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The Unusual Functions of Geosmin

The compounds responsible for the earthy smell of recent rain are produced by a wide variety of bacteria and fungi. Recent research sheds light on why microbes bother.

Connor Lynch

There are few surer heralds of spring than petrichor. It's the earthy aroma that wafts up after a good rain and comes primarily from chemical compounds called terpenes.

Geosmin, for example, is a terpene most commonly associated with *Streptomyces* bacteria, although other bacteria and fungi also make it, and it's found in soils and bodies of fresh water the world over. Its ubiquity has long fascinated scientists—not least because it hasn't been clear why its various producers make it.

Liana Zaroubi, a PhD candidate at Simon Fraser University in British Columbia, Canada, first came to this mystery as an undergrad at Concordia University in Montreal in 2015. She took a class with Brandon Findlay on chemical ecology and recalls being intrigued by the bonus question he posed on the final exam: "What do you think geosmin does, and how would you test that?"

She ended up joining his lab as a master's student so she could look into that question. "I thought it was super interesting," she says.

After months spent reviewing the literature and testing hypothesis after hypothesis, she and Findlay considered whether geosmin and another terpene that contributes to petrichor, 2-methyl-isoborneol (2-MIB), might indirectly deter predators. Although these chemicals aren't themselves toxic to animals, other compounds the bacteria make are, so geosmin and 2-MIB could be an aposematic signal, like the coloration of many poisonous insects that tells hungry birds to dine elsewhere.

An initial round of experiments with bacteria-eating amoebae went poorly, Zaroubi says. The organisms are very slow predators, and geosmin is highly unstable, she explains. The amoebae would need weeks to get to the bacteria in the researchers' experimental setup, but the geosmin would degrade in days, or even hours. "So we thought of faster predators, like nematodes."

First, the researchers tested whether *C. elegans* would react to the presence of geosmin. They found that while the chemical didn't appear to affect the nematodes' health, it drastically affected their movements, causing them to move much faster and to make more frequent changes in direction. Mutant worms with deficiencies in detecting soluble and volatile odorants showed no such behavioral changes, suggesting the wildtype animals were smelling or tasting the compound.

Next, the researchers plopped *C. elegans* and *Streptomyces coelicolor*, a bacterium that produces both geosmin and 2-MIB, into a petri dish. On the whole, the worms avoided the bacteria, the team found. But if the researchers engineered either the bacteria not to produce the chemicals, or the worms to be deficient in detecting those chemicals, the nematodes more frequently consumed the bacteria—and became ill from the toxic metabolites also produced by the microbes.

"Geosmin thus acts as an aposematic signal," the authors write in their paper, "honestly and reliably advertising the unpalatability of its producers and providing a mutual benefit to predator and prey."

While the chemical didn't appear to affect the nematodes' health, it drastically affected their movements.

It's the first time aposematic signaling has been documented in bacteria, says Findlay. He adds that it's unsurprising that geosmin and 2-MIB should make good aposematic signals: composed of hydrocarbons arranged into rings or chains, the compounds are very good at fitting into cellular receptors. But because they also degrade so rapidly, they can't accumulate in the environment or travel very far, meaning that they accurately reveal the organism producing

them right here, right now.

“As a chemical messenger, that makes [them] very, very valuable,” Findlay says.

The study is just one of a handful of recent papers identifying possible functions for geosmin and 2-MIB. For example, research by scientists at the Swedish University of Agricultural Sciences demonstrated that the two chemicals actually attract springtails, which feed on the bacteria producing them with no ill effects from the toxins. In turn, the springtails distribute bacterial spores in their fecal pellets and by carrying them on their bodies, helping the microbes move to new environments.

Some fly species have also found ways to interpret the smelly signal of petrichor. While working at the Max Planck Institute for Chemical Ecology in Germany in 2012, sensory neuroecologist Marcus Stensmyr published a paper showing that fruit flies are repelled by geosmin, even when it’s added to vinegar.

“Flies absolutely love vinegar,” says Stensmyr, now at Lund University in Sweden. “Anything that can make it less attractive must be important.” This aversion, the team showed, is governed by a single receptor, tuned specifically to geosmin and capable of detecting the chemical at concentrations as low as 1 part per 100 million, he says.

It’s not clear why flies don’t like geosmin. It’s possible fly larvae are sensitive to toxins produced by various geosmin makers, Stensmyr suggests. It could also have to do with competition for food. Some molds, such as *Penicillium*, that produce geosmin eat the yeast that grows on rotting fruit. Since fruit fly larvae also eat yeast, the presence of mold, as signaled by geosmin, means that larvae laid on a particular piece of fruit could starve.

Follow-up research from Stensmyr found that female *Aedes aegypti* mosquitoes, which possess a very similar geosmin-specific receptor, react completely differently. “They loved it,” he says.

This makes sense, given that mosquitoes are insensitive to the toxins the bacteria produce and, in fact, mosquito larvae eat geosmin-making bacteria. Stensmyr notes that female mosquitoes in his study prioritized egg-laying sites where geosmin was present. “If you just look at mosquitoes and flies, which are not too distantly related, this compound seems to be very important,” he says. “But it has different meanings.”

Stensmyr says it’s likely that a huge number of animals are capable of detecting geosmin. Even humans are highly sensitive to it, being able to smell geosmin at concentrations as low as 400 parts per trillion. “We have the example of nematodes, we have it from insects, we have it from humans; we have a whole range of animal phyla in between that possibly also react to this chemical, or can use it in one way or another.” Indeed, some animals respond to the compound in ways that appear totally unrelated to the bacteria. Research from the 1990s suggests geosmin might help European glass eels find freshwater, a function that Stensmyr speculates may have been used by humans’ ancestors as well. And low, but not high, concentrations of the chemical appear to suppress stinging behavior in honey bees.

Geosmin may hold yet more secrets. Zaroubi notes, for example, that fungal strains that produce the chemical don’t appear to use the same gene pathway as bacteria to make it, meaning perhaps that geosmin production has evolved multiple times independently. Findlay adds that the research can help scientists view aposematism in a new way: from the perspective of the predator, rather than just the prey producing the don’t-eat-me signal.

Aposematic signals depend “on both the sender and the receiver of the signal,” he says. “In our case, we have pretty full control over the genetics of these nematodes. So we can interrogate the evolution from both sides, from more than one angle. I’m super excited about that.”

https://bit.ly/3QjHAYD

Europe's Last Panda? New Discovery of Species Closely Related to Giant Panda

Fossilized teeth originally found in the 1970s actually belong to a new, sizeable close relative of the modern giant panda.

A new species of panda has been uncovered by scientists who state it is currently the last known and "most evolved" European giant panda. It lumbered through the forested wetlands of Bulgaria around six million years ago.

Unearthed from the bowels of the Bulgarian National Museum of Natural History, two fossils of teeth originally discovered in the eastern European nation in the late 1970s, provide new evidence of a sizable relative of the modern giant panda. Unlike today's iconic black and white bear, however, it was not purely reliant on bamboo for sustenance.

Reconstruction of A. nikolovi sp. nov. from Bulgaria. Artwork by Velizar Simeonovski, Chicago. **Credit: © Velizar Simeonovski, Chicago**

"Although not a direct ancestor of the modern genus of the giant panda, it is its close relative," explains the Museum's Professor Nikolai Spassov, whose findings are published today (August 1, 2022) in the peer-reviewed *Journal of Vertebrate Paleontology*.

"This discovery shows how little we still know about ancient nature and demonstrates also that historic discoveries in paleontology can lead to unexpected results, even today."

The teeth, an upper carnassial tooth and an upper canine, were originally cataloged by paleontologist Ivan Nikolov. He added them to the museum's trove of fossilized treasures after they were unearthed in northwestern Bulgaria decades ago. This new species is named *Agriarctos nikolovi* in his honor.

"They had only one label written vaguely by hand," recalls Professor Spassov. "It took me many years to figure out what the locality was and what its age was. Then it also took me a long time to realize that this was an unknown fossil giant panda."

The coal deposits in which the teeth were found – which have imbued them with a blackened hue – suggest that this ancient panda inhabited forested, swampy regions. There, during the Miocene epoch, it likely consumed a largely vegetarian diet – but not purely reliant on bamboo!

Fossils of the staple grass that sustains the modern panda are rare in the European fossil record, especially in the Bulgarian late Miocene period. Additionally, the cusps of the teeth do not appear strong enough to crush the woody stems. Instead, it likely fed on softer plant materials—aligning with the general trend toward increased reliance on plants in this group's evolutionary history.

Sharing their environment with other large predators likely drove the giant panda lineage toward vegetarianism.

"The likely competition with other species, especially carnivores and presumably other bears, explains the closer food specialization of giant pandas to vegetable food in humid forest conditions," states Professor Spassov.

A. nikolovi's teeth nonetheless provided ample defense against predators, the paper speculates. In addition, the canines are comparable in size to those of the modern panda, suggesting that they belonged to a similarly sized or only slightly smaller animal.

The authors propose that *A. nikolovi* may have become extinct as a result of climate change, probably because of the 'Messinian salinity crisis'. This event, in which the Mediterranean basin dried up, significantly altered the surrounding terrestrial environments.

"Giant pandas are a very specialized group of bears," Professor

Spassov adds. “Even if *A. nikolovi* was not as specialized in habitats and food as the modern giant panda, fossil pandas were specialized enough and their evolution was related to humid, wooded habitats. It is likely that climate change at the end of the Miocene in southern Europe, leading to aridification, had an adverse effect on the existence of the last European panda.”

Co-author Qigao Jiangzuo, from Peking University, China, was primarily responsible in helping to narrow down the identity of this strange beast to belonging to the Ailuropodini – a tribe within the Ursidae bear family. While this group of animals is best known by its only living representative, the giant panda, they once ranged across Europe and Asia. Intriguingly, the authors propose two potential pathways for the distribution of this group.

One possible evolutionary trajectory has the Ailuropodini heading out of Asia and concluding in *A. nikolovi* in Europe. However, Professor Spassov does add caution to this hypothesis, stating that the paleontological data show that “the oldest members of this group of bears were found in Europe.” This suggests that the group may have developed in Europe and then headed to Asia, where the ancestors of another genus, *Ailurarctos*, developed. These early pandas may then have later evolved into *Ailuropoda*—the modern giant panda.

Reference: “Discovery of a late Turolian giant panda in Bulgaria and the early evolution and dispersal of panda lineage” 1 August 2022, Journal of Vertebrate Paleontology.
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Low Calcium, Potassium Key Risk Factors for Kidney Stones

. . . as well as their symptomatic recurrence

Pam Harrison

Low dietary calcium and potassium intake are important risk factors for the development of incident kidney stones as well as their symptomatic recurrence, a population-based study of dietary factors shows.

"Our research is of particular importance as recommendations for preventing symptomatic recurrence of kidney stones has largely been based on dietary factors associated with the incidence rather than the recurrence of stone formation," Api Chewcharat, MD, Mayo Clinic, Rochester, Minnesota, said in a video discussing the study.

"We recommend a daily intake of calcium of approximately 1200 mg and a diet that is high in potassium, especially high in fruits and vegetables, in order to prevent both incident and recurrent symptomatic kidney stone formation," he stressed.

The study was published online August 1, 2022 in the *Mayo Clinic Proceedings*.

Lower Dietary Calcium, Potassium, and Fluid Associated With Increased Incidence

Some 411 patients with incident symptomatic kidney stone formation were recruited. Diets were compared between them and 384 controls. Patients were seen at the Mayo Clinic in either Minnesota or Florida between January 1, 2009 and August 31, 2018.

"Dietary factors were based on a Viocare, Inc, food frequency questionnaire administered during a baseline in-person study visit," Chewcharat and colleagues observed.

During a median follow-up of 4.1 years, 73 patients experienced a symptomatic recurrence. In a fully adjusted analysis, a dietary calcium intake < 1200 mg/d was associated with incident stone formation.

Similarly, among participants with a fluid intake < 3400 mL/d — about nine 12-oz glasses of fluid — was also associated with incident stone formation, as was a lower intake of dietary potassium,

caffeine, and phytate. Phytate is an antioxidant found in whole grains, nuts, and other foods that can increase calcium absorption and urinary calcium excretion.

After excluding patients who were taking either a thiazide diuretic or a calcium supplement, lower dietary calcium and potassium, fluid, and phytate intake remained significantly associated with incident stone formation.

However, only lower dietary calcium intake was associated with a higher risk for symptomatic recurrence, although a lower dietary potassium intake was also associated with a higher risk for symptomatic recurrence in an analysis that adjusted for body mass index, fluid, and energy intake.

As the authors suggest, patients may be less keen to adjust their diet to prevent the development of incident kidney stones. On the other hand, they may be much more willing to adjust their diet to prevent their symptomatic recurrence. The US Department of Agriculture currently recommends that individuals get approximately 1200 mg/d of dietary calcium which, given the study results, appears to be justified for the prevention of symptomatic stone recurrence.

A higher calcium diet is associated with a higher urinary pH, and citrate confers an alkali load which helps protect against the formation of calcium oxalate stones. Foods that are high in potassium also contain more fluid, citrate, and phytate, which, again, have been reported to be protective against kidney stones. "Changing your diet to prevent kidney stones can be very difficult," Andrew Rule, MD, a nephrologist at the Mayo Clinic said in a statement.

"Thus, knowing the dietary factors that are most important for preventing kidney stone recurrence can help patients and providers know what to prioritize," he added.

The authors have no conflicts of interest to declare.

Mayo Clinic Proceedings. Published online August 1, 2022. Full text

https://bit.ly/3zzsvLJ

NY county with polio has pitiful 60% vaccination rate; 1,000s may be infected

Hundreds need to be infected for one paralytic case to arise. And the virus keeps moving.

Beth Mole

The vaccine-derived poliovirus that left an unvaccinated US resident with the country's first case of paralytic polio in nearly a decade has been genetically linked to spread in two other countries: the United Kingdom and Israel. Now that it has been detected in the US, health officials fear it has spread to hundreds or even thousands of people in a poorly vaccinated New York county.

On Monday, officials in New York urgently encouraged unvaccinated residents to get vaccinated "as soon as possible" to prevent further spread of the virus.

"Polio is very contagious, and an individual can transmit the virus even if they aren't sick," the New York State Department of Health said in a news release today. The virus spreads easily via a fecal-oral route through poor hygiene and sanitation. The virus transmits through direct contact with an infected person or contaminated food or water. "Symptoms, which can be mild and flu-like, can take up to 30 days to appear, during which time an infected individual can be shedding virus to others," the health department added.

About 1 in 200 people infected with poliovirus develop paralysis, according to the US Centers for Disease Control and Prevention. That means for the one case of paralytic polio to have arisen in New York—which was not linked to any international travel—hundreds of others were likely already infected.

Pockets of risk

Most Americans have been vaccinated against poliovirus, making them safe from the dangerous virus. The three-dose inactivated polio vaccine (IPV), given in the first 24 months with a fourth-dose

booster between the ages of 4 and 6, is part of the CDC's standard immunization schedule. According to CDC data from 2015, nearly 93 percent of US children received their three doses of IPV by the age of 2.

But, the paralytic polio case in New York was found in Rockland County, a northern suburb of New York City, which has pockets of low vaccination rates. In fact, in 2019, the county struggled with an explosive measles outbreak due to the same problem.

According to the state health department, Rockland County currently has a polio vaccination rate of just 60.5 percent among 2-year-olds, compared to the statewide average of 79 percent.

The paralytic case in Rockland, which occurred in an unvaccinated young adult, was first reported by authorities on July 21, but the person's symptoms began in June. Since then, transmission likely continued, with epidemiologists now saying that thousands could be infected.

Multinational spread

And that's just in the US. On Friday, the Global Polio Eradication Initiative (GPEI) announced that the strain of vaccine-derived poliovirus behind the Rockland case—a type 2 VDPV—is genetically linked to viruses detected in wastewater sampling in London and Jerusalem, suggesting a sustained, multinational spread of the dangerous virus.

To be clear, vaccine-derived poliovirus strains evolve from oral polio vaccines (OPV), which are no longer used in the US or the UK. (Israel uses both IPV and OPV.) The oral polio vaccines use weakened viruses that, if able to spread from person to person amid poor sanitation and low vaccination rates, can mutate to regain disease-causing capabilities. It's unclear where and how this VDPV2 originated and spread.

"It is vital that all countries, in particular those with a high volume of travel and contact with polio-affected countries and areas, strengthen surveillance in order to rapidly detect any new virus importation and to facilitate a rapid response," GPEI said. "Countries, territories, and areas should also maintain uniformly high routine immunization coverage at the district level and at the lowest administrative level to protect children from polio and to minimize the consequences of any new virus being introduced."

Officials in New York are heeding that call, opening vaccination clinics and urging residents to line up for shots, particularly children.

"Polio is a dangerous disease with potentially devastating consequences," New York State Health Commissioner Mary Bassett said in a statement. "In the United States, we are so fortunate to have available the crucial protection offered through polio vaccination, which has safeguarded our country and New Yorkers for over 60 years. Given how quickly polio can spread, now is the time for every adult, parent, and guardian to get themselves and their children vaccinated as soon as possible."

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Mammal ancestor looked like a chubby lizard with a tiny head and had a hippo-like lifestyle

The animal lived before the rise of the dinosaurs and was likely amphibious.

By Jamie Carter

An animal that lived before the dinosaurs looked like a rotund lizard with a very small head and had a hippo-like semiaquatic lifestyle, according to fossils that were recently excavated in France.

The amphibious animal, which represents a previously unknown genus and species of mammal ancestor, measured about 12 feet (4 meters) long, researchers reported in the October issue of the journal Palaeo Vertebrata, published online in July. They dubbed the new species *Lalieudorhynchus gandi*; it lived about 265 million

years ago on the Pangaea supercontinent, just before the era of the dinosaurs.

Fossils of the unusual animal were first discovered in 2001 in the Lodève Basin in southern France, by study co-author and paleontologist Jörg Schneider, a professor in the Department of Paleontology and Stratigraphy at the University of Freiberg in Germany, and doctoral candidate Frank Körner.

Lalieudorhynchus might have had a hippo-like lifestyle, spending much of its time in water. **(Image credit: Frederik Spindler)**

They found two large ribs, each measuring 24 inches (60 centimeters) long, in a rocky streambed. During later visits to the site, Körner found additional bones from the mystery animal: a femur measuring 14 inches (35 cm) long, and a shoulder blade measuring 20 inches (50 cm) long.

Their analysis has been 20 years in the making, largely because the fossils were encased in concrete-hard sandstone and their preparation took years to complete, the researchers reported in the study.

From this partial but well-preserved skeleton, the paleontologists deduced that the primitive creature was a type of caseid — an extinct group of fossil reptiles that possessed mammalian traits and are thought to be mammal ancestors — in the genus Lalieudorhynchus. Described in the press release as a “chubby lizard” and as a 3.5-meter-long “pile of meat”, the creature lived during the Permian, a period that began about 299 million years ago and ended about 252 million years ago with the onset of the Triassic period (and the rise of the dinosaurs).

Caseids were mainly herbivores — perhaps some of the earliest herbivores in evolutionary history. They had small heads and barrel-shaped bodies that held large digestive tracts for breaking down plants, and despite their reptilian appearance, caseids were ancestors of mammals. .

"The highly diverse group of mammal ancestors was the dominant group before the dinosaur ages," Frederik Spindler, co-author of the study and scientific director at the Dinosaur Museum Altmühltal in Denkendorf, Germany, told Live Science. When Spindler examined the newfound fossils, he concluded that they belonged to a new species. There have been fewer than 20 species of caseids identified in the fossil record to date; most came from the United States and Russia, but some have recently been found in southern Europe, Spindler said.

However, *L. gandi* could be a particularly advanced species of caseid, unlike any seen before, Spindler added. "New genera are diagnosed by detailed anatomical comparisons," and the analysis on *L. gandi* was conducted by lead study author Ralf Werneburg, director of the Natural History Museum at Bertholdsburg Castle in Schleusingen, Germany, Spindler said. Werneburg identified five unique features "that are not known in any other caseids, and 20 more that make up a unique combination within this family," Spindler explained.

This newly identified creature is not a so-called missing link in any evolutionary lineage of the mammal family tree, but its status as one of the youngest caseids yet found may be significant for understanding mammalian evolution. "It increases the known diversity of large caseids, marking them as a very important herbivorous group," Spindler said. What's more, *L. gandi* could be the pinnacle of evolution for all caseids before they went extinct, meaning that the species had the most advanced features in the group, Spindler said.

The structure of *L. gandi*'s bones, which were spongy and flexible when viewed under a microscope, hinted to the study authors that

the ancient caseid may have led a semiaquatic lifestyle, much like that of modern hippos. In life, *L. gandi* likely weighed hundreds of pounds, and all that body weight may have required extra support from immersion in water, according to the study.

However, *L. gandi* is not a hippo relative, and any similarities to modern hippos are in the ancient animal's habits and not its anatomy, Spindler said.

"Spongy bones can imply a diving lifestyle in some extinct amphibians and marine reptiles," Spindler said. By comparison, most mammals — including hippos — have denser bone tissue. "Our new caseid would swim better, whereas hippos walk closer to the ground," Spindler said.

"A low browsing semiaquatic lifestyle is what large caseids share with hippos, if we are right," Spindler said. "One could say that *Lalieudorhynchus gandi* 'invented' a niche that hippos repeated later."

Originally published on Live Science.

https://bit.ly/3BRbIq6

Study: 6,000-Year-Old Watermelon from Libya Was Used for Its Nutritious Seeds, Not Its Flesh

Pulp of the Libyan watermelon was white and bitter, matching the inference this plant was used for its seeds, instead of its pulp

Iconographic evidence from Egypt suggests that watermelon pulp was consumed there as a dessert as early as 4,360 years ago. The oldest known watermelon seeds, about 6,000 years old, were found during an archaeological dig from Neolithic settlements in Libya, but whether these were watermelons with sweet pulp or other forms is unknown.

Citrullus seeds from Uan Muhuggiag, Libya. Scale bar – 1 mm. **Image credit: A. Bieniek.**

To shed light on this mystery, an international team of scientists generated genome sequences from the Libyan seeds and another set of 3,300-year-old watermelon seeds from Sudan, as well as from worldwide herbarium collections made between 1824 and 2019. Their results show that the pulp of the 6,000-year-old Libyan watermelon was white and bitter, matching the inference that this plant was used for its nutritious seeds, instead of its pulp.

Scientists generally agree that watermelons (*Citrullus lanatus*) came from Africa, but exactly where and when watermelons with red, sweet flesh were first domesticated from their wild form is debatable.

The most recent data point to watermelon getting its start in the Nile Valley, which is consistent with archaeological evidence.

However, the 6,000-year-old seeds discovered at Uan Muhuggiag, a rock shelter in what is now the Sahara Desert in Libya, seemed at odds with this explanation.

“The oldest seeds of watermelons cannot be securely identified as either belonging to a sweet-pulped domesticated form, or instead to one of the bitter-pulped wild forms,” explained co-senior author Professor Susanne Renner, a researcher in the Department of Biology at Washington University, Saint Louis and the Faculty of Biology, Systematic Botany and Mycology at the University of Munich.

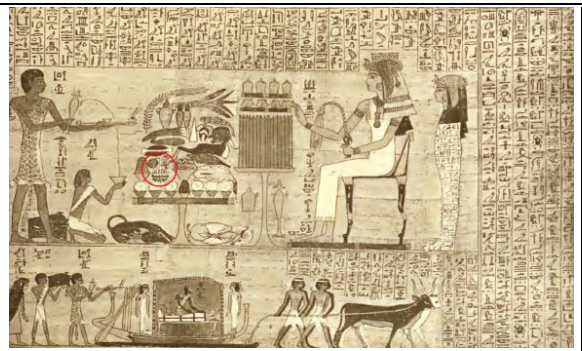
“The seeds of the seven species of the genus *Citrullus* are basically undistinguishable.”

“Now, having a chromosome-level genome, we can be sure that Neolithic Libyans were using a bitter-fleshed watermelon.”

“We suspect they used the fruits to get at the (numerous!) seeds, which even today are eaten air-dried or roasted or also boiled in soups or stews.”

In the new study, Professor Renner and her colleagues sequenced DNA from 6,000 and 3,300 year-old watermelon seeds from archeological sites in Libya and northern Sudan.

"These seeds were a riddle because they were thought to be the oldest true watermelon seeds," said co-senior author Dr. Guillaume Chomicki, a researcher in the School of Bioscience at the University of Sheffield.



Papyrus de Kamara illustrating a Citrullus fruit (red circle), interpreted as a wild watermelon; the globose striped fruit is reminiscent of the morphology of the Kordofan melon. **Image credit: Renner et al., doi: 10.1073/pnas.2101486118.**

"Yet they were from Libya, which was never thought to be the cradle of watermelon domestication."

The authors also sequenced the genomes from geographically widespread herbarium specimens collected between 1824 and 2019. They analyzed the data together with resequenced genomes from important germplasm collections.

They discovered that the 6,000-year-old Libyan seeds came from a form of *Citrullus* that was genetically close to today's seed-use, bitter-fleshed, egusi-type watermelon (*Citrullus mucosospermus*), now found in Ghana, Benin, and Nigeria in West Africa.

According to the team, the likely use of the Libyan seeds as a snack matches the traces of cracking from human teeth found in a computer-tomographic study of seeds from the Uan Muhuggiag site.

"An unexpected new insight is that *Citrullus* appears to have initially been collected or cultivated for its seeds, not its sweet flesh, consistent with seed damage patterns induced by human teeth in the oldest Libyan material," Dr. Chomicki said.

"This study documents the use of the seeds (rather than the fruit) of a watermelon relative more than 6,000 years ago, prior to the domestication of the watermelon."

"Watermelons — the wild species, as well as the domesticated form — have very numerous seeds that are tasty and oil-rich," Professor Renner said.

"Different from the pulp, the seeds never contain the extremely bitter cucurbitacin chemical. Snacking on those easily available nutritious seeds may have been a good thing."

The findings were recently published in the journal *Molecular Biology and Evolution*.

Osca A. Pérez-Escobar et al. Genome sequencing of up to 6,000-yr-old Citrullus seeds reveals use of a bitter-fleshed species prior to watermelon domestication. Molecular Biology and Evolution, published online July 30, 2022; doi: 10.1093/molbev/msac168

https://go.nature.com/3bvvPzI

Pig organs partially revived in dead animals — researchers are stunned

Scientists warn that the findings aren't yet clinically relevant but say the research raises ethical questions about the definition of death.

Max Kozlov

Researchers have restored[1] circulation and cellular activity in the vital organs of pigs, such as the heart and brain, one hour after the animals died. The research challenges the idea that cardiac death — which occurs when blood circulation and oxygenation stops — is irreversible, and raises ethical questions about the definition of death. The work follows 2019 experiments[2] by the same scientists in which they revived the disembodied brains of pigs four hours after the animals died, calling into question the idea that brain death is final.

The latest experiments are "stunning", says Nita Farahany, a neuroethicist at Duke University in Durham, North Carolina. Although this study is preliminary, she says it suggests that some perceived limitations of the human body might be overcome in time.

In the work, published on 3 August in *Nature*[1], researchers

connected pigs that had been dead for one hour to a system called OrganEx that pumped a blood substitute throughout the animals' bodies. The solution — containing the animals' blood and 13 compounds such as anticoagulants — slowed the decomposition of the bodies and quickly restored some organ function, such as heart contraction and activity in the liver and kidneys. Although OrganEx helped to preserve the integrity of some brain tissue, researchers did not observe any coordinated brain activity that would indicate the animals had regained any consciousness or sentience.

As with the 2019 paper, the study is likely to reinvigorate a debate about the definition of death and the ethics of post-mortem organ donation. The authors warn that these results do not show that the pigs have somehow been reanimated after death, especially in the absence of electrical activity in the brain. "We made cells do something they weren't able to do" when the animals were dead, says team member Zvonimir Vrselja, a neuroscientist at Yale University in New Haven, Connecticut. "We're not saying it's clinically relevant, but it's moving in the right direction."

Circulation restarts

Nenad Sestan, a Yale neuroscientist and member of the team, predicted that these experiments might work in the light of the 2019 pig-brain study, because the brain is the organ most susceptible to oxygen deprivation. "If you can regain some function in a dead pig brain, you can do it in other organs, too," he says.

To find out, he and his co-authors modified the BrainEx solution and the technique used for that study. "BrainEx was tailored for a specific organ, but we had to find a common denominator that works for all organs with OrganEx," says Vrselja. In the OrganEx solution, the researchers included compounds that would suppress blood clotting and the immune system, which is more active elsewhere in the body than in the brain, he says.

Sestan's team obtained pigs from a local farm breeder and monitored them for three days before sedating them, putting them on a ventilator and inducing cardiac arrest by delivering a shock to their hearts. After confirming a lack of pulse, the researchers removed the animals from the ventilators. One hour after the pigs died, the team restarted the ventilators and anaesthesia. Some of the pigs were then attached to the OrganEx system; others received no treatment or were hooked up to an extracorporeal membrane oxygenation (ECMO) machine, which some hospitals use in a last-ditch effort to supply oxygen to and remove carbon dioxide from the body.

After six hours, the researchers noticed that circulation had restarted much more effectively in pigs that had received the OrganEx solution than in those that had received ECMO or no treatment. Oxygen had begun flowing to tissues all over the bodies of the OrganEx animals, and a heart scan detected some electrical activity and contraction. But the heart had not fully restarted, and it's unclear what exactly it was doing in those animals, says team member David Andrijevic, a neuroscientist at Yale.

The researchers also noticed that the livers of the OrganEx pigs produced much more of a protein called albumin than did the livers of pigs in the other groups. And cells in each of the vital organs of the OrganEx pigs responded to glucose much more than did the animals in the other groups, suggesting that the treatment had kick-started metabolism.

The findings are striking given how quickly after death decomposition begins, says Vrselja. Within minutes of the heart stopping, the body becomes deprived of oxygen and enzymes begin digesting cell membranes, leading to organs rapidly losing their structural integrity.

The researchers also found that more genes responsible for cellular function and repair were active across all major organs in the OrganEx group compared with the ECMO or no-treatment groups.

Involuntary movements

Curiously, only the OrganEx pigs started involuntarily jerking their head, neck and torso after receiving an injection of contrast dye that helped the scientists to visualize the animals' brains following treatment. The researchers didn't have a good explanation for the movements, noting that it's unlikely that the impulses arose in the brain, given the lack of electrical activity. It's possible that the movements arose in the spinal cord, which can control some motor functions independently of the brain, they say.

If the findings of cellular restoration can be replicated in animals and eventually in humans, their implications for human longevity could be as "profound" as the advent of CPR and ventilators, says Farahany. That's because the technique could one day be used to preserve organs for transplantation — which are in short supply — or even resuscitation.

ECMO is currently used in an attempt to preserve the organs of some dead people for donation, or to try to resuscitate people following a heart attack. For these purposes, doctors typically need to start ECMO soon after the heart attack or death — and success rates can be low, depending on injury severity, says Sam Shemie, a critical-care physician at the McGill University Health Centre in Montreal, Canada.

Given the difference in how the pigs' organs fared with OrganEx compared with ECMO, this is potentially a "landmark" study that could "significantly increase the number of organs that could be recovered for transplantation", says Gabriel Oniscu, a transplant surgeon at the Royal Infirmary of Edinburgh, UK.

Before that can happen, further research to assess the viability of the recovered organs will be crucial, says Shemie.

Ethical challenges

With these potential implications come ethical challenges, says Farahany, especially if the technique could one day restore brain activity after death.

The researchers note that electrical activity in the pigs' brains might have been absent because the solution pumped through was at 28 ºC — colder than normal body temperature — or because it included anaesthetic compounds and neuronal blockers that could have suppressed such signals. Farahany says it will be important for future researchers to test for any restoration of brain activity, particularly in light of the neck-jerking the researchers observed during the experiment.

The study also further emphasizes that death is not a moment but a process, making it challenging to come up with a uniform way to declare a person dead, says Arthur Caplan, a bioethicist at New York University. That means that the legal definition of death will continue to adapt as medicine continues to advance, he adds. "People tend to focus on brain death, but there's not much consensus on when cardiac death occurs," he says. "This paper brings that home in an important way."

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https://wb.md/3QfhDcU

Long COVID Comes in Three Forms: Study

Scientists have found three types of long COVID, which have their own symptoms and seem to appear across several coronavirus variants, according to a new preprint study published on MedRxiv that hasn't yet been peer-reviewed.

Carolyn Crist

Long COVID has been hard to define due to its large number of symptoms, but researchers at King's College London have identified three distinct profiles — with long-term symptoms

focused on neurological, respiratory, or physical conditions. So far, they also found patterns among people infected with the original coronavirus strain, the Alpha variant, and the Delta variant.

"These data show clearly that post-COVID syndrome is not just one condition but appears to have several subtypes," Claire Steves, PhD, one of the study authors and a senior clinical lecturer in King's College London's School of Life Course & Population Sciences, said in a statement.

"Understanding the root causes of these subtypes may help in finding treatment strategies," she said. "Moreover, these data emphasize the need for long-COVID services to incorporate a personalized approach sensitive to the issues of each individual."

The research team analyzed ZOE COVID app data for 1,459 people who have had symptoms for more than 84 days, or 12 weeks, according to their definition of long COVID or post-COVID syndrome.

They found that the largest group had a cluster of symptoms in the nervous system, such as fatigue, brain fog, and headaches. It was the most common subtype among the Alpha variant, which was dominant in winter 2020-2021, and the Delta variant, which was dominant in 2021.

The second group had respiratory symptoms, such as chest pain and severe shortness of breath, which could suggest lung damage, the researchers wrote. It was the largest cluster for the original coronavirus strain in spring 2020, when people were unvaccinated.

The third group included people who reported a diverse range of physical symptoms, including heart palpitations, muscle aches and pain, and changes to their skin and hair. This group had some of the "most severe and debilitating multi-organ symptoms," the researchers wrote.

The researchers found that the subtypes were similar in vaccinated and unvaccinated people based on the variants investigated so far. But the data showed that the risk of long COVID was reduced by vaccination.

In addition, although the three subtypes were present in all the variants, other symptom clusters had subtle differences among the variants, such as symptoms in the stomach and intestines. The differences could be due to other things that changed during the pandemic, such as the time of year, social behaviors, and treatments, the researchers said.

"Machine learning approaches, such as clustering analysis, have made it possible to start exploring and identifying different profiles of post-COVID syndrome," Marc Modat, PhD, who led the analysis and is a senior lecturer at King's College London's School of Biomedical Engineering & Imaging Sciences, said in the statement.

"This opens new avenues of research to better understand COVID-19 and to motivate clinical research that might mitigate the long-term effects of the disease," he said.

Sources

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https://bit.ly/3QpU1lU

'Ghost footprints' left by ancient hunter-gatherers discovered in Utah desert

The eerie prints appear only after it rains.

By Harry Baker

Archaeologists recently stumbled upon a set of mysterious "ghost footprints" in the salt flats of a Utah desert. These unusual ancient tracks get their eerie name not because they are from an ethereal realm, but due to their earthly composition: They become visible only after it rains and the footprints fill with moisture and become darker in color, before disappearing again after they dry out in the sun.

Researchers accidentally discovered the unusual impressions in

early July as they drove to another nearby archaeological site at Hill Air Force Base in Utah's Great Salt Lake Desert. The team initially only found a handful of footprints, but a thorough sweep of the surrounding area using ground-penetrating radar (GPR) revealed at least 88 individual footprints belonging to a range of adults and children, potentially as young as 5 years old. (The GPR technique works by firing radio waves into the ground that bounce off objects that are hidden under the surface.)

Two of the ghost footprints uncovered in Utah's Great Salt Lake Desert.
(Image credit: U.S. Air Force photo by R. Nial Bradhsaw)

The ghostly prints were left by bare human feet at least 10,000 years ago when the area was still a vast wetland. However, researchers suspect that the tracks could date back as far as 12,000 years ago during the final stretch of the last ice age during the Pleistocene epoch (2.6 million to 11,700 years ago).

The discovery of so many ancient footprints is a "once-in-a-lifetime discovery," Anya Kitterman, the cultural resource manager at Hill Air Force Base who oversaw the archaeological work, said in a statement (opens in new tab). "We found so much more than we bargained for." However, the discovery has not yet been published in a peer-reviewed journal because researchers are still analyzing the footprints.

The Great Salt Lake Desert was once covered by a large, salty lake similar to the nearby Great Salt Lake — the largest saltwater lake in the Western Hemisphere — which the desert is named after. The ancient lake slowly dried up due to changes in Earth's climate triggered by the end of the last ice age, which left behind the salts that were once dissolved in the water. But during the transition from lake to dry salt flats, the area was briefly a large wetland that was occupied by humans up until 10,000 years ago, according to the statement.

During this time, the conditions would have been perfect to create the ghost footprints, the researchers said.

People appear to have been walking in shallow water, with the sand rapidly infilling their print behind them, much as you might experience on a beach," lead researcher Daron Duke, an archaeologist with Far Western Anthropological Research Group, a private firm that specializes in cultural resources management, said in the statement. "But under the sand was a layer of mud that kept the print intact after infilling." The footprints have since been filled in with salt as the wetlands dried out, making them indistinguishable from the surrounding landscape when they're dry, Duke added.

Normally, when it rains, the water is quickly absorbed deep into the surrounding sediment, which means the ground quickly returns to its normal color. But when the rain falls on top of the hidden muddy footprints, the water gets trapped, creating patches of dark and wet sediment that stand out from their surroundings.

Less than a mile (1.6 kilometers) away from where the tracks were uncovered, a previous research group uncovered a hunter-gatherer camp dating to 12,000 years ago, where the humans who left the prints might have lived. Archaeological finds at the site included an ancient fireplace, stone tools used for cooking, a pile of more than 2,000 animal bones and charred tobacco seeds, which are the earliest evidence of tobacco use in humans.

The researchers involved with the new finding have collected some of the footprints in order to determine their exact age. Using radiocarbon dating, researchers hope to be able to analyze small pieces of organic material that could have been trapped in the sediment by the foot of whoever left the prints, according to the statement.

This region is a hotspot for ancient human trackways. In September 2021, a study revealed that 60 human footprints in White Sands National Park in New Mexico dated to between 21,000 and 23,000 years ago, making them the oldest "unequivocal evidence" of humans in the Americas. These footprints were also discovered using GPR.

"We have long wondered whether other sites like White Sands were out there and whether GPR would be effective for imaging footprints at other locations," Thomas Urban, an archaeologist at Cornell University who developed the GPR survey technique used at White Sands and more recently at the Hill Air Force Base, said in a statement (opens in new tab). "The answer to both questions is yes."

The researchers say that these types of discoveries are important because they are direct evidence of human settlement in the area and are much more visceral than other nearby archaeological discoveries. "There is an immediate human connection to seeing human footprints," Duke said. "To see them from a distant past, especially so much different than it looks today, can be impactful."

https://wb.md/3oT9RcW

Rapid Smell Loss a Biomarker of Alzheimer's Disease Risk?

Those who experienced rapid loss of sense of smell more likely to be subsequently diagnosed with mild cognitive impairment or dementia

Jennie Smith

Rapid deterioration in sense of smell is a strong predictor of both Alzheimer's-related cognitive impairment and loss of volume in specific brain regions linked to both Alzheimer's disease and smell, according to new research findings.

Olfactory dysfunction is common in late life and well documented among people with Alzheimer's disease. However, it was unknown whether faster olfactory decline predicts either onset of Alzheimer's disease or structural brain changes associated with Alzheimer's disease.

In a study published online in Alzheimer's and Dementia, Jayant M. Pinto, MD, and his colleagues at the University of Chicago Medical Center reported that among older adults with normal cognition at baseline, people who experienced rapid loss of sense of smell were more likely to be subsequently diagnosed with mild cognitive impairment (MCI) or dementia, compared with those who did not.

Participants were recruited from Rush University's Memory and Aging Project, a longitudinal cohort of older adults who undergo yearly cognitive and sensory exams, including a scratch test of 12 common smells to identify. The Rush study "was ahead of the curve in looking at smell," Pinto said in an interview. "It gave us a very valuable resource with which to attack these questions."

Pinto has long investigated links between smell and accelerated aging; in 2014 his group published the finding that olfactory dysfunction could predict death within 5 years in older adults, and in 2018 they reported that olfactory dysfunction could predict dementia.

Smell and Cognition Over Time

For the current study, Pinto said, "we were able to look at the question not just using a single point in time, but a more granular trajectory of smell loss. Measuring change year by year showed that the faster people's sense of smell declined, the more likely they were to be diagnosed with MCI or Alzheimer's disease."

Pinto and his colleagues evaluated results from 515 adults (mean age 76.6, 78% female, 94% White) with no cognitive impairment and at least 3 years of normal results on smell tests at baseline. The subjects were followed for a mean 8 years. One hundred subjects (19%) were diagnosed with MCI or dementia by the end of the study period. A subset of the cohort (n = 121) underwent structural

magnetic resonance imaging (MRI) between their final smell tests and the study's end. Of these, most still had normal cognition; 17 individuals had MCI.

Patients' individual trajectories of smell loss were mapped as slopes. After adjusting for expected differences in age and sex, the investigators found steeper decline associated with greater risk of incident MCI or dementia (odds ratio, 1.89; 95% confidence interval, 1.26-2.90; $P < .01$). The risk was comparable to that of carrying an apo E ε4 allele, the key risk variant for late-onset Alzheimer's disease, but was independent of apo E status. The association was strongest among subjects younger than 76 years.

Olfactory Decline and Brain Volume

Pinto and his colleagues, including lead author Rachel R. Pacyna, a 4th-year medical student at the University of Chicago, also sought to identify brain volume changes corresponding with olfactory decline and Alzheimer's disease. The researchers hypothesized that certain brain regions not seen affected in Alzheimer's disease would remain unchanged regardless of olfactory status, but that regions associated with smell and Alzheimer's disease would see smaller volumes linked with olfactory decline.

Faster olfactory decline did predict lower gray matter volume in olfactory regions, even after controlling for apo E status and other known risk factors. Conversely, cognitively unimpaired patients undergoing MRI saw more gray matter volume in primary olfactory and temporal brain regions, compared with those with cognitive symptoms.

Taken together, the findings suggest that "change in sense of smell is better than looking at sense of smell at one time point," Pinto commented. "There are other reasons people have impaired sense of smell: car accidents, COVID, other viruses and infections. But if you identify on a time course those who are starting to lose it faster, these are the people on whom we need to focus."

Not Yet Diagnostic

More work needs to be done to establish thresholds for smell loss that could be useful in clinical or investigative settings as a marker of dementia risk, Pinto acknowledged. "Everyone gets their hearing tested; everyone gets their vision tested. It's not as easy to get your sense of smell tested. But this study is telling people that if we were to start measuring it routinely, we could actually use it."

Smell testing "could become a component of a diagnostic battery that includes things like genotyping and cerebrospinal fluid markers, but adds a little more information. It could be useful in clinical prevention trials to identify people at the highest risk, as smell loss presents quite a few years before MCI or Alzheimer's disease."

The investigators acknowledged that their findings need to be replicated in more diverse cohorts that better represent the Alzheimer's population in the United States. Another limitation of their study, they said, was that the method used to calculate the rate of olfactory decline "was based on slope of measured time points assuming linearity, which may oversimplify the complexity of olfactory changes in normal aging and during the preclinical Alzheimer's disease period." The study was funded by the National Institutes of Health. Pinto disclosed receiving consulting fees from Sanofi/Regeneron, Optinose, and Genentech not related to this work.

https://bit.ly/3p0j3w5

400-year-old Ecuadoran beer resurrected from yeast

400-year-old yeast specimen has been resurrected and used to reproduce what is believed to be Latin America's oldest beer

by Paola LÓPEZ

Inside an old oak barrel, Ecuadoran bioengineer Javier Carvajal found the fungus of fortune: a 400-year-old yeast specimen that he has since managed to resurrect and use to reproduce what is believed to be Latin America's oldest beer.

That single-cell microorganism, taken from just a splinter of wood, was the key to recovering the formula for an elixir first brewed in Quito in 1566 by friar Jodoco Ricke, a Franciscan of Flemish origin who historians believe introduced wheat and barley to what is now the Ecuadoran capital.

"Not only have we recovered a biological treasure but also the 400-year-old work of silent domestication of a yeast that probably came from a chicha and that had been collected from the local environment," Carvajal told AFP.

Chicha is a fermented corn drink brewed by the Indigenous people of the Americas before Spanish colonization.

Carvajal, who already had experience recovering other yeasts, found out about the ancient Franciscan brewery in Quito while reading specialist beer magazines.

It took him a year to do so, but he finally managed to find a barrel from the old brewery in 2008. It was stored in Quito's San Francisco Convent, an imposing three-hectare complex built between 1537 and 1680, which is now a museum.

After extracting a splinter, Carvajal used a microscope to find a tiny yeast specimen, which after a long period of cultivation he was able to resurrect. In his laboratory at the Catholic University of Ecuador, Carvajal takes a small vial containing a variety of the Saccharomyces cerevisiaerescatada yeast.

"It lives here in a little container. It's very humble, but it is the star" of the laboratory, said the 59-year-old.

Filling the holes

Carvajal, who comes from a brewing family, found an article in an industry magazine that vaguely described the formula for the Franciscans' 16th century drink.

Little by little, he pieced together bits of information to revive the brew with cinnamon, fig, clove and sugarcane flavors.

"There were a massive number of holes in the recipe and my job was to fill those holes," said Carvajal. "It is a work of beer archeology within the microbial archeology" he had to carry out to rescue the yeast, which generates the majority of the drink's flavor.

After a decade of investigation and testing, Carvajal in 2018 began producing the beer at his home—but the pandemic frustrated his attempts to commercialize it. He still has not come up with a launch date for his product, nor a price.

Carvajal compares his work, centuries after the Franciscans domesticated the yeast, to intensive care on a molecular scale.

"It is as if they were dormant, like dried seeds but having deteriorated over the years. So you have to reconstruct them, fluidize them, hydrate them and see if their vital signs return."

Historian Javier Gomezjurado, who wrote a book on Quito beverages, told AFP that the brewery in the San Francisco Convent was the first brewery in hispanic America. It began operations in 1566, but there were just eight friars in the convent at that time and production was minimal, said Gomezjurado.

With the introduction of machinery into the brewing industry, ancient formulas began to disappear. The brewery closed in 1970.

For Carvajal, resurrecting the yeast and the age-old methods used to make the ancient recipe was simply a labor of love for "the value of the intangible."

https://wb.md/3P0dwAl

Skin Test Accurately IDs Alzheimer's Even in the Presence of Comorbid Pathologies

A minimally invasive skin test can accurately diagnose Alzheimer's Disease (AD) with high sensitivity and specificity, even in the presence of comorbid pathologies, new research suggests.

Pauline Anderson

The test, which measures factors related to synaptic connections in the brain, could be added to other testing to "tremendously enhance

the certainty of making [an AD] diagnosis," Daniel Alkon, MD, chief scientific advisor at SYNAPS Dx, the company behind the test, told *Medscape Medical News.* The findings were presented at the Alzheimer's Association International Conference (AAIC) 2022.

Better Specificity Needed

Clinical trials testing potential AD therapies typically include patients without a definitive diagnosis for AD dementia. That is because diagnoses are often uncertain, particularly during the first 4-5 years of the disease.

Several tests to detect AD signs have been developed. These include MRI and PET scan tests for amyloid plaque, cerebrospinal fluid, and plasma measures of soluble amyloid and tau, and blood levels of tau.

However, none of these tests have been extensively validated at autopsy, said Alkon. Previous studies have shown over 50% of patients do not have AD alone. Instead, they also have other pathologies, such as Parkinson's Disease, frontal lobe dementia, or multi-infarct dementia, Alkon noted.

"It's not enough for a test to discriminate Alzheimer's from a control person who is not demented. It is only valuable if you can discriminate it from other kinds of dementia," Alkon said.

He noted that while beta-amyloid and tau are used as "pathological red flags" to identify AD at autopsy, they are not great at definitively diagnosing the disease because they are not closely correlated with cognitive deficits.

There is an "urgent unmet medical need" for a highly accurate, easily accessible AD biomarker, he said.

Enter the industry certified DISCERN test (SYNAPS Dx) that measures factors related to synaptic connections in the brain, which Alkon said is a better indicator of AD than amyloid or tau. Such factors include synaptic loss, neuronal death, inflammation, amyloid deposition, and hyperphosphorylation of tau protein.

One of the assays in the test is the Morphometric Imaging assay, which was previously shown to closely correlate skin cell abnormalities with dementia and presence of AD pathology in the brains of patients with AD. "The studies correlate what's happening in the brain of a patient with what's happening elsewhere," said Alkon. "The inference is [that] the disease has systemic expression; it's not just affecting the brain but affecting the whole system."

New and Unique?

In the current study, researchers obtained a small skin sample through a skin punch biopsy from 74 participants. Of these participants, 26 had AD, which was later confirmed following an autopsy; 21 had non-AD dementia (non-ADD); and 27 did not have dementia and acted as the control group.

The investigators found that AD cell lines formed large aggregates, while non-ADD or control-group cell samples formed smaller and more numerous aggregates. The researchers then counted the number of aggregates and measured the aggregates' average area.

This led them to distinguish patients with AD from those with non-ADD. The probability distributions of the morphometric imaging signals showed clear separation of the measurements for individual patients with AD and for group values for patients with non-ADD.

Based on these results, the sensitivity of the MI assay for diagnosing AD was determined to be 100% (95% CI, 86% - 100%), while the specificity was also 100% (95% CI, 84% - 100%).

Researchers also used samples from patients with dementia who were older than 55 years and who had a blinded autopsy examination. AD specificity held up even in cases with pathologic co-morbidity, including AD with dementias such as Parkinson's disease, Pick's disease, and frontal lobe dementia.

"What's new and unique is we have shown we can measure AD even in patients who have comorbidity; that is, patients who have these other dementias," said Alkon.

Next Steps

Alkon noted this type of research is time-consuming and requires "resources, persistence and determination." A death and confirming autopsy can take place years after a skin test and clinical diagnosis.

The company's main laboratory already analyzes samples of suspected AD cases, but "we are getting ready to launch nationally," said Alkon.

"Clinicians should use all available armamentarium measurements they can before making a diagnosis of Alzheimer's Disease, and they should be thorough and cautious," he added. The company is currently seeking US Food and Drug Administration approval of the skin test and has received breakthrough status.

The test could help rule out other causes of dementia for which there are treatments, such as a thyroid disorder, major depression, and vitamin B12 deficiency, Alkon noted.

He acknowledged that if the test does indicate AD, there are few effective treatments available. "In my opinion, none of the drugs available today actually treat the underlying disease," he said.

However, he noted that could change. Alkon is also president of Synaptogenix, a company developing a therapeutic aimed at enhancing the synaptic growth pathway.

Early Days

Commenting on the study for *Medscape Medical News*, Rebecca Edelmayer, PhD, senior director of scientific engagement at the Alzheimer's Association, said she is encouraged by this skin puncture test and other research into Alzheimer's diagnostics.

However, she cautioned these tests are at a very early stage. "An important step in moving these tests forward for broader use is to study them in large-scale clinical trials," Edelmayer said.

She noted the DISCERN test analyzes protein kinase C (PKC) signaling markers, which have not yet been validated in large trials to support their use as a diagnostic for AD.

Edelmayer also pointed out this test does not have FDA clearance. "It's important for consumers to be informed about how broad or not these tools have been evaluated," she said.

There is currently no single test that diagnoses AD, she added.

The study was funded by SYNAPS.

Alzheimer's Association International Conference (AAIC) 2022: Abstract 63141. Presented July 31, 2022.

https://wb.md/3dfJzPe

Dermatologists Share Vitiligo Breakthrough News With Patients

Patients with vitiligo can now have even skin tones on their body with a US FDA-approved, easy-to-use topical treatment

Marcia Frellick

For the first time, patients with vitiligo who have long lived with patches of skin that are without pigment can now have even skin tones on their faces and other bodily regions with a US Food and Drug Administration (FDA)-approved, easy-to-use topical treatment.

In July, a cream formulation of ruxolitinib (Opzelura), a Janus kinase (JAK) inhibitor, became the first repigmentation treatment approved by the FDA for nonsegmental vitiligo, the most common form of the disease.

Topical ruxolitinib was first approved in September 2021 for atopic dermatitis, and dermatologists are already writing prescriptions for its new vitiligo indication. "The FDA approval of ruxolitinib for repigmentation of vitiligo is historic and groundbreaking," Seemal Desai, MD, a dermatologist with the University of Texas Southwestern Medical Center, Dallas, told *Medscape Medical News*.

The news brings hope to patients 12 years and older who suffer from the psychosocial effects of the disease, which is estimated to affect 1.9 million to 2.8 million adults in the United States.

The announcement followed FDA approval a month earlier of

another dermatologic milestone — an oral JAK inhibitor, baricitinib, which became the first treatment for patients with alopecia areata.

For Desai, the ruxolitinib news is personal. His brother, also a physician, has lived a lifetime with vitiligo. His family experience, Desai said, showed him "what a disease like this can do to a person psychologically."

Seemal Desai said his early exposure helped lead to his own decision to dedicate his career to pigmentary diseases.

His brother won't personally benefit from the cream because his skin has been completely depigmented and repigmentation is not of interest to him, Desai said. But both brothers are excited as physicians. "It's really quite an emotional moment," he said.

Getting the News to Patients

As dermatologists introduce the topical treatment to patients, common questions center on why this cream is different and whether it is safe. David Rosmarin, MD, vice chair of research and education, Department of Dermatology, Tufts Medical Center, Boston, led the Topical Ruxolitinib Evaluation in Vitiligo Study 1 and 2 (TruE-V1, TruE-V2), conducted in North America and Europe. He summarized some key findings.

"If patients have involvement on the face, trunk, or extremities, the data show that about half the patients at 52 weeks will get half or more of their pigment back," he told *Medscape Medical News*.

Results for the face alone are even better. "Half the patients will get 75% or more pigment back in the face," Rosmarin said.

In addition, analysis of subgroups shows benefit for all patients. "Patients seem to respond similarly well across all subgroups — across gender sex, age, ethnicity, and race," Rosmarin said.

However, anatomic region matters, he pointed out. Skin of the head and neck responds the best, followed by skin of the trunk and extremities. The hands and feet are the most difficult to repigment because there are few hair follicles, which help enable repigmentation.

He added that it's important to understand patients' goals, and dermatologists shouldn't assume that all who have vitiligo will want to undergo repigmentation. They may be interested in the new treatment but may not want it for themselves, he explained.

Explaining Risks

Patients may ask about the boxed warning on the label that lists risk of heart attack, stroke, cancer, infections, blood clots, and death. Dermatologists can explain that that warning pertains to the whole JAK class and was based on patients with rheumatoid arthritis, Rosmarin said. He added, "We didn't see a signal for heart attack and stroke for patients using the topical. But it's still important to discuss the label as the FDA states it."

There are two main side effects, Rosmarin said: acne (about 6% of treated patients get it, and it's usually mild) and application-site reactions. "Luckily, the medication has a tendency not to sting or burn, which is not the case with some of our other treatments. It's very well tolerated," he said.

Patients should also know that repigmentation can take time, because initially, the immune system is directed to calm down with treatment, and then pigment must travel back to the affected sites.

Some patients may have a response in as early as 2–3 months, and others need more time, Rosmarin said.

Treatment responses among adolescents have been particularly good. Responses regarding the skin of the face have been similar to those of adults. "However, on the body, they respond even better," Rosmarin said. "About 60% achieve 50% or more repigmentation on the whole body."

It's important that ruxolitinib has been approved for persons aged 12 years and older, he said, because "about half the patients will develop vitiligo by the age of 20."

Approval and Insurance Coverage

FDA approval will help with reimbursement for the expensive treatment. The label indicates that patients should not use more than one 60-g tube a week. Currently, the out-of-pocket cost for one tube can be close to $2000, according to GoodRx.

Raj Chovatiya, MD, PhD, assistant professor of dermatology and director of the Center for Eczema and Itch at Northwestern University Feinberg School of Medicine in Chicago, said that in recent years, vitiligo patients, aware that their condition could be treated by JAK inhibitors, have been paying out of pocket at compounding pharmacies, which take oral versions of the medication and compound them into topical formulations.

Unlike baricitinib, which is used to treat severe alopecia areata, and other oral JAK inhibitors, testing for TB and hepatitis is not required for initiating treatment with ruxolitinib, so no delay is necessary, Chovatiya said.

He noted, however, that patients with vitiligo may have given up on effective care after experiencing little or no improvement with topical corticosteroids, phototherapy, or topical calcineurin inhibitors. "They end up losing steam, are less motivated on therapy, and are lost to care," he said.

Dermatologists, he said, may need to proactively find these patients and tell them the good news. "Now that we have really good targeted therapeutic options, it's really up to us to figure out how to bring these people back to the clinic and educate them," Chovatiya said.

Unanswered Questions to Address

Some questions are still unanswered, lead study author Rosmarin said. Two big questions are how long people will need to continue using ruxolitinib cream and whether depigmentation will recur if people stop using it.

Another aspect of therapy being studied is whether the cream will be even more effective in combination with other treatments.

"The main combination we think about is ruxolitinib with phototherapy — a light treatment — because light could stimulate those pigment cells," Rosmarin said,

He noted that light therapy was included in phase 2 testing and that patients did respond. "What we need and what's planned is a larger study looking at the combination to see whether it is synergistic or not. The longer patients use the cream, the more benefit we see," Rosmarin said.

Desai has served as an investigator and/or consultant to several companies, including Incyte. Rosmarin received honoraria as a consultant for Incyte, AbbVie, Abcuro, AltruBio, Arena, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, Concert, CSL Behring, Dermavant, Dermira, Janssen, Kyowa Kirin, Lilly, Novartis, Pfizer, Regeneron, Revolo Biotherapeutics, Sanofi, Sun Pharmaceuticals, UCB, and VielaBio. He has also received research support from Incyte, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Dermira, Galderma, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron; and has served as a paid speaker for Incyte, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Incyte, Janssen, Lilly, Novartis, Pfizer, Regeneron, and Sanofi. Coughlin is on the board of the Pediatric Dermatology Research Alliance and the International immunosuppression and Transplant Skin Cancer Collaborative. Chovatiya has served as an advisory board member, consultant, and/or investigator for Incyte, AbbVie, Arcutis, Arena, Argenx, Beiersdorf, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, EPI Health, L'Oréal, National Eczema Association, Pfizer Inc., Regeneron, Sanofi, and UCB. He has been a speaker for Incyte, AbbVie, Dermavant, Eli Lilly and Company, LEO Pharma, Pfizer Inc., Regeneron, Sanofi, and UCB.

https://bit.ly/3Jzcnyw

Why early Romans used lopsided dice

Solving the mystery of why people living during Roman Empire times used lopsided dice in their games

by Bob Yirka , Phys.org

A pair of researchers, one with the University of California, Davis, the other Drew University, believe they may have solved the mystery of why people living during the time of the Roman Empire used lopsided dice in their games. In their paper published in the journal *Archaeological and Anthropological Sciences*, Jelmer Eerkens and Alex de Voogt, describe their study of dice used

during the days of the Roman Empire.

During the time of the Roman Empire, people played a game called taberna (similar to backgammon) which involved throwing dice. The dice were made out of bone, metal or clay and had symbols shown on the faces to represent numbers, as with modern dice. But they differed markedly in shape. The Roman dice were usually elongated or made into other odd shapes that made them asymmetrical.

Map of modern-day Netherlands showing location of Roman sites included in this study (number corresponds to number of dice measured at each location) along with three examples of dice on right. **Credit: Archaeological and Anthropological Sciences (2022). DOI: 10.1007/s12520-022-01599-y**

In this new effort, the researchers studied 28 die from the period and found that 24 of them were asymmetrical. They found a pattern in the irregularity—icons representing one and six were often present on larger opposing surfaces.

Prior research has shown that asymmetry in a die can impact the probability of a given side landing face up. Based on their measurements, the researchers calculated that the difference in size would change the odds of rolling a given a number, on average, from one in six to one in 2.4.

To find out if the Romans made their dice asymmetrical as a means of cheating, the researchers conducted an experiment—they asked 23 students to place marks on reproductions of the asymmetrical Roman dice. The researchers reasoned that because the students would not know the purpose of the experiment and had no incentive to cheat, they would mostly place the marks randomly.

But that was not the case, the students still placed the one and six on the larger sides.

When asked why, many suggested it was easier because starting on a large side meant ending on a large side where they would need to place the most pips—a finding that suggests the Romans were not trying to cheat, they were just trying to make life easier for themselves.

It also suggests that they were not too concerned about which face was assigned which number because they believed that many random events, such as dice throwing were governed by the fates.

But the researchers also note, that more clever people likely figured out over time that certain die throws were more likely to wind up a one or a six, and thus would choose one or the other.

More information: *Jelmer W. Eerkens et al, Why are Roman-period dice asymmetrical? An experimental and quantitative approach, Archaeological and Anthropological Sciences (2022). DOI: 10.1007/s12520-022-01599-y*

https://bit.ly/3Quo8bR

Researchers show that locusts can 'sniff' out human cancer

Not only "smell" the difference between cancer cells and healthy cells, but can also distinguish between different cancer cell lines

by Matt Davenport, Michigan State University

Researchers at Michigan State University have shown that locusts can not only "smell" the difference between cancer cells and healthy cells, but they can also distinguish between different cancer cell lines.

However, patients need not worry about locusts swarming their doctors' offices. Rather, the researchers say this work could provide the basis for devices that use insect sensory neurons to enable the early detection of cancer using only a patient's breath.

Although such devices aren't on the immediate horizon, they're not as far-fetched as they might sound, said the authors of the new

research shared May 25 on *BioRxiv*.

Part of that is because people have grown accustomed to technology that augments or outperforms our natural senses. For example, telescopes and microscopes reveal otherwise invisible worlds. The success of engineered devices can make it easy to overlook the performance of our natural tools, especially the sense organ right in front of our eyes.

"Noses are still state of the art," said Debajit Saha, an assistant professor of biomedical engineering at MSU. "There's really nothing like them when it comes to gas sensing."

That's why we trust dogs and their super-sniffers to detect telltale smells of drugs, explosives and, more recently, health conditions including low blood sugar and even COVID-19.

Scientists are working on technology that can mimic the sense of smell, but nothing they've engineered can yet compete with the speed, sensitivity and specificity of old-fashioned biological olfaction.

"People have been working on 'electronic noses' for more than 15 years, but they're still not close to achieving what biology can do seamlessly," said Saha, who also works in the Institute of Quantitative Health Science and Engineering, or IQ.

This lack of gas-sensing devices creates an opportunity when it comes to early detection of diseases, especially those like cancer, for which early intervention can save lives. When cancer is caught in its first stage, patients have an 80% to 90% chance of survival. But if it's not caught until stage 4, those numbers plummet to 10% to 20%.

Cancer cells work differently than healthy cells, and they create different chemical compounds as they work and grow. If these chemicals make it to a patient's lungs or airways, the compounds could be detected in exhaled breath.

"Theoretically, you could breathe into a device, and it would be able to detect and differentiate multiple cancer types and even which stage the disease is in. However, such a device isn't yet close to being used in a clinical setting," Saha said.

So Saha and his team are developing a new approach. Instead of trying to engineer something that works like biology, they thought: Why not start with the solutions biology has already built after eons of evolution, and engineer from there? The team is essentially "hacking" the insect brain to use it for disease diagnosis, Saha said.

"This is a new frontier that's almost unexplored," he said.

Saha and his team chose to work with locusts as their biological component for a few reasons. Locusts have served the scientific community as model organisms, like fruit flies, for decades. Researchers have built up a meaningful understanding of their olfactory sensors and corresponding neural circuits. And, compared with fruit flies, locusts are larger and more rugged.

This combination of features allows the MSU researchers to relatively easily attach electrodes to locust brains. The scientists then recorded the insects' responses to gas samples produced by healthy cells and cancer cells, and then used those signals to create chemical profiles of the different cells.

This isn't the first time Saha's team has worked on something like this. In 2020, while at Washington University in St. Louis, he led research that detected explosives with locusts, work that factored into an MSU search committee recruiting Saha, said Christopher Contag, the director of IQ.

"I told him, 'When you come here, we'll detect cancer. I'm sure your locusts can do it,'" said Contag, the inaugural James and Kathleen Cornelius Chair, who is also a professor in the Department of Biomedical Engineering and in the Department of Microbiology and Molecular Genetics.

One of Contag's research focuses had been understanding why cells from mouth cancers had distinct appearances under his team's

microscopes and optical tools. His lab found different metabolites in different cell lines, helping account for the optical differences. It turned out that some of those metabolites were volatile, meaning they could become airborne and sniffed out.

"The cells looked very different metabolically, and they looked different optically," Contag said. "We thought it made a lot of sense to look at them from a volatiles perspective."

Saha's locust sensors provided the perfect platform to test that. The two Spartan groups collaborated to investigate how well the locusts could differentiate healthy cells from cancer cells using three different oral cancer cell lines.

"We expected that the cancer cells would appear different than the normal cells," Contag said. "But when the bugs could distinguish three different cancers from each other, that was amazing."

Although the team's results focused on cancers of the mouth, the researchers believe their system would work with any cancer that introduces volatile metabolites into breath, which is likely most cancer types.

The team is starting a collaboration with Steven Chang, director of the Henry Ford Head and Neck Cancer program, to test its detection system with human breath.

The researchers are also interested in bringing the chemical sensing power of honeybees into the fold. The MSU team already has promising results using honeybee brains to detect volatile lung cancer biomarkers.

Again, people need not worry about seeing swarms of insects in their physicians' offices. The researchers' goal is to develop a closed and portable sensor without an insect, just the biological components needed to sense and analyze volatile compounds—possibly before other, more invasive techniques can reveal the disease.

"Early detection is so important, and we should use every possible tool to get there, whether it's engineered or provided to us by millions of years of natural selection," Contag said. "If we're successful, cancer will be a treatable disease."

More information: *Alexander Farnum et al, Harnessing insect olfactory neural circuits for noninvasive detection of human cancer, BioRxiv (2022). DOI: 10.1101/2022.05.24.493311*

https://bit.ly/3JK28Yk

The TB Vaccine Mysteriously Protects Against Lots of Things. Now We Know Why

Researchers have now pinpointed the biological mechanism behind the off-target effects of the tuberculosis vaccine.

Felicity Nelson

When babies in the African countries of Guinea Bissau and Uganda were given the tuberculosis vaccine, something remarkable happened. Instead of the vaccine only protecting against the target bacteria – *Myocbacterium tuberculosis* – the tuberculosis vaccine offered broad protection against a range of unrelated infections, including respiratory infections and serious complications such as sepsis.

Australian researchers have now pinpointed the biological mechanism behind the off-target effects of the tuberculosis vaccine.

The team administered the Bacille Calmette-Guérin (BCG) vaccine to 63 infants within ten days of their birth and compared their progress to a control group of 67 infants who did not receive the BCG vaccine.

The researchers took blood samples from the infants and examined circulating white blood cells called monocytes in both groups.

Monocytes are part of the human body's innate immune system, which provides the first line of defense against pathogens and is not specific to any one disease.

Looking at these monocytes, researchers found distinct epigenetic differences – changes to the way genes are expressed or control

which genes are active and which are switched off – between the vaccinated group and the unvaccinated group that lasted on average around 14 months after vaccination.

In vaccinated babies, the BCG vaccine reprogrammed or 'trained' monocytes to be more responsive to pathogens in general, and this epigenetic signature was passed down to the next generation of monocytes for more than a year after vaccination.

According to the researchers, this is the mechanism behind the broad, protective effect of BCG vaccines seen in African countries.

"For the first time, we have shown how the BCG vaccine can have long-lasting effects on the immune system of infants," says Boris Novakovic, senior author and molecular biologist at the Murdoch Children's Research Institute (MCRI) in Melbourne, Australia.

The researchers also used an *in vitro* experiment to explore these epigenetic changes in detail.

They isolated monocytes from healthy adults and exposed the cells to two types of the BCG vaccine and detected distinct changes in different types of epigenetic modifications. These included DNA methylation – molecular tags adoring the DNA sequence – and histones – bulky proteins around which DNA strands are wound.

Monocytes respond to pathogens using receptors on the cell's outside surface. When these receptors contact a pathogen, it triggers the monocyte cell to 'eat' the pathogen (phagocytosis), which also causes a cascade of events inside the cell where one protein switches on another protein and so on, until this triggers a change in the gene expression of the cell.

Prior exposure to the BCG vaccine repackages the monocyte DNA in a way that speeds this whole process up and gets the genes required to respond to threats switched on quickly, Novakovic told ScienceAlert.

Putting monocytes on high alert makes them more responsive to all infections, not just tuberculosis.

It was previously thought that the innate immune system had no way of remembering previous infections, unlike the adaptive immune system (which uses T cells and specific antibodies to remember the pathogens it has encountered before).

Over the last decade, scientists have discovered that the innate immune system can actually produce a non-specific memory, called 'trained immunity'.

"That's been the breakthrough," Novakovic told ScienceAlert.

It's not just the BCG vaccine that makes the innate immune system hyperresponsive. Other live attenuated vaccines that use a weakened form of the virus to protect against diseases such as polio, measles, and smallpox have a similar effect.

Conditions that put stress on the body, such as obesity and high cholesterol, or injuries, also make the innate immune system more responsive. That's not always a good thing.

While the study by Novakovic and colleagues focused on the underlying biological mechanisms of trained immunity, there are some real-world implications.

In countries where infant mortality is high, vaccinating against tuberculosis, measles, or smallpox may have a beneficial effect in protecting infants against a range of other infections.

In an Australian context where babies rarely die of infectious diseases, there is greater interest in the potential use of the BCG vaccine to prevent allergies and eczema in kids, Novakovic said.

The thinking is that the BCG vaccine may have a beneficial effect on the developing immune system. A study from MCRI researchers published in *Allergy* last year found that BCG vaccination had a modest beneficial effect in preventing eczema in infants predisposed to developing the common skin condition.

The epigenetics study was published in *Science Advances*

https://bit.ly/3A6F2rK

Extinct Pathogens Ushered The Fall of Ancient Civilizations, Scientists Say

Thousands of years ago, across the Eastern Mediterranean, multiple Bronze Age civilizations took a distinct turn for the worse at around the same time.

Michelle Starr

The Old Kingdom of Egypt and the Akkadian Empire both collapsed, and there was a widespread societal crisis across the Ancient Near East and the Aegean, manifesting as declining populations, destruction, reduced trade, and significant cultural changes.

As usual, fingers have been pointed at climate change and shifting allegiances. But scientists have just found a new culprit in some old bones.

In remains excavated from an ancient burial site on Crete, in a cave called Hagios Charalambos, a team led by archaeogeneticist Gunnar Neumann of the Max Planck Institute for Evolutionary Anthropology in Germany found genetic evidence of bacteria responsible for two of history's most significant diseases – typhoid fever and plague.

Therefore, the researchers said, widespread illnesses caused by these pathogens cannot be discounted as a contributing factor in the societal changes so widespread around 2200 to 2000 BCE.

"The occurrence of these two virulent pathogens at the end of the Early Minoan period in Crete," they wrote in their paper, "emphasizes the necessity to re-introduce infectious diseases as an additional factor possibly contributing to the transformation of early complex societies in the Aegean and beyond."

Yersinia pestis is a bacterium responsible for tens of millions of deaths, most occurring in the course of three devastating global pandemics. Catastrophic as this disease was in centuries gone by, its impact prior to the Plague of Justinian, which started in 541 CE, has been difficult to gauge.

Recent technological and scientific advances, particularly the recovery and sequencing of ancient DNA from old bones, are revealing some of that lost history.

We now suspect, for example, that the bacterium has been infecting people since at least the Neolithic period.

Last year, scientists revealed that a Stone Age hunter-gatherer likely died of plague thousands of years before we had evidence of the disease reaching epidemic proportions.

However, the genomic evidence recovered had so far been from colder regions. Little is known about its impact on ancient societies in warmer climates, such as those in the Eastern Mediterranean, thanks to the degradation of DNA in the higher temperatures.

So Neumann and his team went digging through bones recovered from a site on Crete known for its remarkably cool and stable conditions.

They recovered DNA in teeth from 32 individuals who died between 2290 and 1909 BCE. The genetic data revealed the presence of quite a few common oral bacteria, which was expected.

Less expected was the presence of *Y. pestis* in two individuals and two *Salmonella enterica* lineages – a bacterium typically responsible for typhoid fever – in two others. This discovery suggests that both pathogens were present and possibly transmissible in Bronze Age Crete.

But there's a caveat. Each of the lineages discovered is now extinct, making it harder to determine just how their infections might have affected communities.

The lineage of *Y. pestis* they uncovered probably couldn't be transmitted through fleas – one of the traits that made other lineages of the bacterium so contagious in human populations.

The flea vector carries the bubonic version of the plague; humans

become infected when the bacterium enters the lymphatic system via a flea bite. Therefore, the transmission route of this ancient form of the bacterium could be different and cause a different form of plague; pneumonic plague, which is transmitted via aerosols, for example.

The researchers said that the *S. enterica* lineages also lacked key traits that contribute to severe disease in humans, so the virulence and transmission routes of both pathogens remain unknown.

Nevertheless, the discovery suggests that both pathogens were circulating; in regions of Crete with high population densities, they could have run somewhat rampant.

"While it is unlikely that *Y. pestis* or *S. enterica* were the sole culprits responsible for the societal changes observed in the Mediterranean at the end of the 3rd millennium BCE," the researchers wrote in their paper, "we propose that, given the [ancient] DNA evidence presented here, infectious diseases should be considered as an additional contributing factor; possibly in an interplay with climate and migration, which has been previously suggested."

Because diseases like plague and typhoid do not leave traces on bones, they are not frequently noticed in the archaeological record. The team suggests that more detailed genetic screening of more remains from the Eastern Mediterranean could help uncover the extent of the impact these diseases had on the civilizations who lived there.

The research has been published in *Current Biology*.