bacteria. This is due to the presence of a unique ingredient, now identified as methylglyoxal, which has specific antimicrobial properties.

Using medical-grade Manuka honey, the team used the Layer-by-Layer assembly technology to create alternating layers of negatively-charged honey and positively-charged conventional biocompatible polymer to modify the surface of electrospun membrane, each layer just 10-20 nanometers thick.

Tested in-vitro on different soft tissue cell lines to test their biocompatibility, the functionalised meshes were exposed to a range of common bacterial infections such as MRSA, Staphylococcus and E coli.

"Too little honey and it won't be enough to fight the infection but too much honey can kill the cells," explains Dr Gentile. "By creating this 16-layerd 'charged sandwich' we were able to make sure the honey was released in a controlled way over two to three weeks which should give the wound time to heal free of infection."

Dr Mancuso adds:

"With our study we have demonstrated the promising combination of a naturally-derived antibacterial agent with a nanotechnology approach, which may be translated to the design and development of novel medical devices with advanced functionality."

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A common drug could help restore limb function after spinal cord injury

In mouse study, nerve pain drug gabapentin promotes regeneration of neural circuits

Long-term treatment with gabapentin, a commonly prescribed drug for nerve pain, could help restore upper limb function after a spinal cord injury, new research in mice suggests.

In the study, mice treated with gabapentin regained roughly 60 percent of forelimb function in a skilled walking test, compared to restoration of approximately 30 percent of forelimb function in mice that received a placebo.

The drug blocks activity of a protein that has a key role in the growth process of axons, the long, slender extensions of nerve cell bodies that transmit messages. The protein stops axon growth at times when synapses form, allowing transmission of information to another nerve cell.

The research showed that gabapentin blocks the protein from putting on its brakes, which effectively allowed axons to grow longer after injury.

"There is some spontaneous recovery in untreated mice, but it's never complete. The treated mice still have deficits, but they are significantly better," said senior author Andrea Tedeschi, assistant professor of neuroscience at The Ohio State University.

"This research has translational implications because the drug is clinically approved and already prescribed to patients," he said. "I think there's enough evidence here to reconsider how we use this drug in the clinic. The implication of our finding may also impact other neurological conditions such as brain injury and stroke."

The regained function in mice occurred after four months of treatment - the equivalent of about nine years in adult humans.

"We really have to consider that rebuilding neuronal circuits, especially in an adult central nervous system, takes time. But it can happen," said Wenjing Sun, research assistant professor of neuroscience at Ohio State and first author of the publication.

The study is published in the Journal of Clinical Investigation.

The spinal cord injury in these mice is located near the top of the spine. Humans with this type of injury generally lose enough sensation and movement to require assistance with daily living tasks.

After receiving gabapentin for four months, the treated mice were better able to move across a horizontal ladder and spread their forelimb toes than untreated mice. When the researchers used a special technique to silence neurons in the repair pathway they had targeted, there was no difference in functional recovery between treated and untreated mice.

"Now we can comfortably say that whatever we see in terms of structural and functional alterations of this motor pathway is really meaningful in promoting recovery in these mice," Tedeschi said.

Tedeschi noted that in this study, treatment with gabapentin occurred much earlier than is typical in human medicine, when it is prescribed to treat existing neuropathic pain and other neurological conditions.

"Gabapentin is given when the nervous system is already having issues associated with maladaptive plasticity that hinders normal function. We are giving it much, much earlier, when the nervous system may be more responsive to programming an adaptive repair process," he said.

A retrospective study of European medical data published in 2017 showed that individuals who had received anticonvulsants - gabapentin or a similar drug - early after spinal cord injury regained motor function. It was not a clinical trial, but the analysis showed an association between taking a class of drugs called gabapentinoids and regaining muscle strength.

Plenty of questions remain: how and when to adjust the amount of gabapentin used for treatment, and whether the drug could be combined with other interventions used to promote repair of an injured spinal cord at chronic stages. But testing the effectiveness of the drug in larger animal models is a logical next step prior to embarking on clinical trials, Tedeschi said.

"With all the evidence and mechanistic insight we provide, I feel like we are in a better situation to start planning a more translational type of research," he said. "It's the right time to try."

Tedeschi's research focuses on neurons in the corticospinal tract - specifically motor neurons that carry signals from the central nervous system to the body telling muscles to move. These cells are particularly important in controlling voluntary movement, which is impaired in cervical spinal cord injuries modeled in the study.

This work builds upon the recent discovery of the regulatory role of a neuronal receptor called alpha2delta2 in controlling axon growth ability. Tedeschi and colleagues have determined that alpha2delta2 facilitates synapse formation by putting on the brake for axon growth, an essential step during the development of the central nervous system.

The researchers discovered in the current study that after a cervical spinal cord injury, affected motor neurons above the spine increased the expression of this receptor, interfering with axons' ability to regrow. If axon repair doesn't go as expected and neuronal circuits are reorganized improperly, individuals with spinal cord injury may experience uncontrolled movement and pain.

"When neuronal circuits need to be rebuilt after injury, we need to down-regulate the expression of the receptor so axons can re-engage in an active growth program. And we found that it's doing

exactly the opposite," said Tedeschi, also a member of Ohio State's Chronic Brain Injury Discovery Theme.

"Because this receptor can be pharmacologically blocked through administration of clinically approved drugs called gabapentinoids - for example, gabapentin and pregabalin - that's a very powerful target that you can modulate as long as you take the drug."

This research was funded by the Craig H. Neilsen Foundation, the Marina Romoli Onlus Association, the Ohio State University Neuroscience Research Institute, and grants from the National Institute of Neurological Disorders and the National Institutes of Health. Additional Ohio State co-authors are Molly J. E. Larson, Conrad M. Kiyoshi, Alexander J. Annett, William A. Stalker and Juan Peng.

http://bit.ly/34WuqlN

Got a migraine? Relief may already be on your medicine shelf

A research review in The American Journal of Medicine shows that aspirin can be considered a possible clinical option to other, more costly treatment and preventive options for migraines

Philadelphia, December - According to a new report in *The American Journal of Medicine*, published by Elsevier, aspirin can be considered an effective and safe option to other, more expensive medications to treat acute migraines as well as prevent recurrent attacks. A review of randomized evidence suggests efficacy and safety of high dose aspirin in doses from 900 to 1,300 milligrams taken at the onset of acute symptoms. The data also support a lower dose of from 81 to 325 milligrams as a possible preventive option.

"Aspirin provides a possible clinical option for primary healthcare providers to relieve the debilitating symptoms of acute migraine headaches and prevent recurrent attacks. Aspirin's side effect profile and low cost may also favour its use," noted senior author Charles H. Hennekens, MD, DrPH, the first Sir Richard Doll Professor & Senior Academic Advisor to the Dean of the Charles E. Schmidt College of Medicine at Florida Atlantic University, Boca Raton, FL, USA. The investigators reviewed the randomized evidence for high dose aspirin in treatment and low dose aspirin in prevention of migraine headaches.

Migraine headache is the third most common disease in the world affecting about one in seven people. More prevalent than diabetes, epilepsy, and asthma combined, migraine headaches are among the most common and potentially debilitating disorders encountered by primary healthcare providers. Migraines are also associated with an increased risk of stroke. There are effective prescription medications available to treat acute migraine headaches as well as to prevent recurrent attacks. Nonetheless, in the United States many patients are not adequately treated for reasons that include limited access to healthcare providers, lack of health insurance, or high co-pays, which make expensive medications of proven benefit unaffordable. The rates of uninsured (or underinsured) have been estimated to be 8.5 percent nationwide and 13 percent in Florida. Furthermore, for all patients, the prescription drugs may be poorly tolerated or contraindicated.

Professor Hennekens mused that, "If aspirin were only half as effective, 10 times more expensive, and available by prescription, then perhaps patients and, possibly some of their healthcare providers, would take it more seriously."

"Despite the fact that aspirin is an over-the-counter drug," Dr. Hennekens cautioned, "as is the case for any drug used long term, it should be prescribed by a healthcare provider."

Joseph S. Alpert, MD, Editor-in-Chief of *The American Journal of Medicine* and Professor of Medicine, University of Arizona Department of Medicine, Tucson, AZ, USA, commented in an accompanying editorial, "My take home message from this thoughtful and carefully researched review is that physicians should always try the simple and inexpensive high dose aspirin regimen as the initial therapeutic attempt for migraine headache control. If aspirin works to abort or ameliorate the headaches, then it should be

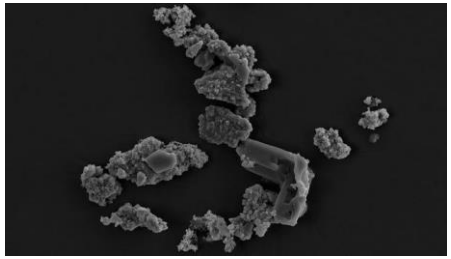
tried as a prophylactic measure to see if it can prevent the occurrence of these debilitating headaches. Hopefully, this would lead to less disability and loss of employment time for these patients who are so common in the US and throughout the world."

http://bit.ly/33WqE8A

Meteorite-loving microorganism

Archaeon can crunch meteorite and feed on it

Chemolithotrophic microorganisms derive their energy from inorganic sources. Research into the physiological processes of these organisms - which are grown on meteorite - provides new insights into the potential of extraterrestrial materials as a source of accessible nutrients and energy for microorganisms of the early Earth. Meteorites may have delivered a variety of essential compounds facilitating the evolution of life, as we know it on Earth.



These are meteorite dust fragments colonized and bioprocessed by M. sedula.
Credit: Tetyana Milojevic

An international team around astrobiologist Tetyana Milojevic from the University of Vienna explored the physiology and metal-microbial interface of the extreme metallophilic archaeon *Metallosphaera sedula*, living on and interacting with extraterrestrial material, meteorite Northwest Africa 1172 (NWA 1172). Assessing the biogenicity based on extraterrestrial materials provides a valuable source of information for exploring the putative extraterrestrial bioinorganic chemistry that might have occurred in the Solar System.

Archaeon prefers meteorites

Cells of *M. sedula* rapidly colonize the meteoritic material, much faster than the minerals of terrestrial origin. "Meteorite-fitness seems to be more beneficial for this ancient microorganism than a diet on terrestrial mineral sources. NWA 1172 is a multimetallic material, which may provide much more trace metals to facilitate metabolic activity and microbial growth. Moreover, the porosity of NWA 1172 might also reflect the superior growth rate of *M. sedula*", says Tetyana Milojevic.

Investigations on nanometer scale

The scientists traced the trafficking of meteorite inorganic constituents into a microbial cell and investigated iron redox behavior. They analyzed the meteorite-microbial interface at nanometer scale spatial resolution. Combining several analytical spectroscopy techniques with transmission electron microscopy, the researchers revealed a set of biogeochemical fingerprints left upon *M. sedula* growth on the NWA 1172 meteorite. "Our investigations validate the ability of *M. sedula* to perform the biotransformation of meteorite minerals, unravel microbial fingerprints left on meteorite material, and provide the next step towards an understanding of meteorite biogeochemistry", concludes Milojevic.

Publication in **Scientific Reports**

Tetyana Milojevic, Denise Kölbl, Ludovic Ferrière, Mihaela Albu, Adrienne Kish, Roberta Flemming, Christian Koeberl, Amir Blazevic, Ziga Zebec, Simon Rittmann, Christa Schleper, Marc Pignitter, Veronika Somoza, Mario Schimak, and Alexandra Rupert (2019) Exploring the microbial biotransformation of extraterrestrial material on nanometer scale. Sci. rep. DOI 10.1038/s41598-019-54482-7

http://bit.ly/38dUUbS

Medicine against bone disease found in the leaves of saussurea (トウヒレン属)

Bacterial bone infections are quite resistant to antibiotics and require new therapeutic approaches

Saussurea controversa is a perennial herbaceous plant that has been traditionally used by the people of the Far East, Siberia, Tibet, and Mongolia to treat liver, kidney, digestive tract, and locomotive diseases. Its dried leaves are sold in pharmacies because their decoction is widely used as a medicine against cold and bronchitis.

To understand what substances this plant owes its medicinal properties to, a team of scientists from Siberian State Medical University and Tomsk Polytechnic University extracted individual components from the plant and determined their composition. To do so, they passed the substances in gas form through a special station. As the substances were of different size, it took them different time to pass through it. The useful components of the decoction included flavonoids and polysaccharides. These groups of substances are known for their antimicrobial properties and the ability to speed up bone tissue regeneration. Flavonoids are small aromatic molecules, while polysaccharides are high molecular weight hydrocarbons. However, both have a positive effect on bone tissue regeneration.

Infectious locomotive diseases are considered one of the most difficult to treat. The microorganisms that attack bone tissue are often resistant to antibiotics. The restoration of the bone also plays an important role in the healing process. Medics from BFU suggested using Saussurea extract to treat bone tissue infections and tested its ability to affect stem cells. To do so, the extract of Saussurea leaves was added to the substrate with such cells. The growth of the cell culture slowed down under the influence of plant polysaccharides. It turned out that Saussurea did not stimulate the division of stem cells, but made them turn into bone tissue. This was confirmed by specific colouring.

To test the antibacterial properties of Saussurea, the team from BFU added the extract of its leaves into substrate with Staphylococcus aureus. These bacteria cause such deadly diseases as osteomyelitis, endocarditis, pneumonia, and sepsis. Moreover, they are highly resistant to a wide range of antibiotics making the therapy long and complicated. The experiment showed the decrease of S. aureus growth in the substrate with Saussurea compared to a control group.

"The isolated components have antimicrobial and regenerative properties. Our plan is to participate in the development of a medicinal drug for comprehensive treatment of bone diseases and injuries associated with the risk of infectious complications. Plant materials are less toxic. They can be administered as regular pills making the treatment much easier," concluded Larisa Litvinova, MD, a head of the Basic Laboratory for Immunology and Cell Biotechnologies, Professor of the Department of Fundamental Medicine, Institute of Medicine, Kant Baltic Federal University.

http://bit.ly/369F28w

Fungus produces active agent in a medicinal herb

Plant does not produce the active ingredients itself, they are made by a fungus that lives in the tissue of the flowers

Tatarinow's aster is used in traditional Chinese medicine to treat a number of ailments; the plant contains an active ingredient known as astin—and it is this agent which cancer researchers are now investigating. However, the plant does not produce the astins itself, as was assumed for a long time; instead, they are made by a fungus that lives in the tissue of the flowers.

Tatarinow's aster (Aster tataricus) シオン（紫苑) contains the drug astin only if it contains the fungus which makes it, C. asteris. Christiane Henno

The discovery was made by an international team including Dr. Thomas Schafhauser and Professor Wolfgang Wohlleben from the University of Tübingen, and Dr. Linda Jahn, Professor Jutta Ludwig-Müller and Professor Karl-Heinz van Pée of the Technische Universität Dresden. The researchers were successful in isolating the fungus, Cyanodermella asteris, and in cultivating it independently of the host plant. They have therefore laid the foundations for large-scale biotechnological production of astins.

The study has been published in the latest *Proceedings of the National Academy of Sciences*.

Collecting medicinal plants from the wild may endanger their survival. Even if plants are cultivated for the production of natural substances, difficulties arise: plant growth is comparatively slow; the substances are often only produced in small quantities and have to be extracted from the plant in complex processes. "The goal is therefore often cost-effective biotechnological production, as is the case here with astins," says Thomas Schafhauser. Astins bind to an important human regulatory protein; this may allow them to be used to suppress immune responses and to combat tumor growth.

"In order to develop a biotechnological process, we need to know which genes are involved and the metabolic pathway leading to production of the required substance," says Schafhauser. "Astins have an unusually complex chemical structure. Comparisons with similar substances indicate that bacteria or fungi make astins." The researchers discovered the fungus C. asteris living in the plant. In the researchers' experiments, the fungus was easy to propagate and cultivate outside the plant. It also produced large amounts of astin. "In addition, we fully sequenced the fungal genome," Schafhauser says. In the decoded genome, the team found the genes that are responsible for the synthesis of the astin molecule. This is an important requirement for the development of biotechnological methods for the commercial production of astin.

Cooperation between different species

In experiments, the researchers proved that individuals of the Aster tataricus did not produce astin unless the fungus C. asteris was present. The function could be restored by re-infection with the fungus. "Furthermore, these plants contained the variant astin A, which the fungus could not produce when cultivated individually," Linda Jahn reports. "We assume that the fungus and the plant work together to their mutual advantage in symbiosis, and that the plant gives a signal for the production of astin A or processes the astin from the fungus itself."

Such metabolic pathways, which require symbiosis between two or more biological partners, have so far been largely unexplored. "It may be that they are very common, but we do not know enough about them," says Jahn. In the case of Tatarinow's aster, it is unclear to what extent the complex substance astin provides an advantage. It could play a role in fending off predators or pathogens.

More information: *Thomas Schafhauser et al. Antitumor astins originate from the fungal endophyte Cyanodermella asteris living within the medicinal plant Aster tataricus. Proceedings of the National Academy of Sciences, December 2, 2019.* *www.pnas.org/cgi/doi/10.1073/pnas.1910527116*

http://bit.ly/38kSjwz

Brewing beer that tastes fresh longer

Lager yeast to make more molecules that protect beer against staling

Unlike wine, which generally improves with time, beer does not age well. Usually within a year of bottling, the beverage starts to develop an unpleasant papery or cardboard-like flavor that drinkers describe as "stale." Now, researchers reporting in ACS' *Journal of Agricultural and Food Chemistry* have engineered lager yeast to make more molecules that protect beer against staling, resulting in improved flavor stability.

Scientists have linked stale beer flavors to aldehyde compounds, such as (*E*)-2-nonenal and acetaldehyde. Many of these compounds are produced by yeast during fermentation, and chemical reactions during beer storage can increase their levels. Brewers have tried different approaches to reduce levels of these compounds, such as controlling the fermentation conditions or adding antioxidants, but staling remains a problem for the beer industry. That's why Qi Li and colleagues wanted to genetically modify lager yeast to produce more of a molecule called NADH. Extra NADH could boost the activities of natural yeast enzymes that change aldehydes into other

types of compounds that don't contribute to a stale flavor, the researchers reasoned.

The researchers used a genetic technique called "overexpression," in which they artificially increased the levels of various genes related to NADH production. With this method, they identified four genes that, when overexpressed, increased NADH levels. The team found that beer from the overexpressing yeast contained 26.3-47.3% less acetaldehyde than control beer, as well as decreased levels of other aldehydes. In addition, the modified strains produced more sulfur dioxide, a natural antioxidant that also helps reduce staling. Other flavor components were marginally changed. This approach could be useful for improving the flavor stability and prolonging the shelf life of beer, the researchers say.

The authors acknowledge funding from the National Natural Science Foundation of China, Priority Academic Program Development of Jiangsu Higher Education Institutions, Program of Introducing Talents of Discipline to Universities, Postgraduate Research & Practice Innovation Program of Jiangsu Province, the Fundamental Research Funds for the Central Universities and China Scholarship Council.

The abstract that accompanies this study is available here.

http://bit.ly/2P0KkNF

Famous Fox Domestication Experiment Challenged

The tamed foxes, whose appearances changed with breeding, weren't wild to begin with, say the authors of a new study.

Emily Makowski

A paper published yesterday (December 3) in *Trends in Ecology and Evolution* criticizes a famous experiment on fox taming and casts doubt on domestication syndrome, the idea that a variety of physical traits change when an animal goes from wild to tame.

Above: Flickr.Com, Zoofanatic

In the 1950s, geneticist Dmitri Belyaev conducted a well-known animal domestication experiment at the Institute of Cytology and Genetics in Novosibirsk, Russia, in which he tamed silver foxes (*Vulpes vulpes*) by selectively breeding the friendliest ones.

Within 10 generations, the foxes showed dog-like behaviors, such as seeking out human contact and licking people's hands and faces. Their appearance also changed—they developed tails that curled up, spotted coats, and floppy ears similar in appearance to other domesticated animals such as dogs, cows, and pigs. This led Belyaev and other researchers to suggest that certain physical traits evolve with tameness, a phenomenon that came to be known as domestication syndrome.

But Belyaev's foxes weren't wild to begin with, say the authors of the new study, led by geneticist Elinor Karlsson at the University of Massachusetts Medical School and the Broad Institute of MIT and Harvard. Genetic testing suggests that the foxes Belyaev obtained were from a Canadian fur farm, where farmers may have already been breeding animals to have unusual spotted patterns. And Belyaev started his experiment with a relatively small population of 130 foxes, which could have made traits such as spots spread more quickly.

Researchers had already raised questions about the foxes' tameness in the past. When the late Raymond Coppinger, a dog evolution researcher at Hampshire College, visited the International Fox Museum and Hall of Fame on Prince Edward Island, Canada, he was taken aback to see pictures of spotted foxes that looked just like Belyaev's foxes, reports *The New York Times*.

"The paper provides the final nail in the coffin to the idea of a universal set of traits characterizing all domesticated animals," Marcelo Sánchez-Villagra, a paleobiologist at the University of Zurich who studies domestication and was not involved in the study, tells the *Times*.

Additionally, Karlsson's team did not find conclusive evidence that dogs hold their tails differently from wild species of foxes or

wolves, and found limited evidence that it happens in other mammals. “Our main point is not that domestication syndrome doesn’t exist, but just that we don’t think there is enough evidence to be confident it does exist,” Karlsson tells *The Washington Post*.

http://bit.ly/38ke6EI

Harmful Bacteria Masquerade as Red Blood Cells to Evade the Immune System

Studying the stealthy strategy could help researchers develop new treatments for group A strep infections, which kill more than 500,000 people each year

By Katherine J. Wu smithsonian.com

Even single cells must sometimes be masters of disguise.

Various types of harmful bacteria, for example, masquerade as human cells to evade the immune system, blanketing their surfaces with molecules that resemble our own. The clever trick effectively gives the pathogens “cloaks of invisibility,” says David Gonzalez, a biochemist and microbiologist at the University of California, San Diego.

Now, Gonzalez and his team have discovered a new form of this microbial mimicry that’s especially macabre. To avoid being snuffed out by the immune system, the bacteria that cause strep throat tear apart red blood cells and then dress themselves in the debris, as reported today in the journal *Cell Reports*.

When this strategy works, the bacteria, called Group A *Streptococcus* (group A strep), remain concealed while they wreak havoc on the body, the study’s mouse experiments show. But when a protein in the bacteria responsible for the sanguine disguise is snipped out of the strep genome, the microbes are left exposed, allowing the immune system to attack the pathogens and prevent a potentially deadly infection.

Understanding the biology behind group A strep’s bloody disappearing act might aid the search for new drugs that “uncloak the bacteria so they can be effectively cleared or killed,” says Martina Sanderson-Smith, a molecular microbiologist at the University of Wollongong in Australia who wasn’t involved in the study. “This is an example of discovery science at its best.”

Among pathogens, group A strep is something of a Swiss Army knife. These versatile microbes can colonize the skin, throat, genitals and more, and they infect hundreds of millions of people each year. Many infections don’t progress further than an annoying rash or sore throat, but under more dire circumstances, the bacteria can threaten lives with conditions like rheumatic fever, toxic shock syndrome or flesh-eating disease.

Though antibiotics against group A strep exist, resistance to some drugs is growing among strains worldwide, and no vaccines are commercially available. Finding new treatments to combat these pathogens, Gonzalez says, could prevent some of the 500,000-plus deaths they cause annually.

Much of how group A strep manages to outsmart the body’s defenses remains mysterious. To better understand the bacteria’s elusive ways, Gonzalez and his lab have spent the past few years studying the suite of molecules produced by the pathogen during infection. Some of these molecules stick to red blood cells, including a handful of proteins that can rip the cells to shreds.

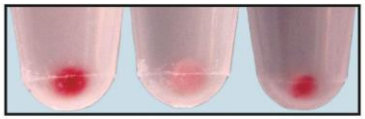
But when the researchers used nanoparticles coated with pieces of blood cells as bait, they snared a new protein called S protein. Instead of tearing blood cells apart, this molecule allowed the bacteria to cling to the pieces left behind.

At first, the seemingly innocuous stickiness of S protein baffled Gonzalez and his team. But they soon realized it might allow the bacteria to pass as the very cells they’d destroyed—the microscopic equivalent of wolves in sheep’s clothing.

The deception is an unusual tactic, but an effective one, says co-first author Anaamika Campeau, a biochemist in Gonzalez's lab. To hide any features that might incriminate group A strep as foreign invaders, the microbes plaster themselves with pieces of cells the immune system sees all the time and knows not to attack, she explains. "Once we kind of came to that idea, it all sort of fell into place."

The interaction between group A strep and red blood cells was so strong that the bacteria turned bright crimson when plopped into solutions of human blood. Immune cells, flummoxed by the bloody disguise, largely failed to capture and kill the would-be invaders.

When the researchers generated a mutant strain of the bacteria that couldn't make S protein, however, it struggled to disguise itself, turning only faintly pink in the presence of blood. The modified pathogens didn't fool the immune cells, which quickly gobbled up their targets.



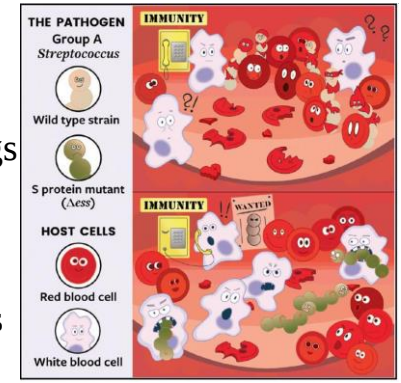
***Normal group A strep (right) turn bright red when they're mixed with red blood cells, disguising themselves as the blood cells. Group A strep missing S protein (middle) are only faintly pink. A strain with S protein added back (right) look normal.* (Wierzbicki et al. / Cell Reports 2019)**

To test the potency of S protein's evasive effects, the researchers then injected each of the two bacterial strains into mice. While nearly all the animals infected with typical group A strep rapidly lost weight and died, every mouse that got the mutant microbes survived and remained at a healthy size.

The difference was so striking that, at first, Gonzalez and his team were certain they'd made a mistake. But even with more than the lethal dose of mutant bacteria, he says, "the mice were still just as happy as can be."

Microbes mimicking host cells isn't a new biological trick, says Tiara Pérez Morales, a molecular microbiologist at Benedictine University who wasn't involved in the study. But the new study puts a plot twist on an old story. "They're putting on a costume and pretending they're red blood cells," she says. "I don't think I can think of anything else like it."

The loss of S protein so severely hamstrings the bacteria that the molecule could be an appealing target for new drugs in the future, Sanderson-Smith says. Blocking the protein's activity during infection would essentially leave the bacteria in the buff, helping immune cells identify and destroy the pathogens.



***A graphical abstract of pathogen Group A Streptococcus camouflaged as red blood cells.* (Dorota Wierzbicki)**

Gonzalez hopes that S-protein-based treatments will go beyond simply unmasking group A strep. After receiving a hefty dose of the mutant bacteria, mice began to churn out immune proteins—an indication, he says, that the altered strain had alerted the body to its presence without causing it serious harm. The microbes, it seemed, had become a living vaccine.

The team then conducted a final experiment, dosing mice with either the mutant bacteria or a saline solution before reinfecting them with normal group A strep three weeks later. While 90 percent of the animals given saline died within ten days, seven out of the eight mice that had first been exposed to the mutant strain pulled through.

"That was exciting to see," says Pérez Morales, adding that the findings could prove especially significant if they can be repeated in other members of the *Streptococcus* genus, which includes several other pathogens that appear to also make S protein.

But Pérez Morales and Sanderson-Smith caution that a lot more needs to happen before human vaccination can be considered.

Microbes and the immune cells they parry with are extremely complex and ever-evolving, and what works in mice doesn't always translate into people. Other vaccine candidates have shown promise over the years, but they've encountered several hurdles that have kept them out of the clinic.

Still, as the issue of antibiotic resistance continues to balloon worldwide, this study highlights the importance of taking creative new approaches to treatment. "We need alternatives," Pérez Morales says. "We can't just keep hitting this problem with antibiotics."

http://bit.ly/2P10hTZ

Early humans domesticated themselves, new genetic evidence suggests

Humans may lack the large, pronounced facial features of our primate ancestors like Neanderthals because we have "self-domesticated."

By Michael Price

When humans started to tame dogs, cats, sheep, and cattle, they may have continued a tradition that started with a completely different animal: us. A new study—citing genetic evidence from a disorder that in some ways mirrors elements of domestication—suggests modern humans domesticated themselves after they split from their extinct relatives, Neanderthals and Denisovans, approximately 600,000 years ago.

"The study is incredibly impressive," says Richard Wrangham, a biological anthropologist at Harvard University who was not involved in the new work. It's "a really beautiful test," he adds, of the long-standing idea that humans look so different from our primate ancestors precisely because we have become domesticated.

Domestication encompasses a whole suite of genetic changes that arise as a species is bred to be friendlier and less aggressive. In dogs and domesticated foxes, for example, many changes are physical: smaller teeth and skulls, floppy ears, and shorter, curlier tails. Those physical changes have all been linked to the fact that domesticated animals have fewer of a certain type of stem cell, called neural crest stem cells.

Modern humans are also less aggressive and more cooperative than many of our ancestors. And we, too, exhibit a significant physical change: Though our brains are big, our skulls are smaller, and our brow ridges are less pronounced. So, did we domesticate ourselves?

Giuseppe Testa, a molecular biologist at University of Milan in Italy, and colleagues knew that one gene, *BAZ1B*, plays an important role in orchestrating the movements of neural crest cells. Most people have two copies of this gene. Curiously, one copy of *BAZ1B*, along with a handful of others, is missing in people with Williams-Beuren syndrome, a disorder linked to cognitive impairments, smaller skulls, elfinlike facial features, and extreme friendliness.

To learn whether *BAZ1B* plays a role in those facial features, Testa and colleagues cultured 11 neural crest stem cell lines: four from people with Williams-Beuren syndrome, three from people with a different but related disorder in which they have duplicates instead of deletions of the disorder's key genes, and four from people without either disorder. Next, they used a variety of techniques to tweak *BAZ1B*'s activity up or down in each of the stem cell lines.

That tweaking, they learned, affected hundreds of other genes known to be involved in facial and cranial development. Overall, they found that a tamped-down *BAZ1B* gene led to the distinct facial features of people with Williams-Beuren syndrome, establishing the gene as an important driver of facial appearance.

When the researchers looked at those hundreds of *BAZ1B*-sensitive genes in modern humans, two Neanderthals, and one Denisovan, they found that in the modern humans, those genes had accumulated loads of regulatory mutations of their own. This

suggests natural selection was shaping them. And because many of these same genes have also been under selection in other domesticated animals, modern humans, too, underwent a recent process of domestication, the team reports today in *Science Advances*.

Wrangham cautions that many different genes likely play a role in domestication, so we shouldn't read too much evolutionary importance into *BAZ1B*. "What they've zeroed in on is one gene that is incredibly important … but it's clear there are going to be multiple other candidate genes."

William Tecumseh Fitch III, an evolutionary biologist and cognitive scientist at the University of Vienna, says he is skeptical of "precise parallels" between human self-domestication and animal domestication. "These are processes with both similarities and differences," he says. "I also don't think mutations in one or a few genes will ever make a good model for the many, many genes involved in domestication."

As for why humans might have become domesticated in the first place, hypotheses abound. Wrangham favors the idea that as early people formed cooperative societies, evolutionary pressures favored mates whose features were less "alpha," or aggressive. "There was active selection, for the very first time, against the bullies and the genes that favored their aggression," he adds. But so far, "Humans are the only species that have managed this."

https://wb.md/2RxWI9y

Few Med Students Come From Rural Areas, Study Finds

***Students from rural areas made up only 4.3% of all incoming medical students in 2017, according to a study published online yesterday in* Health Affairs.**

Marcia Frellick

There were even fewer students from underrepresented racial/ethnic minority groups who came from rural backgrounds — less than 0.5% of students.

"If the number of rural students entering medical school were to become proportional to the share of rural residents in the US population, the number would have to quadruple," write Scott A. Shipman, MD, MPH, director of primary care initiatives and clinical innovations at the Association of American Medical Colleges in Washington, DC, and colleagues.

The 2017 numbers cap off a 15-year decline in rural students entering medical school, the authors point out, and that is particularly concerning because medical students who grow up in a rural setting are much more likely to practice there and are more likely to enter primary care, research has shown.

The combination of heightened healthcare needs in rural areas and the worsening physician shortages in these areas underscores the importance of the findings.

The authors note that rural populations have higher rates of many chronic illness, get fewer recommended preventive services, and have seen fewer gains in life expectancy than urban populations. They also have higher rates of maternal and infant deaths.

In the current physician workforce, only 11% practice in rural communities. Yet more than 62% of all federally designated primary care Health Professional Shortage Areas are in rural parts of the country. "This gap in access to physician care is likely to be an important contributor to increased rural morbidity and mortality," the authors write.

The urban–rural gap is also widening in the application process for medical schools. The number of rural applicants dropped by 18% from 2002 to 2017. During the same period, the number of urban applicants increased by 59%. "The declining pool of rural applicants suggests that more needs to be done to help rural

children and young adults identify a pathway to becoming a physician," the authors write.

They suggest that high schools increase awareness of medical careers and help students prepare their college applications. Colleges can offer MCAT preparation courses and opportunities to shadow physicians and offer financial aid education to introduce medical education as an attainable goal instead of a pipe dream, they say. The researchers note that the decline in medical students coming from rural backgrounds has happened even against a backdrop of substantial medical school expansion.

Rural Students May Be Missed Among Traditional Minority Groups

New schools may be focusing more on recruiting the traditionally unrepresented minority students and those from lower-income households but may be missing an important underrepresented group, the researchers suggest.

"Having new and established schools consider rural background as an important component of a diverse student body and tracking the schools' effectiveness in increasing diversity in this area could have a significant impact on the dearth of rural students, thereby supporting the future adequacy of the rural workforce," they explain.

The authors acknowledge that situating medical school campuses in rural areas has cost constraints, but more clinical rotations could be offered there, "especially longitudinal integrated clerkships."

Not included in this analysis were some factors that may influence admission decisions. For instance, prior research has shown that rural students don't tend to do as well as their urban counterparts in multiple "mini-interviews." They may also have less research experience and that may be highly valued by some medical schools.

"These factors require further study and potential interventions to ensure that rural applicants are competitive," Shipman and colleagues write.

The researchers used the 2013 Rural-Urban Continuum Codes of each medical school applicant's birth and high school graduation county to set the definition for rural background in this study.

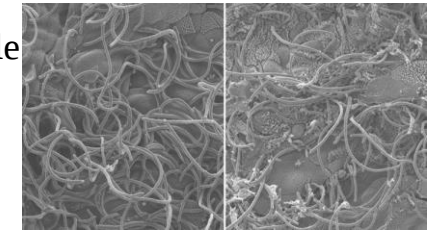
The study had no specific funding. The study authors have disclosed no relevant financial relationships.

Health Aff. Published online December 3, 2019. Abstract

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

'Stomach-ache' neurons rush to the rescue when bacteria invade

Gut neurons that trigger unpleasant symptoms also rally the body's defenses against Salmonella.



Nerve cells in the gut have a leading role in preventing a misery that afflicts millions of people every year: diarrhea and vomiting caused by infection with *Salmonella* bacteria.

Protective bacteria (left) carpet a portion of a mouse's intestine but are less dense in mice lacking nerve cells that keep the bacteria in place. **Credit: Nicole Lai, Anja Nordstrom and Isaac Chiu**

Nerve cells called nociceptors monitor the gut and, if they notice problems, trigger a defense response, such as stomach pain. To investigate these cells' defensive powers, Isaac Chiu at Harvard Medical School in Boston and his colleagues bred mice missing one class of nociceptors. The team then infected the mice with the bacterium *Salmonella enterica*, a common cause of intestinal distress. One day later, the mice without nociceptors had nearly 100 times more bacteria in one portion of the gut than normal mice did.

The researchers also found that when nociceptors are active, the density of gut cells that provide entry points for *Salmonella* bacteria is lower. The nerve cells also maintain the presence of beneficial gut microbes called segmented filamentous bacteria, which ward off *Salmonella* infection.

Targeting nociceptors might yield effective treatments for infectious and inflammatory diseases, the authors say.

http://bit.ly/2P17dRf

Even 50-year-old climate models correctly predicted global warming

Climate models dating back to the early 1970s accurately foretold how greenhouse gases would fuel a hotter future, such as the July heat wave that sent Parisians flocking to the Fountaine du Trocadéro.

By Warren Cornwall

Climate change doubters have a favorite target: climate models. They claim that computer simulations conducted decades ago didn't accurately predict current warming, so the public should be wary of the predictive power of newer models. Now, the most sweeping evaluation of these older models—some half a century old—shows most of them were indeed accurate.

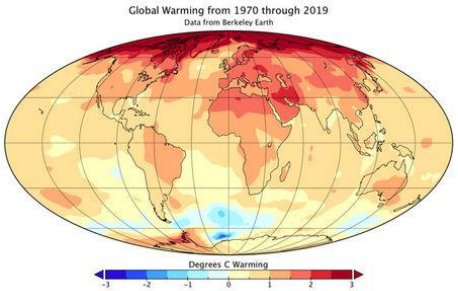
"How much warming we are having today is pretty much right on where models have predicted," says the study's lead author, Zeke Hausfather, a graduate student at the University of California, Berkeley.

Climate scientists first began to use computers to predict future global temperatures in the early 1970s. That's when newfound computing power coincided with a growing realization that rising carbon dioxide levels could boost global temperatures. As the issue gained public attention, critics questioned the reliability of rudimentary model predictions. Even a 1989 news article in *Science* radiated skepticism, stating that "climatologists may have a gut feeling that the greenhouse effect is heating up the Earth, but they have not been close to proving it."

Today, the models are much more sophisticated. Mainframe computers driven by paper punch cards have given way to supercomputers running trillions of calculations in 1 second. Modern models account for myriad interactions, including ice and snow, changes in forest coverage, and cloud formation—things that early modelers could only dream of doing. But Hausfather and his colleagues still wanted to see how accurate those bygone models really were.

The researchers compared annual average surface temperatures across the globe to the surface temperatures predicted in 17 forecasts. Those predictions were drawn from 14 separate computer models released between 1970 and 2001. In some cases, the studies and their computer codes were so old that the team had to extract data published in papers, using special software to gauge the exact numbers represented by points on a printed graph.

Most of the models accurately predicted recent global surface temperatures, which have risen approximately 0.9°C since 1970. For 10 forecasts, there was no statistically significant difference between their output and historic observations, the team reports today in *Geophysical Research Letters*.



Global temperatures have risen approximately 0.9°C since 1970, though some areas have warmed much more than others. **Berkeley Earth**

Seven older models missed the mark by as much as 0.1°C per decade. But the accuracy of five of those forecasts improved enough to match observations when the scientists adjusted a key input to the models: how much climate-changing pollution humans have emitted over the years. That includes greenhouse gases and aerosols, tiny particles that reflect sunlight. Pollution levels hinge on a host of unpredictable factors. Emissions might rise or fall because of regulations, technological advances, or economic booms and busts.

To take one example, Hausfather points to a famous 1988 model overseen by then–NASA scientist James Hansen. The model predicted that if climate pollution kept rising at an even pace, average global temperatures today would be approximately 0.3°C warmer than they actually are. That has helped make Hansen's work a popular target for critics of climate science.

Hausfather found that most of this overshoot was caused not by a flaw in the model's basic physics, however. Instead, it arose because pollution levels changed in ways Hansen didn't predict. For example, the model overestimated the amount of methane—a potent greenhouse gas—that would go into the atmosphere in future years. It also didn't foresee a precipitous drop in planet-warming refrigerants like some Freon compounds after international regulations from the Montreal Protocol became effective in 1989.

When Hausfather's team set pollution inputs in Hansen's model to correspond to actual historical levels, its projected temperature increases lined up with observed temperatures.

The new findings echo what many in the climate science world already know, says Piers Forster, an expert in climate modeling at the United Kingdom's University of Leeds. Still, he says, "It's nice to see it confirmed."

Forster notes that even today's computer programs have some uncertainties. But, "We know enough to trust our climate models" and their message that urgent action is needed, he says.

The new research is a useful exercise that "should provide some confidence that models can be used to help provide guidance regarding energy policies," adds Hansen, now director of the Climate Science, Awareness and Solutions Program at Columbia University.

He communicated with *Science* from Madrid, where world leaders are gathering this week for the 25th annual United Nations climate conference. Delegates from around the world are negotiating how to implement emissions cuts agreed to at the 2016 meeting in Paris. Meanwhile, a U.N. report issued last month showed greenhouse gas emissions have continued to climb since then, and that many of the biggest polluting countries aren't on track to meet their promises.

http://bit.ly/36iMD4B

How Microbiomes Affect Fear

New studies help to explain how microbes in the gut can shape a host's fear responses.

Elena Renken ***Writing Intern***

Our brains may seem physically far removed from our guts, but in recent years, research has strongly suggested that the vast communities of microbes concentrated in our digestive tract open lines of communication between the two. The intestinal microbiome has been shown to influence cognition and emotion, affecting moods and the state of psychiatric disorders, and even information processing. But how it could do so has been elusive.

Until recently, studies of the gut-brain relationship have mostly shown only correlations between the state of the microbiome and operations in the brain. But new findings are digging deeper, building on research that demonstrates the microbiome's involvement in responses to stress. Focusing on fear, and specifically on how fear fades over time, researchers have now tracked how behavior differs in mice with diminished microbiomes. They identified differences in cell wiring, brain activity and gene expression, and they pinpointed a brief window after birth when restoring the microbiome could still prevent the adult behavioral deficits. They even tracked four particular compounds that may help to account for these changes. While it may be too early to predict what therapies could arise once we understand this relationship between the microbiome and the brain, these concrete differences substantiate the theory that the two systems are deeply entwined.

Pinning down these mechanisms of interaction with the brain is a central challenge in microbiome research, said Christopher Lowry, an associate professor of integrative physiology at the University of Colorado, Boulder. “They have some tantalizing leads,” he added.

Coco Chu, the new study’s lead author and a postdoctoral associate at Weill Cornell Medicine, was intrigued by the concept that microbes inhabiting our bodies could affect both our feelings and our actions. Several years ago, she set out to examine these interactions in fine-grained detail with the help of psychiatrists, microbiologists, immunologists and scientists from other fields.

The researchers performed classical behavioral training on mice, some of which had been given antibiotics to dramatically diminish their microbiomes and some of which had been raised in isolation so that they had no microbiome at all. All the mice learned equally well to fear the sound of a tone that was followed by an electric shock. When the scientists discontinued the shocks, the ordinary mice gradually learned not to fear the sound. But in the mice with depleted or nonexistent microbiomes, the fear persisted — they remained more likely to freeze at the sound of the tone than the untreated mice did.

Peering inside the medial prefrontal cortex, an area of the outer brain that processes fear responses, the researchers noticed distinct differences in the mice with impoverished microbiomes: Some genes were expressed less. One type of glial cell never developed properly. Spiny protrusions on the neurons associated with learning grew less plentifully and were eliminated more often. One type of cell showed lower levels of neural activity. It’s as if the mice without healthy microbiomes couldn’t learn to be unafraid, and the researchers could see it on a cellular level.

The researchers also set out to learn how the condition of the microbiome in the gut caused these changes. One possibility was that microbes send signals to the brain through the long vagus nerve, which carries sensations from the digestive tract to the brain stem. But snipping the vagus didn’t alter the behavior of the mice. It also seemed possible that the microbiomes might stir up responses in the immune system that affect the brain, but the numbers and proportions of immune cells in all the mice were similar.

But the researchers did pinpoint four metabolic compounds with neurological effects that were far less common in the blood serum, cerebrospinal fluid and stool of the mice with impaired microbiomes. Some of the compounds were already linked to neurological disorders in humans. The team speculated that the microbiome might produce certain substances in abundance, with some molecules making their way into the brain, according to the microbiologist David Artis, the director of the Jill Roberts Institute for Research in Inflammatory Bowel Disease at Weill Cornell Medicine and the senior author on the study.

In many laboratories, there’s a growing interest in tracking specific bacterial substances that are involved in nervous system signaling, said Melanie Gareau, an associate professor of anatomy, physiology and cell biology at the University of California, Davis. Numerous metabolites and pathways are probably involved in such processes.

Research on other disorders like depression has also pointed to the involvement of particular compounds created by microbes, but there’s still no consensus on which ones contribute to any condition, said Emeran Mayer, a professor of medicine and director of the G. Oppenheimer Center for Neurobiology of Stress and Resilience at the University of California, Los Angeles. And although the intestinal microbiome is clearly altered in many people with brain conditions, it’s often unclear if that change is a cause or an effect, he said. Differences in the microbiome might give rise to neurological problems, but the conditions could also change the microbiome.

There's disagreement within the field not just about the consequences of diseased microbiomes, but also about healthy ones. "For a long time, we've been focused on this idea that we could identify specific types of bacteria that provide either risk or resilience to stress-related disorders, and it may be that it doesn't have to be a particular microbe," Lowry said. Even in healthy people, microbiomes vary widely. Particular microbes might not matter if a microbiome has enough diversity — just as there are many kinds of thriving forests, and one individual type of tree may not be necessary.

Still, the study of microbial effects on the nervous system is a young field, and there is even uncertainty around what the effects are. Previous experiments reached inconsistent or contradictory conclusions about whether microbiome changes helped animals to unlearn fear responses. What gives extra weight to the findings from Chu and her colleagues is that they can point to evidence for a specific mechanism causing the behavior they observed. Animal studies like this one are especially helpful in cementing a clear connection between the nervous system and the microbiome, even if they don't point to treatments for humans, said Kirsten Tillisch, a professor of medicine at the David Geffen School of Medicine at UCLA. "The way that humans process emotion, physical sensation and cognition in the brain is just so different than in animals that it's just very difficult to translate," she said.

In theory, the presence of certain microbial substances might help predict who is most vulnerable to disorders like post-traumatic stress disorder. Experiments like these could even identify pathways of communication between the brain and the microbiome that could be targeted by treatments. "That's always the big hope from these mouse experiments, that we're getting close to interventions," Mayer said, and the studies often generate striking results through rigorous methods. But the operations of the human brain aren't fully reflected in mice. Moreover, the interactions of the brain and the gut microbiome differ in humans and mice, and diet-driven differences between their respective microbiomes add to the disparity.

For humans, interventions targeting the microbiome might be most effective in infancy and childhood, when the microbiome is still developing and early programming takes place in the brain, Mayer said. In this new research, the scientists saw a specific window of time in infancy when mice needed a typical microbiome to extinguish fear normally when they grew up. Mice that were totally isolated from microbes for their first three weeks were then mixed in with mice that had typical microbiomes. The germ-free mice picked up the microbes of the other mice and developed rich microbiomes, but when they grew up and went through the same fear unlearning experiments, they still showed deficits. At only a few weeks old, they were still too old to learn to extinguish their fear normally.

But when microbiomes were restored in newborn mice, who gained rich microbiomes after they were placed with foster parents, the infant mice grew up to behave normally. In the first few weeks after birth, the microbiome appeared to be critical — an insight that fits smoothly into the larger idea that circuits governing fear sensitivity are impressionable during early life, Tillisch said.

The kind of fear unlearning that the researchers tested is a fundamental skill in an evolutionary sense, Artis said. Knowing what merits fear and adapting when it no longer poses a threat can be crucial to survival. An inability to extinguish fear is also present in PTSD and tied to other brain disorders, so deepening scientific knowledge around the mechanisms that influence this circuitry could illuminate core human behaviors and pave the way for potential therapies.

On an evolutionary timescale, human microbiomes have changed as more people have come to live in cities, and brain disorders have become increasingly prominent. The swarms of microbes inhabiting each of us have evolved with our species, and it's vital that we understand how they impact both physical and mental health, Lowry said. Our environments may affect our nervous systems by way of the microbiome, adding new layers of complexity to the study of health and disease in the brain.

https://bbc.in/2PsWqXr

Typhoid vaccine 'works fantastically well'

A new typhoid vaccine works "fantastically well" and is being used to help stop an almost untreatable strain of the infection, doctors say.

By James Gallagher Health and science correspondent

Cases of the bacterial disease fell by more than 80% in trials, published in the New England Journal of Medicine. Experts said the vaccine was a game-changer and would reduce the "terrible toll wrought by typhoid". Nine million children are being immunised in Pakistan, where typhoid is now extremely resistant to antibiotics.

What is typhoid fever?

Typhoid fever is caused by highly contagious *Salmonella Typhi* bacteria and spread through contaminated food and water.

It is a disease of poverty, most common in countries with poor sanitation and a lack of clean water.

Symptoms include:

- ***prolonged fever***
- ***headache***
- ***nausea***
- ***loss of appetite***
- ***constipation***

It causes fatal complications, such as internal bleeding, in one in 100 people.

Precise numbers on typhoid are hard to collect but it affects between 11 and 21 million people around the world each year and kills 128,000 to 161,000.

World Health Organization: Typhoid fever

What happened in the trial?

More than 20,000 children - aged from nine months to 16 years - in Kathmandu Valley, Nepal, took part in the trial. Typhoid is a major public-health problem in the area. Half of the children were given the vaccine and their cases of typhoid fell by 81% in the first year of the study.

"It works fantastically well in preventing this disease affecting some of the world's most vulnerable children," Prof Andrew Pollard, from the University of Oxford, who has been involved in the trials, told BBC News.

"The burden of typhoid is so huge, we're seeing families taking children into hospital to be treated and being plunged into poverty paying for the costs of investigation and treatment with antibiotics.

"The arrival of this vaccine to control the disease is a pretty exciting moment."

The children in Nepal, as well as those taking part in trials in Malawi and Bangladesh, will now be followed to see how long protection lasts.

Typhoid Vaccine Acceleration Consortium director Dr Kathleen Neuzil said the vaccine could "reduce disease and save lives in populations that lack clean water and improved sanitation".

Why is a vaccine needed?

The World Health Organization has warned typhoid has acquired a "crazy amount" of antibiotic resistance and the world is "reaching the limit" of current treatments.

With rapid urbanisation in the developing world, the most effective preventative measure - clean water and flushing toilets - is unachievable for many countries. And while there are two typhoid

vaccines already available, neither is licensed for children under the age of two, so the most vulnerable people are unprotected.

How bad is the situation in Pakistan?

Pakistan has an outbreak of what is called extensively drug-resistant (XDR) typhoid fever.

"Right now in Pakistan, a strain of typhoid has developed resistance to all but one of the antibiotics we use to treat the disease, threatening to take us back to the days when typhoid killed as many as one-fifth of the people that contracted it," Dr Seth Berkley, chief executive of Gavi, the Vaccine Alliance, told BBC News.

It started in Hyderbad, in Sindh province, in November 2016 and more than 10,000 people have been infected.

Gavi is now paying for nine million children to be vaccinated and Sindh province will now become the first region in the world to add the vaccine to routine childhood immunisations.

Dr Berkley said: "This vaccine is a game-changer in the battle against typhoid, it also couldn't have arrived at a better time.

"This vaccine should play a key role in bringing this dangerous outbreak under control and, once introduced into more countries' routine immunisation programmes, reducing the terrible toll wrought by typhoid worldwide."

Prof Pollard added: "It is really exciting to have a new intervention, in a very rapid space of time, that can not only prevent the disease but help in the fight against anti-microbial resistance."

http://bit.ly/351rVWM

Modern technology and old-fashioned legwork solve science mystery

Video shows single-cell organism making complex decisions

HANOVER, N.H. - A life of avoidance, detachment and relocation might not be suitable for all, but for the single-cell eukaryote *Stentor roeseli*, confirmation of this idiosyncratic behavior pattern has been a long time coming.

In a study appearing in *Current Biology*, researchers at Dartmouth College and Harvard Medical School hope to put to rest a century-old scientific debate by demonstrating that the low-level organism *S. roeseli* is capable of decision making. They also offer the video evidence to prove it.

In 1906, American biologist Herbert Spencer Jennings reported that *Stentor roeseli* exhibited complex behavior. In response to an irritating stimulus, Jennings said that *S. roeseli* engaged in four distinct behaviors--bending, ciliary alteration, contraction and detachment.

The news that the organism, which lacks a central nervous system, possessed sophisticated sensing and response mechanisms sent waves through the scientific community. The findings also played a key role in early scientific debates about animal behavior.

Over a half-century later, the Jennings research was debunked by a 1967 experiment that failed to replicate Jennings' results. That study was accepted by the science community even though it used a different species of organism.

Now, the Dartmouth-Harvard Medical School team have confirmed Jennings' original finding.

Through a series of analyses conducted in part at Dartmouth's Neukom Institute for Computational Science on a project that began at Harvard close to a decade earlier, researchers observed the same avoidance behavior that Jennings noted over one hundred years ago.

"Our results provide strong evidence that Jennings' original observations about Stentor behavior were correct, which should help to resolve the long-standing confusion," said Joseph Dexter a fellow at Dartmouth's Neukom Institute for Computational Science and a lead author on the study.

"We now have a transparent dataset, and we invite researchers to view the full set of videos to learn more about the complexities of how *S. roeseli* responds to stimulation."

Stentor roeseli is a colorless, trumpet-shaped protozoa that is visible to the naked eye and resembles the sound horn of a Gramophone.

To reconstruct Jennings' experiment, the team first had to acquire the specific species of organism used in the early 1900s. After an effort that included wading through ponds in southeastern Massachusetts, the team obtained a sample from a golf course in Manchester, England through local supplier Sciento.

The researchers then developed a platform for manipulating the organism that allowed them to target the delivery of an irritant. They settled on using polystyrene beads to stimulate reactions from the organism in the test. This was a departure from the powder used in the original experiment, but it led to an observable response that is thought to be part of a generalized avoidance strategy in *S. roeseli*.

As the beads were fed through a microinjection needle using a gravity-based system, the researchers worked to keep the microscope image in focus while they observed and recorded the experiment.

In the video, the researchers demonstrate how *S. roeseli* avoids the irritant by bending away or changing the beat of its hair-like cilia to keep from ingesting it. In response to the irritation, the organism might also contract into a protective ball, or detach from the piece of algae it is anchored to and swim to a new site.

After years of field work, video microscopy, micromanipulation and quantitative analysis, the researchers finally had the evidence that they needed to confirm Jennings' finding that the single-cell organism is capable of complex avoidance behavior.

"The results are the culmination of a long, highly-collaborative process. It was quite satisfying to work on a problem with such an interesting history and to confront some unusual challenges along the way," said Dexter.

"Our findings show that single cells can be much more sophisticated than we generally give them credit for," said senior researcher Jeremy Gunawardena, associate professor of systems biology in the Blavatnik Institute at Harvard Medical School.

"They have to be 'clever' at figuring out what to avoid, where to eat and all the other things that organisms have to do to live. I think it's clear that they can have complex ways of doing so."

In addition to demonstrating how the organism responds to stimulus, the research team also confirmed Jennings' finding that *S. roeseli* uses a hierarchy of behaviors.

While the team found few instances of the organism following the full hierarchy, they observed many partial instances with varying orders of occurrence, ultimately concluding that the behavior hierarchy exists.

According to the paper, the team considers the behavior hierarchy a form of "sequential decision making in the sense that when given similar stimulation repeatedly, the organism 'changes its mind' about which response to give, thereby following the observed hierarchy."

By generating a much larger and richer dataset than the early 1900s experiment, the team also demonstrates that the organism's decision making is distinct from habituation or classical conditioning.

The team notes that the choice between contraction and detachment in the organism resembled the same probability of a fair coin toss.

Sudhakaran Prabakaran, currently with the University of Cambridge and IISER Pune, also participated in this research project.

https://wb.md/2LCBhQT

Intermittent Fasting--What's the Key to Success?

Evidence that a relatively modest time-restricted eating plan can significantly improve blood parameters among individuals with the metabolic syndrome

F. Perry Wilson, MD, MSCE

Welcome to Impact Factor, your intermittent dose of commentary on a new medical study. I'm Dr F. Perry Wilson.

I want you to think about the first calorie you consumed yesterday. Mine was probably the sugar in my coffee around 6 AM.

Now think about the last calorie you consumed yesterday. Mine would have been some sugar in my tea around 9:30 PM.

Most adults in the United States are like me, consuming calories over an approximately 15-hour period.

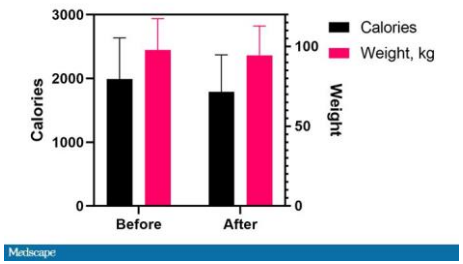
But if you haven't been living under a pizza lately, you will have heard of intermittent fasting, a dietary plan that extols the virtue of prolonged fasts to reset the metabolism. The details on any individual plan vary, but the central idea revolves around time-restricted eating—limiting caloric consumption to specific hours on the clock. And now, thanks to this paper appearing in *Cell Metabolism*, we have some evidence that a relatively modest time-restricted eating plan can significantly improve blood parameters among individuals with the metabolic syndrome.

This is a small but nicely done study. Nineteen individuals with metabolic syndrome who had a daily eating interval of about 15 hours were followed for 3 months, during which they were asked to restrict their eating to a 10-hour window—think 8 AM to 6 PM.

Other than that, there were no particular requirements. Participants could eat whatever they wanted and however much they wanted, provided it was in that timeframe.

By and large, this was a compliant bunch, reducing their eating window to just over 10 hours. Detailed dietary profiling found that they weren't skipping meals but compressing them—eating breakfast a bit later and dinner a bit earlier.

And in that process, they ended up taking in fewer calories, about 200 fewer calories a day than during the baseline period. That reduction in caloric intake led to a fair amount of weight loss: around 7 pounds over the 3-month study.

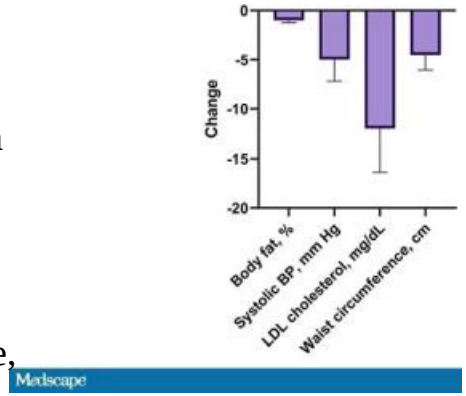


Several metabolic parameters improved. Body fat and systolic blood pressure decreased, LDL cholesterol went down, and the average participant lost about 4 cm of waist circumference.

But not everything changed so dramatically. Fasting blood sugar and hemoglobin A1c got a bit lower, but not to the point of statistical significance, for example.

There were a lot of measurements done in this study; 32 are reported in the outcome table, so we need to be a bit worried about false positives. But that's not really the main limitation here.

The main limitation is that these patients were enrolled in a study. See, without a control group, we don't know if the beneficial changes seen were due to the effects of intermittent fasting or just because the patients knew they were being "watched."



They had to log in to an app, go to study visits, and so on. That alone may be enough to change behaviors in a beneficial direction.

In other words, we don't have great support here for particularly large, unique effects of intermittent fasting compared with other diets that lead to calorie restriction.

And this leads to one of my central theories of diet studies: Any diet that makes it harder to eat, whether you are limiting certain types of foods or certain times of day, will probably [lead to weight loss]. One of the central drivers of the obesity epidemic is our *ad libitum* access to food. We often see promising results like this when we simply limit that free access.

What I like about time-restricted eating is that it's pretty easy to explain: Eat inside these hours, don't eat outside of these hours. That's a bit easier than explaining how, for example, ketosis works. But in the end, the key to any diet plan is adherence. Researchers contacted these participants 3 months after the study ended. At that point, only five were still adherent to the calorie window.

Future studies examining novel dietary interventions would do well to prove that participants not only understand the diet but can stick with it.

F. Perry Wilson, MD, MSCE, is an associate professor of medicine and director of Yale's Program of Applied Translational Research. His science communication work can be found in the Huffington Post, on NPR, and here on Medscape. He tweets @methodsmanmd and hosts a repository of his communication work at www.methodsman.com.

http://bit.ly/38jEcb1

Recordings reveal that plants make ultrasonic squeals when stressed

For the first time, plants have been recorded making airborne sounds when stressed

By Adam Vaughan

Although it has been revealed in recent years that plants are capable of seeing, hearing and smelling, they are still usually thought of as silent. But now, for the first time, they have been recorded making airborne sounds when stressed, which researchers say could open up a new field of precision agriculture where farmers listen for water-starved crops.

Itzhak Khait and his colleagues at Tel Aviv University in Israel found that tomato and tobacco plants made sounds at frequencies humans cannot hear when stressed by a lack of water or when their stem is cut.

Microphones placed 10 centimetres from the plants picked up sounds in the ultrasonic range of 20 to 100 kilohertz, which the team says insects and some mammals would be capable of hearing and responding to from as far as 5 metres away. A moth may decide against laying eggs on a plant that sounds water-stressed, the researchers suggest. Plants could even hear that other plants are short of water and react accordingly, they speculate.

The spiny pincushion cactus has been found to emit sounds when stressed
Jose A. Bernat/Getty Images

"These findings can alter the way we think about the plant kingdom, which has been considered to be almost silent until now," they write in their study, which has not yet been published in a journal.

Previously, devices have been attached to plants to record the vibrations caused by air bubbles forming and exploding – a process known as cavitation – inside xylem tubes, which are used for water transport. But this new study is the first time that sounds from plants have been measured at a distance.

On average, drought-stressed tomato plants made 35 sounds an hour, while tobacco plants made 11. When plant stems were cut, tomato plants made an average of 25 sounds in the following hour, and tobacco plants 15. Unstressed plants produced fewer than one sound per hour, on average.

It is even possible to distinguish between the sounds to know what the stress is. The researchers trained a machine-learning model to

discriminate between the plants' sounds and the wind, rain and other noises of the greenhouse, correctly identifying in most cases whether the stress was caused by dryness or a cut, based on the sound's intensity and frequency. Water-hungry tobacco appears to make louder sounds than cut tobacco, for example.

Although Khait and his colleagues only looked at tomato and tobacco plants, they believe other plants may make sounds when stressed too. In a preliminary study, they also recorded ultrasonic sounds from a spiny pincushion cactus (*Mammillaria spinosissima*) and the weed henbit dead-nettle (*Lamium amplexicaule*). Cavitation is a possible explanation for how the plants generate the sounds, they say.

Enabling farmers to listen for water-stressed plants could "open a new direction in the field of precision agriculture", the researchers suggest. They add that such an ability will be increasingly important as climate change exposes more areas to drought.

"The suggestion that the sounds that drought-stressed plants make could be used in precision agriculture seems feasible if it is not too costly to set up the recording in a field situation," says Anne Visscher at the Royal Botanic Gardens, Kew, in the UK.

She warns that the results can't yet be broadened out to other stresses, such as salt or temperature, because these may not lead to sounds. In addition, there have been no experiments to show whether moths or any other animal can hear and respond to the sounds the plants make, so that idea remains speculative for now, she says.

If plants are making sounds when stressed, cavitation is the most likely mechanism, says Edward Farmer at the University of Lausanne, Switzerland. But he is sceptical of the findings, and would like to see more in the way of controls.

Farmer adds that the idea moths might be listening to plants and shunning stressed ones is a "little too speculative", and there are already plenty of explanations for why insects avoid some plants and not others.

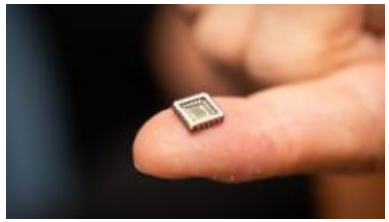
Reference: *bioRxiv, DOI: 10.1101/507590*

http://bit.ly/2RF8K1b

First-Ever Artificial Neuron Could Let Us Repair Brain Injuries with Silicon

Interfacing our brains with computers has proven incredibly hard

By Edd Gent



The merging of man and machine is a staple of sci-fi and at the heart of the philosophy of transhumanism. But interfacing our brains with computers has proven incredibly hard, despite the fact that both essentially run on electrical impulses.

An artificial neuron in its protective casing. **Photo courtesy of *University of Bath***

Imagine, for example, if a brain injury could be repaired with a computer chip. That may not be too far off; this week, researchers reported on a "solid-state neuron" that accurately models the behavior of biological nerve cells. In a paper in *Nature Communications*, the team says the devices could be plugged into biological neural circuits to repair damage or disease.

"Until now neurons have been like black boxes, but we have managed to open the black box and peer inside," project leader Alain Nogaret, from the University of Bath in the UK, said in a press release. "Our work is paradigm-changing because it provides a robust method to reproduce the electrical properties of real neurons in minute detail."

A major reason it's been so hard to accurately replicate the behavior of neurons in silicon is because the way they respond to stimuli is

non-linear. In other words, a signal twice as strong won't necessarily elicit a response that's twice as strong.

The researchers solved the problem by collecting data from two types of rat neuron. The first was from the hippocampus region of the brain, which is involved in learning and memory, and the second from the respiratory center, which controls breathing.

They used this data to estimate the parameters that control how ions flow through the neurons and then used those parameters to create a model that explains how neurons respond to stimuli from other nerves. They then used that model to build analogue silicon chips that accurately modeled the behavior of real neurons.

To test their chips, they subjected them to 60 different stimulation protocols and compared their responses to those seen in rat hippocampal and brain stem neurons. The chips achieved a 94 percent accuracy.

Critically, the bionic neurons use just 140 nanoWatts of power—a billionth the amount of a regular microprocessor, which makes them much more practical for long-term applications inside the body. Each chip is roughly 0.1 millimeters in diameter, but many of them would need to be combined to create a practical implant, which would be a few millimeters wide.

The researchers have already spun out a company called Ceryx to start developing a smart pacemaker that uses the bionic neurons to respond to signals rather than simply providing a steady beat like a regular pacemaker. But they say their approach is generic and could be used to replicate any of the body's many different types of neurons.

That could make it possible to repair defective circuits that cause conditions like heart failure and sleep apnea, but could also potentially replace damaged nerves caused by spinal injuries or help connect robotic limbs to people's nervous systems, the researchers told *The Guardian*.

One potential limitation is that the bionic neurons do not replicate the complex connectivity of real ones. Their model doesn't cover the many branching dendrites that connect neurons to each other, and adding those dynamics might require further components.

The researchers also say they are a long way from replicating larger, more complex brain circuits, and light years off from being able to reproduce an entire brain.

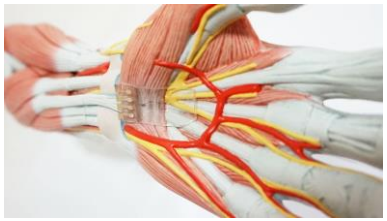
University of Manchester's Stephen Furber, who has designed a million-processor computer called SpiNNaker designed to model large-scale brain networks, told *The Guardian* that using this approach to create networks of even a few hundred million neurons would be unfeasible—and the brain contains roughly 86 billion of them.

"Because the approach is detailed and laboriously painstaking, it can really only be applied in practice to smallish neural units, such as the respiratory neurons described above, but there are quite a few critical small neural control circuits that are vital to keeping us alive," he added.

https://go.nature.com/36iWuY9

Light pulses prod artificial muscle into action

An optical signal triggers mechanical motion thanks to a nerve junction constructed in the laboratory.



A device inspired by the body's network of nerve cells could enable wireless control of artificial muscles and prostheses.

A synthetic version (transparent rectangle) of the junction between a neuron and a muscle is shown on a model of a human hand. **Credit: Y. Lee et al.**

When a neuron commands a muscle to contract, the message travels through a junction called a synapse. The development of a synthetic system that mimics the activity of neurons and synapses to control

artificial muscles would be a fundamental step for bio-inspired robotics, but such a system has proved challenging to create.

Tae-Woo Lee at Seoul National University and Zhenan Bao at Stanford University in California and their colleagues designed a synthetic synapse equipped with a light detector, which allows researchers to control the device with light pulses. The synapse converts these light signals into electrical impulses that can trigger movement of an artificial muscle made from a strip of polymer material. In tests, varying the rate of light pulses helped to control the strip's flexion.

This approach is similar to optogenetic techniques, which genetically modify neurons to render them sensitive to light, the authors write. *Sci. Adv.* (2018)

http://bit.ly/2qDrKSw

Scientists Create a New Kind of Artificial Flesh That Heals Itself Like The Real Thing

Scientists have created a new jelly-like material which has the strength and durability of actual skin

Carly Cassella

Artificial flesh is growing ever closer to the real thing. Scientists in Australia have now created a new jelly-like material which they claim has the strength and durability of actual skin, ligaments, or even bone.

"With the special chemistry we've engineered in the hydrogel, it can repair itself after it has been broken like human skin can," explains chemist Luke Connal from the Australian National University.

"Hydrogels are usually weak, but our material is so strong it could easily lift very heavy objects and can change its shape like human muscles do."

Having a squishy material with such remarkable properties could be huge for the development of next-generation soft robotics and biomedical devices. Creating a shape-changing hydrogel that has multiple functions has proved an ongoing challenge for scientists, even with natural inspiration from jellyfish, sea cucumbers, and Venus fly traps.

While some hydrogels can withstand mechanical stress, others have self-healing properties, and a few more have the abilities to memorise shapes or change colours.

As far as the ANU researchers know, no one else has been able to incorporate all these functions into one all-encompassing gel. At least, not at the speed and efficiency they've achieved.

Putting their material through multiple tests, the authors claim to have created the first dynamic hydrogel that is strong, tough, fatigue resistant, self-healing and able to change shapes and 'remember' them afterwards.

"The advantages of using such a multifunctional hydrogel is further demonstrated through an ability to lift heavy objects in a reversible and repeatable way upon thermal stimulus," the team writes.

Using this material, the researchers made extremely thin films of 'flesh' without any breakage. When these films were heated or cooled, they then changed into different shapes, bending one way or the other before returning back to their original state along with the temperature.

Unlike many other hydrogels, which can sometimes take 10 minutes or more to change shape, the authors say their gel takes only 10 seconds to bend. Here, the key is said to be the gel's dynamic hydrogen bonds and dynamic imine (carbon-nitrogen) bonds, which work together to form "unprecedented properties".

Dynamic bonds have a high response to stimuli, which makes them perfect for environmental adaptation and self-repair, and imine bonds in particular have fast reaction kinetics that can enable rapid self-healing.

What's more, the authors say these materials can be easily prepared using simple chemistry, and if other polymers are added to the molecular mix, perhaps even more functions can be achieved.

If temperature is somehow used as a control, the authors think this gel could one day be moved like an artificial muscle.

"In a lot of science fiction movies, we see the most challenging jobs being done by artificial humanoid robots. Our research has made a significant step towards making this possible," says material engineer Zhen Jiang.

"We anticipate that researchers working on the next-generation of soft robots will be interested and excited about our new way of making hydrogels."

In the meantime, the team is hoping to turn their hydrogel into a 3D-printable ink. The study was published in *Advanced Materials*.

http://bit.ly/2E0aiL1

Asia-wide Genome Mapping Project Reveals Insights Into Asian Ancestry, Genetic Diversity

Asia has at least ten ancestral lineages, whereas northern Europe has a single ancestral lineage

By Bio-IT World News Staff

After a global genetic comparison, a team of international scientists has discovered that Asia has at least ten ancestral lineages, whereas northern Europe has a single ancestral lineage. In their first study reported in *Nature* (DOI: https://doi.org/10.1038/s41586-019-1793-z) this week, the GenomeAsia 100K consortium analyzed the genomes of 1,739 people, which represents the widest coverage of genetic diversity in Asia to date.

The study covers 64 different countries and provides what the authors call "the first comprehensive genetic map for Asia" that will guide scientists in studying diseases unique to Asians, improve precision medicine and identify drugs that may carry higher risk of adverse reactions for certain ethnic groups.

Despite forming over 40% of the world's population, Asian people have previously accounted for only 6% of the world's recorded genome sequences.

The goal of GenomeAsia 100K—which launched in 2016—is to better understand the genome diversity of Asian ethnicities by sequencing 100,000 genomes of people living in Asia. It is a non-profit consortium hosted by Nanyang Technological University, Singapore (NTU Singapore), the only academic member. Its three other members are Macrogen based in South Korea, Genentech, a member of the Roche Group in United States, and MedGenome from India/US.

NTU Professor Stephan C. Schuster, the consortium's scientific chairman and a co-leader of the study, explained the significance of GenomeAsia 100K's initial findings on the vast genomic diversity in Asia in an official statement: "To put it into context, imagine we looked at all people of European and based on the level of their genetic diversity, observed that they could all be grouped into just one ancestral lineage or population. Now, if we took that same approach with our new data from people of Asian, then based on the much higher levels of genetic diversity observed we would say that there are 10 different ancestral groups or lineages in Asia."

How the database of Asian genomes was formed

Over the course of the last three decades prior to the pilot project, thousands of blood and saliva samples have already been collected by scientists and anthropologists from donors across Asia in hopes that one day, a deeper analysis to gain insights into the Asian community can be done.

Of particular interest were participants from remote and isolated communities, who have long been the subjects of study by anthropologists but have not yet undergone genomic analysis, until the GenomeAsia 100K project was kickstarted.

The pilot study included 598 genomes from India, 156 from Malaysia, 152 from South Korea, 113 from Pakistan, 100 from Mongolia, 70 from China, 70 from Papua New Guinea, 68 from Indonesia, 52 from the Philippines, 35 from Japan, and 32 from Russia.

Genomic DNA extracted from the blood and saliva samples was then sequenced in laboratories of the four consortium members in the US, India, South Korea and Singapore. The digital sequencing data were subsequently sent to Singapore for processing and storage.

Singapore was selected by the consortium as the host, as the country offered good travel connections for collaborating scientists, strong supercomputing facilities to crunch the data, and the required cybersecurity standards in its data center for handling sensitive genetic data.

The combined data was compiled and analyzed by NTU scientists, including Asst. Prof Hie Lim Kim, a population genomics expert at the Asian School of The Environment, with the help of the National Supercomputing Centre Singapore (NSCC) and international collaborators.

Different Asian ethnic groups respond differently to mainstream drugs

Every person has approximately 3.2 billion different nucleotides, or building blocks, in their genome, which form their DNA "code".

It's estimated that for the genomes of any two people, 99.9% of this code is the same and on average, 0.1% or three million nucleotides, are different between them.

This genetic variance help humankind colonize the most diverse environments on the planet and make it resilient to disease, but it also results in a differential response to many medicines.

"Genetic variance is the reason we are distinctively different from each other including differences in the diseases that each of us suffer from during our lifetimes. Understanding these differences is the most important source of clues that we have for driving the discovery of innovative new medicines," Andrew Peterson, an author of the paper and an expert in the use of genetics to drive drug discovery, said in a press release.

The frequencies of known genetic variants related to adverse drug response were analyzed for the genomes collected in this study.

For example, Warfarin, a common anticoagulant drug prescribed to treat cardiovascular diseases, likely has a higher than usual risk of adverse drug response for people carrying a certain genetic variant. This particular genetic variant has a higher frequency to appear in those with North Asian ancestry, such as Japanese, Korean, Mongolian or Chinese.

Using data analysis, scientists can now screen populations to identify groups that are more likely to have a negative predisposition to a specific drug.

Moving forward, the GenomeAsia 100K will continue to collect and analyze up to 100,000 genomes from all of Asia's geographic regions, in order to fill in the gaps on the world's genetic map and to account for Asia's unexpected genetic diversity.

http://bit.ly/36f04T2

'Milk Yeast' Originated from Chance Encounter between Fruit Fly and Milk 5,500 Years Ago

Kluyveromyces lactis *originated from a chance encounter between a fruit fly and a pail of milk around 5,500 years ago*

John Morrissey|

Historians often trace the dawn of human civilization back 10,000 years, when Neolithic tribes first settled and began farming in the Fertile Crescent, which stretches through much of what we now call the Middle East. Prehistoric peoples domesticated plants to create the cereal crops we still grow today, and in the Zagros mountains of Iran, Iraq and Turkey, sheep, goats and cows were bred from their

wild relatives to ensure a steady supply of meat and milk. But around the same time as plants and animals were tamed for agriculture, long before anyone even knew of microscopic life, early humans were domesticating microbes too.

In a paper published in the journal *Current Biology*, we discovered how 'milk yeast' — the handy microorganism that can decompose lactose in milk to create dairy products like cheese and yoghurt — originated from a chance encounter between a fruit fly and a pail of milk around 5,500 years ago.

This happy accident allowed prehistoric people to domesticate yeast in much the same way they domesticated crop plants and livestock animals, and produce the cheeses and yogurts billions of people enjoy today.

The domesticated diet

Domestication is evolution directed by a human hand. After wild parents have bred, farmers retain the offspring with properties that are beneficial for future breeding.

Take farmed wheat, for example. This crop species produces a lot more seeds than wild grasses do, because these seeds are the grain that humans harvest.

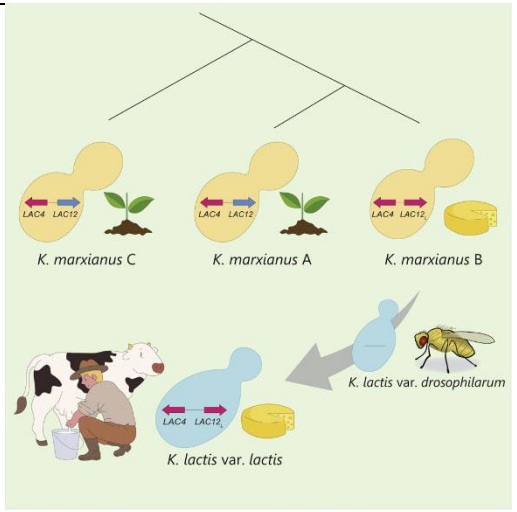
Early farmers deliberately bred pairs of wheat plants that produced lots of grain so that their offspring would inherit this trait. As these pairings were repeated over many generations, grain-rich descendants were gradually created.

It's survival of the fittest, but the fittest are variants that have characteristics that are useful for humans. The wary and vicious wolf becomes the friendly and obedient dog.

Neolithic farmers stumbled on the practice of domesticating microbes when they tried to preserve food by fermenting it.

Fermentation relies on microbes, such as bacteria, yeast and fungi, increasing the acidity of the food to protect it against spoilage. Microbes that were good at making fermented products that were palatable and safe were kept to start the next batch, and so useful microbes were evolved and domesticated.

'Baker's yeast,' or *Saccharomyces cerevisiae*, was a microbe selected from nature to make beer, wine and other fermented drinks 13,000 years ago.



***It is well known that humans domesticated brewer's yeast, and now, Varela* et al *report that another yeast is also the product of human activity. They show that an insect-associated, lactose-negative progenitor of the milk yeast* Kluyveromyces lactis *acquired the genes that enable lactose fermentation from a dairy-adapted population of* K. marxianus. Varela *et al*, doi: 10.1016/j.cub.2019.10.044.**

Kluyveromyces lactis, or milk yeast, is found in French and Italian cheeses made from unpasteurized milk, and in natural fermented dairy drinks like kefir. But the ancestor of this microbe was originally associated with the fruit fly, so how did it end up making many of the dairy products that people eat today?

We believe milk yeast owes its very existence to a fly landing in fermenting milk and starting an unusual sexual liaison.

The fly in question was the common fruit fly, *Drosophila*, and it carried with it the ancestor of *K. lactis*. Although the fly died, the yeast lived, but with a problem — it could not use the lactose in milk as a food source. Instead, it found an unconventional solution — sex with its cousin.

When *K. lactis* arrived with the fly, its cousin *K. marxianus* was already happily growing in the milk.

K. marxianus is able to use lactose for growth because it has two extra proteins which can help break down lactose into simple sugars that it then uses for energy.

The cousins reproduced and the genes needed to use lactose transferred from *K. marxianus* to *K. lactis*.

The end result was that *K. lactis* acquired two new genes and could then grow on lactose and survive on its own.

The fermented product that *K. lactis* made must have been particularly delicious as it was used to start a new fermentation — a routine that has continued to the present day.

We think that by 6,000 years ago, farmers were using fermented goat and sheep milk to make tasty beverages like yoghurt and kefir.

We know that milk-producing animals — cows, sheep, goats — were all domesticated between 8,000 and 10,000 years ago, and analysis of human tartar found on teeth shows that humans were consuming milk, most likely as cheese or other fermented products by 5,500 years ago.

The chance encounter between two yeast species and a little bit of illicit sex made all of this possible.

Who could've imagined that such a random series of events would produce so many of the world's great culinary delicacies?

Javier A. Varela et al. *Origin of Lactose Fermentation in* Kluyveromyces lactis *by Interspecies Transfer of a Neo-functionalized Gene Cluster during Domestication.* Current Biology, *published online December 5, 2019; doi: 10.1016/j.cub.2019.10.044*

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