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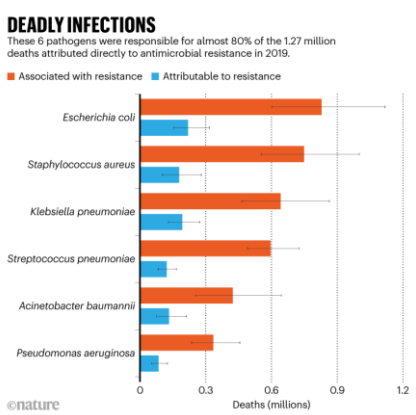
The staggering death toll of drug-resistant bacteria

Global survey shows that in 2019, antimicrobial resistance killed more people than HIV/AIDS or malaria.

Tosin Thompson

Infections caused by antibiotic-resistant bacteria are among the leading causes of death for people of all ages, finds the most comprehensive global study of antimicrobial resistance (AMR) yet.

The analysis[1], published in *The Lancet* on 19 January, estimates that in 2019, 4.95 million people died from illnesses in which bacterial AMR played a part. Of those, 1.27 million deaths were the direct result of AMR — meaning that drug-resistant infections killed more people than HIV/AIDS (864,000 deaths) or malaria (643,000 deaths).



Source: Ref. 1

"AMR is truly a global problem that requires urgent action from policymakers and the health community to avoid preventable deaths," says Mohsen Naghavi, a health-metrics scientist at the University of Washington in Seattle who was part of the research team.

The proportion of bacteria that are resistant to antibiotics is on the rise. "In a world where antibiotic use has become so commonplace, resistant bacteria out-compete those that are killed off by pharmaceuticals," says Naghavi. A 2016 review on antimicrobial resistance estimates that by 2050, as many as ten million people could die each year as a result of AMR. If the situation is left unchecked, "infections that were previously curable with a few days of antibiotics could become incurable", Naghavi warns.

Although there are many studies on the effects of AMR, few have tried to estimate its global impact. Naghavi and his colleagues used data from the 2019 Global Burden of Diseases, Injuries and Risk Factors Study (GBD) — a survey[2] of 369 diseases and injuries among people of all ages in 204 countries and territories — to estimate the number of people who died from infections globally, along with the pathogens responsible and other factors. The team then used all available data on AMR to calculate the prevalence of bacterial AMR in various locations, and the impact that resistance had on mortality.

The team found that in 2019, 1.27 million deaths were directly caused by bacterial AMR, and more than twice that number were associated with it. The three most common sites for bacterial AMR infections were the chest, bloodstream and abdomen — infections in these parts of the body accounted for 78.8% of directly attributable AMR deaths. The six deadliest bacterial pathogens were responsible for nearly three-quarters of all deaths attributed to resistance ***(see* 'DEADLY INFECTIONS'*)***. Antibiotic-resistant *Escherichia coli* alone killed around 200,000 people in 2019.

Tailor-made approach

The figures show that lower-income countries experience the highest rates of AMR-related death. Among the 21 GBD geographical regions, Western sub-Saharan Africa had the highest rate of deaths directly attributable to AMR, with 27.3 per 100,000 people. Australasia had the lowest, with 6.5 deaths per 100,000 people. Both the prevalence of resistance and the number of infections with resistant bacteria are higher in low-income regions than in wealthier countries. Reasons for this include poor sanitation and hygiene, insufficient facilities for testing to inform treatment, and a lack of access to the newest antibiotics and vaccines. "Regional estimates are useful for policy planning specific to the challenges faced by each region," says Naghavi. "One-size-fits-all

approaches are unlikely to be appropriate."

David Weiss, who studies antibiotic resistance at Emory University in Atlanta, Georgia, says that this study is a "wake-up call", but points out that data on AMR in many low- and middle-income countries are scarce. "This highlights the need to greatly expand laboratory capacity in these regions so we can more accurately understand the size and nature of this monster we're fighting," Weiss says. "Immediate and transformational increases in attention and investment are needed. We cannot wait a minute longer."

doi: https://doi.org/10.1038/d41586-022-00228-x ***References***

1. Murray, C. L. J. et al. Lancet https://doi.org/10.1016/S0140-6736(21)02724-0 (2022). Article Google Scholar

*2. Vos, T. et al. Lancet **396**, 1204–1222 (2020). PubMed Article Google Scholar*

Download references

https://bit.ly/3rnqXSh

Researchers discover locations of ancient Maya sacred groves of cacao trees

As much as modern society worships chocolate, cacao—the plant chocolate comes from—it was believed to be even more divine to ancient Mayas.

by Todd Hollingshead, Brigham Young University

The Maya considered cacao beans to be a gift from the gods and even used them as currency because of their value.

As such, cacao bean production was carefully controlled by the Maya leaders of northern Yucatan, with cacao trees only grown in sacred groves. But no modern researcher has ever been able to pinpoint where these ancient sacred groves were located—until now.

Researchers at Brigham Young University, including professor emeritus Richard Terry and graduate students Bryce Brown and Christopher Balzotti, worked closely with archaeologists from the U.S. and Mexico to identify locations the Maya used to provide the perfect blend of humidity, calm and shade required by cacao trees.

While the drier climate of the Yucatan peninsula is inhospitable to cacao growth, the team realized the vast array of sinkholes common to the peninsula have microclimates with just the right conditions.

As detailed in a study newly published in the *Journal of Archaeological Science Reports*, the team conducted soil analyses on 11 of those sinkholes and found that the soil of nine of them contained evidence of theobromine and caffeine—combined biomarkers unique to cacao. Archaeologists also found evidence of ancient ceremonial rituals—such as staircase ramps for processions, stone carvings, altars and offerings like jade and ceramics (including tiny ceramic cacao pods)—in several sinkholes.

"We looked for theobromine for several years and found cacao in some places we didn't expect," said Terry, who recently retired from BYU. "We were also amazed to see the ceremonial artifacts. My students rappelled into one of these sinkholes and said, 'Wow! There is a structure in here!' It was a staircase that filled one-third of the sinkhole with stone."

To extract and analyze the sinkhole soil for cacao biomarkers—specifically theobromine and caffeine—the team developed a new method of soil extraction. This involved drying the soil samples and passing them through a sieve, covering them with hot water, having them centrifuged and passed through extraction disks, and analyzing the extracts by mass spectrometry. To increase the sensitivity of their testing, the research team compared the results of the soil samples to seven control samples with no history of exposure to the biomarkers.

The findings of the BYU study indicate that cacao groves played an important role in ancient rituals and trade routes of the ancient Maya, impacting the entirety of the Mesoamerican economy. A 70-mile Maya "highway" in the area that was the main artery for trade passes near hundreds of sinkholes, so it is likely that the leaders who commissioned the highway development also controlled cacao

production. The evidence of cacao cultivation alongside archaeological findings also supports the idea that cacao was important in the ideological move from a maize god to a sun god.

In one sinkhole near Coba, Mexico, a village 45 minutes from modern day Tulum, the research team found the arm and bracelet of a figurine attached to an incense jar and several ceramic modeled cacao pods. They also found remnant cacao trees growing there, making it quite possible that this sinkhole, named "Dzadz Ion," was the location of a sacred cacao grove during the Late Postclassic period (About A.D. 1000 to 1400).

"Now we have these links between religious structures and the religious crops grown in these sinkholes," Terry said. "Knowing that the cacao beans were used as currency, it means the sinkholes were a place where the money could be grown and controlled. This new understanding creates a rich historical narrative of a highly charged Maya landscape with economic, political and spiritual value."

Researchers for the project also came from University of California, Riverside, the University of Miami, State University of New York, Kent State University, Universidad Nacional Autónoma de Mexico, Instituto Nacional de Antropologia e Historia, and the Cultural Heritage and Archaeology in the Maya Area institution.

More information: *Richard E. Terry et al, Soil biomarkers of cacao tree cultivation in the sacred cacao groves of the northern Maya lowlands, Journal of Archaeological Science: Reports (2022). DOI: 10.1016/j.jasrep.2021.103331*

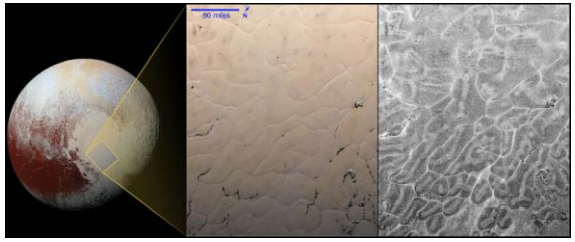
https://bit.ly/3saavEc

Clues to Pluto's History Lie in Its Faults

Studying geological features on Pluto's surface can illuminate the ancient history of how the dwarf planet formed.

by JoAnna Wendel

The world first glimpsed Pluto up close when NASA's New Horizons spacecraft whizzed by it in July 2015. One of the most exciting discoveries scientists made based on New Horizons data was that Pluto, despite orbiting at more than 5 billion kilometers from the Sun, may contain a liquid water ocean under its water ice surface.



This liquid water ocean has huge implications for how Pluto formed and retained enough heat to melt all that ice. In the years since the New Horizons flyby, two general formation hypotheses have emerged.

Scientists studied Pluto's "heart" to better understand how thick its lithosphere is and thus how it formed. **Credit: NASA/JHUAPL/SwRI**

The first starts with a "cold" Pluto, which involves Pluto forming over millions of years by the slow accretion of cold objects. This version of Pluto eventually would have coalesced enough material that radiative heating from the inside would melt the subsurface ocean. The other hypothesis involves a "warm" or "hot" Pluto, in which Pluto formed over a shorter time period in violent collisions that heated its interior, formed the ocean, and eventually cooled the planet into the majority ice ball we know today.

One clue that can help scientists understand Pluto's formation is the thickness of its outer icy crust as well as the geological features that make up its surface. In a new study, *McGovern et al.* focused on Sputnik Planitia, a vast basin that makes up the western portion of Pluto's bright "heart." Sputnik Planitia formed after an impact and eventually filled in with nitrogen ice. Heat driven by convection formed cell-shaped structures in the nitrogen ice, which has captivated scientists. This basin measures 1,500 × 900 kilometers and features a ridge that rises 1 kilometer above the surrounding landscape. Fractures and cracks radiate from the basin like spokes on a bicycle wheel, the authors write.

These fractures and cracks are key to understanding how the nitrogen ice load affects Pluto's surface, which would depend on how thick that surface is. The nitrogen ice pushes down on Pluto's outer layer, or lithosphere. Depending on the thickness of the lithosphere when the nitrogen ice first flowed into the basin, different patterns of cracks would form.

The researchers ran computer models testing various starting conditions for Sputnik Planitia to find the lithosphere thickness that best fits today's geological features. They found that the lithosphere is probably 45–70 kilometers thick and that the initial depth of the impact crater that forms Sputnik Planitia was probably shallow, no more than 3 kilometers deep.

McGovern and colleagues note that their finding is consistent with the "hot" theory of Pluto formation that posits Pluto formed via violent impacts and started out with more liquid, much of which froze over the following millennia. They also note that the stress on the outer shell created by the nitrogen ice is probably facilitating some cryovolcanism at several sites surrounding Sputnik Planitia.

(Journal of Geophysical Research: Planets, https://doi.org/10.1029/2021JE006964, 2021)

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Harnessing a natural geochemical reaction to combat antibiotic resistance

Naturally occurring clay deposits have been shown to harbor antimicrobial properties and kill antibiotic-resistant bacteria

by Anne M Stark, Lawrence Livermore National Laboratory

Antibiotics have allowed for the widespread control of bacterial infections, which had been the leading cause of death historically. However, the overuse of traditional antibiotics in humans and animals has resulted in the emergence of stronger, more potent bacterial strains that are no longer treatable with conventional antibiotics.

Researchers at Lawrence Livermore National Laboratory (LLNL) are exploring alternative treatment options when antibiotics fail. Certain naturally occurring clay deposits have been shown to harbor antimicrobial properties and kill antibiotic-resistant bacteria. These clays have been proposed as a new paradigm for fighting the potentially devastating effects of the post-antibiotic era. Despite their effectiveness, these naturally occurring clays, by their inherent heterogenous properties, exhibit variable antibacterial effectiveness and the synthesis of minerals with reproducible antibacterial activity is needed to harness their therapeutic value. The research appears in *Scientific Reports*.

Antibiotic-resistant pathogens are predicted to account for 10 million annual deaths worldwide by the year 2050. The U.S. currently spends $20 billion a year treating more than 2 million antibiotic-resistant infections that can withstand even the most potent antibiotics. As a result, our approach to medicine and agriculture will require significant changes to successfully maintain current levels of healthcare and food security.

A team of LLNL geochemists, cell biologists and microbiologists set out to produce fully synthetic versions of the naturally occurring antibacterial minerals, while controlling the purity and reactivity of the compounds. The minerals linked to the antibacterial activity of natural samples are smectite clay minerals and iron (Fe)-sulfides (pyrite). The research team, led by Keith Morrison, used hydrothermal reactors to synthesize chemically pure mineral end members that had the correct particle size, surface charge and reactivity of natural samples. In doing this, they overcame the variability in reactivity of the natural samples and were able to create a reproducible dose.

The synthetic antibacterial minerals were tested against the ESKAPE pathogens: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter, which represent the most common

group of human pathogens that "escape" the effects of antibiotics in clinical settings.

"Our results indicate that bacterial pathogens can be killed by the synthetic clays in as little as one hour depending on the dose." Morrison said.

The synthetic minerals formulations work by establishing a geochemical cycle between Fe, smectite and pyrite. This cycle results in the sustained release of Fe^{2+}, hydrogen peroxide and hydroxyl radicals that are slowly titrated into solution to kill bacterial pathogens. This approach is different from the application of metals alone, which require higher concentrations to become bactericidal and maintain soluble metals.

The research also investigated the effects of the antibacterial minerals on mammalian fibroblast cells. LLNL biologist Kelly Martin found that fibroblast cells experienced initial toxicity and a drop in viability. However, the fibroblast cells were able to regenerate when the antibacterial minerals were removed from the cell culture. "These results are very promising and indicate that mammalian cells may experience minimal toxicity while invading pathogens are killed," she said.

Other Livermore scientists involved in the study include Josh Wimpenny and Gaby Loots.

More information: *Keith D. Morrison et al, Synthetic antibacterial minerals: harnessing a natural geochemical reaction to combat antibiotic resistance, Scientific Reports (2022). DOI: 10.1038/s41598-022-05303-x*

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What the rise of oxygen on early Earth tells us about life on other planets

Strongest evidence to date that extremely low oxygen levels exerted an important limitation on evolution for billions of years

When did the Earth reach oxygen levels sufficient to support animal life? Researchers from McGill University have discovered that a rise in oxygen levels occurred in step with the evolution and expansion of complex, eukaryotic ecosystems. Their findings represent the strongest evidence to date that extremely low oxygen levels exerted an important limitation on evolution for billions of years.

"Until now, there was a critical gap in our understanding of environmental drivers in early evolution. The early Earth was marked by low levels of oxygen, till surface oxygen levels rose to be sufficient for animal life. But projections for when this rise occurred varied by over a billion years—possibly even well before animals had evolved," says Maxwell Lechte, a postdoctoral researcher in the Department of Earth and Planetary Sciences under the supervision of Galen Halverson at McGill University.

Ironstones provide insights into early life

To find answers, the researchers examined iron-rich sedimentary rocks from around the world deposited in ancient coastal environments. In analyzing the chemistry of the iron in these rocks, the researchers were able to estimate the amount of oxygen present when the rocks formed, and the impact it would have had on early life like eukaryotic microorganisms—the precursors to modern animals.

"These ironstones offer insights into the oxygen levels of shallow marine environments, where life was evolving. The ancient ironstone record indicates around less than 1% of modern oxygen levels, which would have had an immense impact on ecological complexity," says Changle Wang, a researcher at the Chinese Academy of Sciences who co-led the study with Lechte.

Ironstones are sedimentary rocks deposited along coastlines millions of years ago, which contain abundant granules of iron oxides that contain chemical indicators of the amount of oxygen present at the time of formation. Credit: Maxwell Lechte

"These low oxygen conditions persisted until about 800 million

years ago, right when we first start to see evidence of the rise of complex ecosystems in the rock record. So if complex eukaryotes were around before then, their habitats would have been restricted by low oxygen," says Lechte.

Earth remains the only place in the universe known to harbor life. Today, Earth's atmosphere and oceans are rich with oxygen, but this wasn't always the case. The oxygenation of the Earth's ocean and atmosphere was the result of photosynthesis, a process used by plants and other organisms to convert light into energy—releasing oxygen into the atmosphere and creating the necessary conditions for respiration and animal life.

Searching for signs of life beyond our solar system

According to the researchers, the new findings suggests that Earth's atmosphere was capable of maintaining low levels of atmospheric oxygen for billions of years. This has important implications for exploration of signs of life beyond our solar system, because searching for traces of atmospheric oxygen is one way to look for evidence of past or present life on another planet—or what scientists call a biosignature.

Ironstones within the sedimentary rock layers of the Grand Canyon (Arizona, USA), preserving clues about ancient marine environments. Credit: Susannah Porter

Scientists use Earth's history to gauge the oxygen levels under which terrestrial planets can stabilize. If terrestrial planets can stabilize at low atmospheric oxygen levels, as suggested by the findings, the best chance for oxygen detection will be searching for its photochemical byproduct ozone, say the researchers.

"Ozone strongly absorbs ultraviolet light, making ozone detection possible even at low atmospheric oxygen levels. This work stresses that ultraviolet detection in space-based telescopes will significantly increase our chances of finding likely signs of life on planets outside our solar system," says Noah Planavsky, a biogeochemist at Yale University.

More geochemical studies of rocks from this time period will allow scientists to paint a clearer picture of the evolution of oxygen levels during this time, and better understand the feedbacks on the global oxygen cycle, say the researchers.

More information: *Strong evidence for a weakly oxygenated ocean–atmosphere system during the Proterozoic, Proceedings of the National Academy of Sciences (2022). DOI: 10.1073/pnas.2116101119.*

https://bit.ly/3unlsEQ

Most "Pathogenic" Genetic Variants Have a Low Risk of Actually Causing Disease

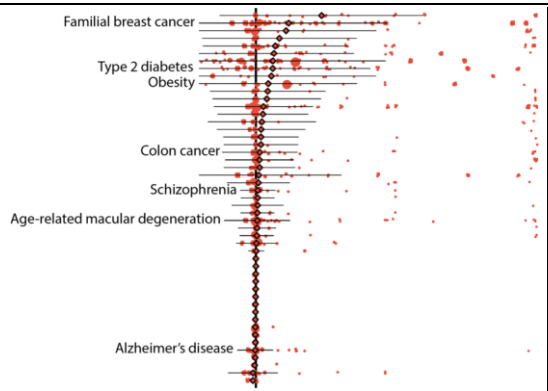
Results of large biobank study by Mount Sinai researchers may help doctors better assess true disease risk.

Imagine getting a positive result on a genetic test. The doctor tells you that you have a "pathogenic genetic variant," or a DNA sequence that is known to raise the chances for getting a disease like breast cancer or diabetes. But what exactly are those chances — 10 percent? Fifty percent? One hundred? Currently, that is not an easy question to answer.

To address this need, researchers at the Icahn School of Medicine at Mount Sinai analyzed the DNA sequences and electronic health record data of thousands of individuals stored in two massive biobanks. Overall, they discovered that the chance a pathogenic genetic variant may actually cause a disease is relatively low — about 7 percent. Nonetheless, they also found that some variants, such as those associated with breast cancer, are linked to a wide range of risks for disease. The results, published in *JAMA*, could alter the way the risks associated with these variants are reported, and one day, help guide the way physicians interpret genetic testing results.

"A major goal of this study was to produce helpful, advanced statistics which quantitatively assess the impact that known disease-

causing genetic variants may have on an individual's risk to disease," said Ron Do, PhD, Associate Professor of Genetics and Genomic Sciences and a member of The Charles Bronfman Institute for Personalized Medicine at Icahn Mount Sinai.



Researchers at the Icahn School of Medicine at Mount Sinai found that most disease-causing mutations have a low risk of actually causing disease.
Credit: Courtesy of Do lab, Mount Sinai, N.Y., N.Y.

Over the past 20 years scientists have discovered hundreds of thousands of variants that could cause a variety of diseases. However, due to the nature of these discoveries, it has been difficult to estimate — or provide statistics on — the true risk of this happening for each gene variant. So far, most estimates have been based on studies involving a small number of subjects, who were either part of a family that had a history of having a disease or were recruited at disease-specific clinics. But studies like these that do not use randomly chosen large populations may produce overestimates of the risk posed by variants.

In this study, the researchers tackled the issue by searching large-scale DNA sequencing data of 72,434 individuals for 37,780 known variants and then scanning each individual's health records for a corresponding disease diagnosis. The extensive search involved 29,039 participants in Mount Sinai's Bio*Me*® Biobank program and 43,395 participants who were part of the UK Biobank.

The study was led by Iain S. Forrest, an MD-PhD candidate in Dr. Do's lab who found inspiration from prior clinical experience he had as part of a postbaccalaureate fellowship at the National Institutes of Health (NIH).

"The idea for the study came out of a brainstorming session," said Mr. Forrest. "Dr. Do and I discussed the need to have a better system for classifying disease risk. Currently, variants are categorized by broad labels such as 'pathogenic' or 'benign.' As I learned in the clinic, there's a lot of grey area with these labels. That's when we realized that the biobanks which link DNA sequence data to electronic health records are an unparalleled opportunity to address this need."

Initial results showed that 157 diseases in their data set could be linked to 5,360 variants that were defined as either "pathogenic" by ClinVar, a widely referenced, NIH-supported public library, or "loss-of-function" as predicted by bioinformatic algorithms. On average, the "penetrance," or chance that a variant was linked to a disease diagnosis, was low, specifically 6.9 percent. Likewise, the average risk difference, which describes the increase in disease risk for an individual who has the variant over an individual who does not have it, was also low.

"At first I was quite surprised by the results. The risks we discovered were lower than I expected," said Dr. Do. "These results raise questions about how we should be classifying the risks of these variants."

Despite these results, the risks associated with some genetic variants remained high. For instance, pathogenic variants of the breast cancer genes *BRCA1* and *BRCA2* both averaged 38 percent penetrance, with individual variants falling between zero and 100 percent.

Further results demonstrated other advantages of using biobank data. In one example, the researchers were able to calculate the risks of individual variants that are associated with age-related disorders, such as some forms of type 2 diabetes and breast and prostate cancers. On average, the penetrance of these variants was about 10 percent for individuals over 70 years of age whereas it was

about 8 percent for those who were older than 20.

The team also found that the presence of some variants could depend on an individual's ethnicity and identified more than 100 variants that are specifically found in individuals of non-European descent. Finally, the authors listed several potential ways the study itself could have under- or overestimated the risks reported.

"While more research is needed to be done, we feel that this study is a good first step towards eventually providing doctors and patients with the accurate and nuanced information they need to make more precise diagnoses," said Dr. Do.

Reference: "Population-Based Penetrance of Deleterious Clinical Variants" by Iain S. Forrest, BS; Kumardeep Chaudhary, PhD; Ha My T. Vy, PhD; Ben O. Petrazzini, BS; Shantanu Bafna, MS; Daniel M. Jordan, PhD; Ghislain Rocheleau, PhD; Ruth J. F. Loos, PhD; Girish N. Nadkarni, MD; Judy H. Cho, MD and Ron Do, PhD, 25 January 2022, JAMA. DOI: 10.1001/jama.2021.23686

This work was supported by the National Institutes of Health (GM124836, GM007280, HL139865, and HL155915).

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Human gut bacteria have sex to share vitamin B12

Your gut bacteria need vitamin B12 just as much as you do. Though DNA is usually passed from parent to child, new research shows gut bacteria transfer genes through "sex" in order to take their vitamins.

Without vitamin B12, most types of living cells cannot function. As a result, there is strong competition for it in nature. A new UC Riverside study demonstrates beneficial gut microbes share the ability to acquire this precious resource with one another through a process called bacterial sex.

"The process involves one cell forming a tube that DNA can pass through to another cell," said UCR microbiologist and study lead Patrick Degnan. "It's as if two humans had sex, and now they both have red hair."

Scientists have known about this process for decades, and its ability to transfer what are known as "jumping genes" between organisms. Until now, the majority of studied examples have been responsible for helping bacterial cells stay alive when people ingest antibiotics.

"We're excited about this study because it shows that this process isn't only for antibiotic resistance. The horizontal gene exchange among microbes is likely used for anything that increases their ability to survive, including sharing vitamin B12," Degnan said.

Results of the study have been published in the journal *Cell Reports*.

Previously, Degnan worked on a project in which he and his colleagues identified an important transporter responsible for getting B12 into gut microbial cells. More recently, he was studying jumping genes, trying to identify what kinds of information they were transferring. Quickly, Degnan recognized the vitamin B12 transporters as the cargo.

To demonstrate what they suspected, Degnan and his team mixed bacteria that could transport B12 and some that couldn't. Being on a dish together gave the bacteria an opportunity to form a tube called a sex pillus that facilitated the transfer. After, they identified that bacteria previously unable to transport B12 were all still alive and had acquired the genes with the ability to transport B12.

They did a second experiment examining the entire genome of the bacteria.

"In a given organism, we can see bands of DNA that are like fingerprints. The recipients of the B12 transporters had an extra band showing the new DNA they got from a donor," Degnan said.

Not only was the experiment successful in test tubes, but also inside mice.

The type of beneficial gut bacteria used in the study are Bacteroides, which reside in the large intestines of most people. One of their most important services to humans is breaking down complex carbohydrates for energy.

"The big, long molecules from sweet potatoes, beans, whole grains,

and vegetables would pass through our bodies entirely without these bacteria. They break those down so we can get energy from them," Degnan explained.

Bacteroides, along with other bacteria, also give our guts a barrier layer that can help restrict pathogens from invading. For example, previous research led by co-author Ansel Hsiao, also at UC Riverside, shows some humans have communities of microbes in their gut that make them more resistant to cholera.

Learning how to keep these bacteria healthy could also help benefit people, given the important services they perform.

"There's no one way to have a healthy microbiome, but generally, having a diverse community of anaerobic bacteria is a healthy thing and can have beneficial effects," Degnan said.

More information: *Katie A. Frye et al, Mobilization of vitamin B12 transporters alters competitive dynamics in a human gut microbe, Cell Reports (2021). DOI: 10.1016/j.celrep.2021.110164*

https://bit.ly/3IUktA6

The cognitive bias that tripped us up during the pandemic

Most of the time, heuristics help us to make good decisions. But sometimes they lead to cognitive biases

by Taha Yasseri, The Conversation

The human brain is a marvelous machine, capable of handling complex information. To help us make sense of information quickly and make rapid decisions, it has learned to use shortcuts, called "heuristics." Most of the time, these shortcuts help us to make good decisions. But sometimes they lead to cognitive biases.

Answer this question as quickly as you can without reading on: which European country was hit the hardest by the pandemic?

If you answered "Italy," you're wrong. But you're not alone. Italy is not even in the top ten European countries by the number of confirmed COVID cases or deaths.

It is easy to understand why people might give a wrong answer to this question—as happened when I played this game with friends. Italy was the first European country to be hit by the pandemic, or at least this is what we were told at the beginning. And our perception of the situation formed early on with a focus on Italy. Later, of course, other countries were hit worse than Italy, but Italy is the name that got stuck in our heads.

The trick of this game is to ask people to answer quickly. When I gave friends time to think or look for evidence, they often came up with a different answer—some of them quite accurate. Cognitive biases are shortcuts and shortcuts are often used when there are limited resources—in this case, the resource is time. This particular bias is called "anchoring bias". It occurs when we rely too heavily on the first piece of information we receive about a topic and fail to update our perception when we receive new information.

As we show in a recent work, anchoring bias can take more complex forms, but in all of them, one feature of our brain is essential: it is easier to stick to the information we have stored first and try to work out our decisions and perceptions starting from that reference point—and often not going too far.

Data deluge

The COVID pandemic is remarkable for many things, but, as a data scientist, the one that stands out for me is the amount of data, facts, stats and figures that are available to pore over.

It was rather exciting to be able to regularly check the numbers online on portals such as Johns Hopkins Coronavirus Resource Center and Our World in Data, or just tune in to almost any radio or TV station or news website to see the latest COVID statistics. Many TV channels introduced program segments specifically to report those numbers daily.

Johns Hopkins data portal

However, the firehose of COVID data that came at us is not

compatible with the rate at which we can meaningfully use and handle that data. Our brain takes in the anchors, the first wave of numbers or other information, and sticks to them.

Later, when it is challenged by new numbers, it takes some time to switch to the new anchor and update. This eventually leads to data fatigue, when we stop paying attention to any new input and we forget the initial information, too. After all, what was the safe length for social distancing in the UK: one or two meters? Oh no, 1.5 meters, or 6 feet. But six feet is 1.8 meters, no? Never mind.

The issues with COVID communication are not limited to the statistics describing the spread and prevalence of the pandemic or the safe distance we should keep from others. Initially, we were told that "herd immunity" appears once 60%–70% of the population has gained immunity either through infection or vaccination.

Later, with more studies and analysis this number was more accurately predicted to be around 90%–95%, which is meaningfully larger than the initial number. However, as shown in our study, the role of that initial number can be profound and a simple update wasn't enough to remove it from people's minds. This could to some extent explain the vaccine hesitancy that has been observed in many countries; after all, if enough other people are vaccinated, why should we be bothered to risk the vaccine's side-effects? Never mind that the "enough" might not be enough.

The point here is not that we should stop the flow of information or ignore statistics and numbers. Instead, we should learn when we deal with information to consider our cognitive limitations. If we were going through the pandemic all over again, I would be more careful with how much data exposure I got in order to avoid data fatigue. And when it comes to decisions, I would take time not to force my brain into shortcuts—I would check the latest data rather than relying on what I thought I knew. This way, my risk of cognitive bias would be minimized.

https://wb.md/3uhsew2

Psychedelic Therapy and Suicide: A Myth Busted?

A commonly held belief that classic psychedelic therapy can trigger suicidal thoughts, actions, or other types of self-harm is not supported by research, and, in fact, the opposite may be true.

Megan Brooks

Results from a meta-analysis of individual patient data showed that psychedelic therapy was associated with large, acute, and sustained decreases in suicidality across a range of clinical patient populations.

"This is the first analysis to synthesize suicidality outcome data from recent clinical trials with psychedelics. It gives us a better understanding of the effects of psychedelics on suicidality in the context of clinical trials," study investigator Cory Weissman, MD, Department of Psychiatry, University of Toronto, Canada, told *Medscape Medical News*.

The evidence suggests psychedelic therapy "may reduce suicidal ideation when administered in the appropriate setting and offered to carefully screened patients," Weissman said.

The findings were published online January 18 in *The Journal of Clinical Psychiatry*.

More Research Needed

The analysis included seven psychedelic therapy clinical trials that had data on suicidality. Five of the trials used psilocybin plus psychotherapy, and two used ayahuasca plus psychotherapy. All seven trials had a "low" risk of bias.

Patients included in the trials had treatment-resistant major depressive disorder (MDD), recurrent MDD, AIDS-related demoralization, and distress related to life-threatening cancer.

The meta-analytic results showed significant decreases in suicidality at all acute time points (80 to 240 minutes post administration) and at most post-acute time points (1 day to 4

months post administration).

Effect sizes for reductions in suicidality were "large" at all acute time points, with standardized mean differences (SMD) ranging from -1.48 to -1.72, and remained large from 1 day to 3–4 months after therapy (SMD range, -1.50 to -2.36).

At 6 months, the effect size for reductions in suicidality with psychedelic therapy was "medium" (SMD, -0.65).

Large effect sizes for reductions in suicidality occurred across the different patient populations represented in the trial, the investigators note.

No study reported any suicide-related adverse events because of administration of a psychedelic. There were also "very few" acute (6.5%) or post-acute (3.0%) elevations in suicidality, "providing support for the safety of psychedelic therapy within controlled contexts," the researchers write.

They caution, however, that large controlled trials that specifically evaluate the effect of psychedelic therapy on suicidality are needed.

Promising Avenue

In an accompanying editorial, Daniel Grossman, BS, and Peter Hendricks, PhD, Department of Health Behavior, University of Alabama at Birmingham, note that results of this review warrant "optimism" for use of psychedelics for treatment of suicidality.

Based on this study and others, classic psychedelic therapy for suicidality appears to be a "promising avenue" for further investigation, they write.

However, research and anecdotes about increased suicidality and other self-harm attributed to psychedelic therapy, "though evidently rare, remain a critical concern" for further research to address, Grossman and Hendricks add.

The hope is that future research "clarifies who is most subject to these risks, what factors best identify them, and how best to navigate their treatment safely," they write.

The meta-analysis had no funding. Weissman receives funding from the Brain and Behavior Research Foundation and serves on the advisory board of GoodCap Pharmaceuticals. Hendricks is on the scientific advisory board of Bright Minds Biosciences Ltd, Eleusis Benefit Corporation, and Rest Pharmaceuticals Inc.

J Clin Psychiatry. Published online January 18, 2022. Abstract, Editorial

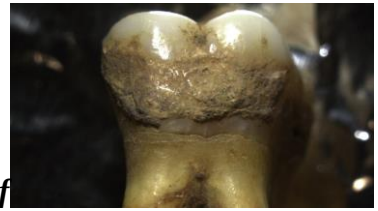
https://bit.ly/3sjlBGT

A taste for wild cereal sowed farming's spread in ancient Europe

Balkan hunter-gatherers ate starchy grains several millennia before they cultivated crops

By Bruce Bower

People living along southeastern Europe's Danube River around 11,500 years ago never planted a crop but still laid the foundation for the rise of farming in that region some 3,000 years later, a new study finds.



Food deposits on the teeth (one shown) of ancient people who inhabited what's now Serbia and Romania contributed to new evidence that hunter-gatherers ate wild cereals for several thousand years before crop cultivation reached Europe. **Emanuela Cristiani**

Hunter-gatherers living in this part of Europe avidly gathered and ate wild cereal grains for several millennia before migrants from southwest Asia introduced the cultivation of domesticated cereals and other plants, say archaeologist Emanuela Cristiani of Sapienza University of Rome and her colleagues. A well-established taste for wild cereals among hunter-gatherers of the central Balkan Peninsula, near what's now Turkey, smoothed the way for farming to take root in Europe, the scientists conclude January 21 in *eLife*.

Previous chemical studies of human bones from Balkan sites indicated that ancient hunter-gatherers had eaten a lot of animal protein, mainly fish. Plant remains have not preserved well at those sites, leaving uncertain any role for grains on the menu of people who lived there.

It's now evident that Balkan hunter-gatherers "balanced their diet with plant foods and did so for millennia before the arrival of agriculture," Cristiani says.

The new findings align with earlier evidence that hunter-gatherers in southwest Asia gradually domesticated wild plant species from around 11,700 to 9,800 years ago, rather than rapidly adopting a farming lifestyle (*SN: 7/4/13*). But in the Balkans, hunter-gatherers consumed wild cereal species unrelated to domesticated strains later brought from southwest Asia, Cristiani's team says.

Until now, the only site outside southwest Asia to yield evidence of hunter-gatherers collecting edible wild plants before the introduction of farming was a cave in Greece.

Cristiani's group looked for microscopic signs of plant eating on the teeth of 60 individuals previously excavated at five sites in Serbia and Romania. Those sites range in age from several thousand years before the introduction of farming to several hundred years after cultivation began.

Food particles extracted from crusty deposits on the teeth of ancient hunter-gatherers contained starch granules and cell structures typical of regional wild cereal species. Starch granules from the same wild cereals were identified on the grinding surfaces of 17 stone implements, dating to as early as around 8,600 years ago, that were previously unearthed at one Balkan site. Hunter-gatherers at that location apparently pounded and ground wild cereals into a coarse flour, the researchers say.

Their findings provide the first direct evidence that southern European as well as southwestern Asian hunter-gatherers incorporated wild plants into their diets well before anyone cultivated crops, says archaeobotanist Elena Marinova of the State Office for Cultural Heritage Baden-Württemberg in Germany. For those ancient people, "the 'paleolithic' diet included starchy grains, not only meat and berries," Marinova says.

https://bit.ly/3Gxy2DY

The first life on Earth depended on a deadly poisonous gas, study suggests

Could the toxic gas used in chemical weapons today have been involved in the birth of life on Earth?

By Paul Sutter

At one time, Earth had no life. Then, it did. Whether the process was gradual or rapid, the transformation of chemistry to biochemistry on our planet was one of the most amazing developments to happen in the universe. It's so rare that to date, we have absolutely no evidence of any form of life anywhere else in the cosmos.

So what, exactly, happened? The answer to that question sits at the intersection of cutting-edge research in astronomy, biology, chemistry and geology. In a recent study, researchers propose that it may take the whole planet to raise a self-replicating molecule, involving a complex interaction of hydrogen-rich meteorites, volcanic activity, warm ponds and an unlikely precursor for life: hydrogen cyanide.

It's an RNA, RNA, RNA world

Earth formed about 4.5 billion years ago, but it immediately suffered countless collisions, including one big enough to tear a chunk out of our planet and create the moon. Eventually, things settled down enough for life to appear, sometime between 4.5 billion and 3.7 billion years ago.

Those early life-forms were almost certainly very different from modern-day ones. That's because modern-day life-forms require three macromolecules: DNA, RNA and proteins. Very roughly, our DNA stores information, the RNA transmits that information to manufacture proteins, and the proteins do most of the work of keeping life alive — including replicating DNA.

This system is so interconnected that it's unlikely that it all

appeared at once in its modern form. But primitive life still needed to perform the basic functions of life: store information, replicate itself and catalyze other chemical reactions.

It's possible that RNA alone is capable of doing all three — definitely not as efficiently as the DNA-RNA-protein combo we have today, but it makes for a plausible starting point for life.

If RNA can get going as a primitive form of life, then Darwinian evolution can take over, enabling more complex and more efficient biochemical processes to emerge. So perhaps to crack the origins of life on Earth, we just need a lot of self-replicating RNA. But where does the self-replicating RNA come from?

A messy birth

In the new study, researchers developed a complex model of the early Earth. It goes a little something like this:

The massive collision that created the moon just happened. Earth's surface cooled from the aftermath, with the oceans just beginning to form and the continents starting to emerge. It was still a pretty nasty place. Meteorites left over from the formation of the solar system constantly battered the young Earth, and active volcanoes covered the face of the planet like a nasty breakout of teenage zits.

Those meteorite impacts, as nasty as they were, delivered a crucial element: hydrogen. Hydrogen is the lightest element, so it doesn't stick around long unless it gets bound up in other molecules.

But as the meteorites were delivering fresh supplies of hydrogen to Earth's atmosphere, those volcanoes were spewing tremendous amounts of carbon dioxide. Also, the oceans were much warmer than they are today, and they were constantly evaporating into the atmosphere. Lastly, undersea vents were leaking methane.

As all those molecules built up in the atmosphere, lightning strikes and ultraviolet radiation from the sun provided the energy to shake things up a bit. In this case, those sources provided the energy necessary to form … hydrogen cyanide.

That's right, hydrogen cyanide. The poisonous gas that can spell certain death for modern-day life may have been the most important molecule in the development of that same life.

Poison pill

The key property of hydrogen cyanide is that it reacts with itself. And because life can be considered a very complex version of chemicals interacting with themselves, hydrogen cyanide seems like an intriguing starting point. Also, hydrogen cyanide reacts with other molecules, like formaldehyde, to produce other interesting biomolecules. Those biomolecules, in turn, are the building blocks of nucleobases, ribose and nucleotides, which then go on to form RNA.

In their work, the researchers found that hydrogen cyanide can rain out of the atmosphere into warm little ponds, where the compound begins its molecular dance with other naturally occurring molecules. They found that during a 100 million year-long period some 4.4 billion years ago, the amount of hydrogen cyanide raining into ponds was enough to create high concentrations of adenine, one of the components of RNA.

Eventually, as meteorites stopped dropping, the hydrogen levels in the atmosphere fell. But by then, enough adenine may have been created to begin the formation of RNA strands, which may have triggered the exploration of self-replication and the beginning stages of life, the researchers explained.

If it seems like a lot of steps, it's because it is. Even though these early life-forms would be considered highly primitive from the perspective of modern life, self-replicating and catalyzing RNA strands are already extremely complex molecules, and their appearance necessarily includes a lot of precursor reactions.

No matter what, something special definitely happened on Earth long ago, and it may have started with hydrogen cyanide.

The study was published in the preprint database arXiv on Jan. 3

and accepted for publication in The Astrophysical Journal.

https://go.nature.com/3J8TPU7

Scientists deliberately gave people COVID — here's what they learnt

Only half of participants who were exposed to the coronavirus developed infections, most with mild symptoms.

Healthy, young people who were intentionally exposed to the coronavirus SARS-CoV-2 developed mild symptoms — if any — in a first-of-its-kind COVID-19 human-challenge study. Such trials present a unique opportunity to study viral infections in detail from start to finish, but are controversial because of the risks they pose to participants.

The UK study of 34 individuals, aged 18–30 years, shows that such trials can be done safely, say scientists, and lays the groundwork for more in-depth studies of vaccines, antivirals and immune responses to SARS-CoV-2 infection. The results were posted[1] on 1 February on the preprint server Research Square and have not been peer reviewed.

Nearly half of the participants who received a low dose of virus did not become infected, and some of those who became infected had no symptoms. Participants who did develop COVID-19 reported mild-to-moderate symptoms, including sore throats, runny noses and loss of smell and taste.

"It presents a potentially important advance in how to assess future vaccine and drug efficacy," says Miles Davenport, an immunologist at the University of New South Wales in Sydney, Australia. "This opens a number of important possibilities to study immunity in a controlled environment."

However, some researchers question whether the insights yielded by the study so far are important enough to justify the risks to participants, such as the potential for long-term side effects. "In my mind, it's still not entirely clear whether these studies are ethically justified, and I'm waiting to see what else they've found," says Seema Shah, a bioethicist at Northwestern University in Chicago, Illinois.

Finding the dose

Human-challenge studies have been used for decades to study influenza, malaria and numerous other infectious diseases. Some researchers argued in favour of conducting such trials with SARS-CoV-2 in the early months of the pandemic, as a way to accelerate the development of vaccines. But others saw challenge trials as too dangerous to be acceptable, when so little was known about the virus and few, if any, effective treatments were available.

The trial, led by researchers at Imperial College London and a Dublin-based commercial clinical-research organization called Open Orphan and its London-based subsidiary hVIVO, was announced in October 2020, and the first participants were exposed to the virus in early 2021. Volunteers received £4,565 (US$6,200) for their participation, which involved at least two weeks of quarantine in a high-level isolation unit at the Royal Free Hospital in London.

The first participants received a very low dose — roughly equivalent to the amount of virus in a single droplet of nasal fluid — of a virus strain that circulated in the United Kingdom in early 2020.

Researchers anticipated that a higher dose would be needed to infect a majority of participants, says Andrew Catchpole, chief scientific officer of hVIVO. But the starting dose successfully infected more than half of the participants.

The virus replicated incredibly rapidly in those who became infected. On average, people developed their first symptoms and tested positive, using sensitive PCR tests, less than two days after exposure, on average.

That contrasts with the roughly five-day 'incubation period' that

real-world epidemiological studies have documented between a probable exposure and symptoms. High viral levels persisted for an average of 9 days, and up to 12 days.

The most common symptoms were typical of other respiratory infections: sore throats, runny noses and sneezing. Fever was less common, and no one developed the persistent cough that had been used as a hallmark of COVID-19, says Catchpole. Around 70% of infected participants lost their senses of smell or taste — another COVID-19 signature — to varying degrees. Such problems persisted for more than six months in five participants and more than nine months in one. Some people developed no symptoms at all, but had as much virus in their upper airways as did participants who exhibited symptoms, and their infections lasted for as long.

Researchers involved in the study want to understand why so many people did not become infected, despite being exposed to SARS-CoV-2. Some uninfected participants had very low levels of virus for short periods of time, suggesting that their immune systems were actively fighting the virus, says Christopher Chiu, a physician-scientist at Imperial College London, who led the study.

Future studies of the challenge-trial participants will attempt to explain why. Previous research has suggested that coronaviruses that cause the common cold might confer protection against COVID-19 in some people. Another possibility is that some people have potent innate immune responses that don't require a previous encounter with a particular pathogen or a closely related virus. "We're trying to understand the fundamentals of why people are protected even though they've not been exposed to a virus like this before," Chiu adds.

His team plans to launch another challenge trial that will expose vaccinated people to the Delta variant of SARS-CoV-2. That study will attempt to identify immune factors that protect people from 'breakthrough' infections after vaccination.

For the time being, human-challenge trials for SARS-CoV-2 will probably enrol only people at very low risk of severe disease, says Catchpole. But as researchers gain experience running these challenge trials safely, it might be possible to expand them to involve at-risk groups, such as older people, Chiu adds.

Concerns linger

The study looked safe and well-conducted, says Matthew Memoli, an infectious-disease physician and virologist at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

It should make some people more comfortable with doing more human-challenge trials for SARS-CoV-2, he adds. Such trials could prove useful in the development of vaccines that protect against a broad range of coronaviruses, not just SARS-CoV-2, he adds.

Meagan Deming, a vaccine scientist and virologist at the University of Maryland in Baltimore, says the study confirms insights gained from other COVID-19 studies, such as the swift rise in viral levels. But it has not eliminated her concerns about exposing people to a strain of SARS-CoV-2 that hasn't been weakened. More than two-thirds of participants who became infected had problems with smell or taste that lasted, in some cases, for more than six months, she notes.

"It sounds like this is the most serious risk that materialized. This is the one to keep an eye on," adds Shah. Moreover, she questions whether the insights gleaned from the study so far justify such risks. "This study reads like a promissory note that ultimately, in conjunction with the other research they're doing, there will eventually be substantial scientific and social benefits. But we're not really seeing that yet."

doi: https://doi.org/10.1038/d41586-022-00319-9

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https://bit.ly/3GATIPS

Did comet's fiery destruction lead to downfall of ancient Hopewell?

Rapid decline of the Hopewell culture might be explained by falling debris from a near-Earth comet that created a devastating explosion over North America

by Michael Miller, University of Cincinnati

The rapid decline of the Hopewell culture about 1,500 years ago might be explained by falling debris from a near-Earth comet that created a devastating explosion over North America, laying waste to forests and Native American villages alike.

Researchers with the University of Cincinnati found evidence of a cosmic airburst at 11 Hopewell archeological sites in three states stretching across the Ohio River Valley. This was home to the Ohio Hopewell, part of a notable Native American culture found across much of the American East.

The comet's glancing pass rained debris down into the Earth's atmosphere, creating a fiery explosion. UC archeologists used radiocarbon and typological dating to determine the age of the event. The airburst affected an area bigger than New Jersey, setting fires across 9,200 square miles between the years A.D. 252 and 383. This coincides with a period when 69 near-Earth comets were observed and documented by Chinese astronomers and witnessed by Native Americans as told through their oral histories.

The study was published in the Nature journal *Scientific Reports*.

UC archeologists found an unusually high concentration and diversity of meteorites at Hopewell sites compared to other time periods. The meteorite fragments were identified from the telltale concentrations of iridium and platinum they contained. They also found a charcoal layer that suggests the area was exposed to fire and extreme heat.

In his lab, lead author Kenneth Tankersley, a professor of anthropology in UC's College of Arts and Sciences, held up a container of tiny micrometeorites collected at the sites. A variety of meteorites, including stony meteorites called pallasites, were found at Hopewell sites.

"These micrometeorites have a chemical fingerprint. Cosmic events like asteroids and comet airbursts leave behind high quantities of a rare element known as platinum," Tankersley said. "The problem is platinum also occurs in volcanic eruptions. So we also look for another rare element found in nonterrestrial events such as meteorite impact craters—iridium. And we found a spike in both, iridium and platinum."

The Hopewell people collected the meteorites and forged malleable metal from them into flat sheets used in jewelry and musical instruments called pan flutes.

Beyond the physical evidence are cultural clues left behind in the masterworks and oral histories of the Hopewell. A comet-shaped mound was constructed near the epicenter of the airburst at a Hopewell site called the Milford Earthworks.

Various Algonquin and Iroquoian tribes, descendants of the Hopewell, spoke of a calamity that befell the Earth, said Tankersley, who is Native American. "What's fascinating is that many different tribes have similar stories of the event," he said.

"The Miami tell of a horned serpent that flew across the sky and dropped rocks onto the land before plummeting into the river. When you see a comet going through the air, it would look like a large snake," he said.

"The Shawnee refer to a 'sky panther' that had the power to tear down forest. The Ottawa talk of a day when the sun fell from the sky. And when a comet hits the thermosphere, it would have exploded like a nuclear bomb."

And the Wyandot recount a dark cloud that rolled across the sky and was destroyed by a fiery dart, Tankersley said. "That's a lot like

the description the Russians gave for Tunguska," he said of a comet airburst documented over Siberia in 1908 that leveled 830 square miles of forest and shattered windows hundreds of miles away.

"Witnesses reported seeing a fireball, a bluish light nearly as bright as the sun, moving across the sky. A flash and sound similar to artillery fire was said to follow it. A powerful shockwave broke windows hundreds of miles away and knocked people off their feet," according to a story in *EarthSky*.

UC biology professor and co-author David Lentz said people who survived the airburst and its fires would have gazed upon a devastated landscape. "It looks like this event was very injurious to agriculture. People didn't have good ways to store corn for a long period of time. Losing a crop or two would have caused widespread suffering," Lentz said.

And if the airburst leveled forests like the one in Russia, native people would have lost nut trees such as walnut and hickory that provided a good winter source of food. "When your corn crop fails, you can usually rely on a tree crop. But if they're all destroyed, it would have been incredibly disruptive," Lentz said.

UC's Advanced Materials Characterization Center conducted scanning electron microscopy and energy dispersive spectrometry of the sediment samples. Inductively coupled plasma mass spectrometry was employed at the University of Georgia's Center for Applied Isotope Studies. The U.S. Geological Survey provided stable carbon isotope analysis.

Despite what scientists know, there is still much they do not, Lentz said. "It's hard to know exactly what happened. We only have a few points of light in the darkness," he said. "But we have this area of high heat that would have been catastrophic for people in that area and beyond." Now researchers are studying pollen trapped in layers of sediment to see how the comet airburst might have changed the botanical landscape of the Ohio River Valley.

Co-author Steven Meyers, a UC geology alumnus, said their discovery might lead to more interest in how cosmic events affected prehistoric people around the world. "Science is just a progress report," Meyers said. "It's not the end. We're always somewhere in the middle. As time goes on, more things will be found."

More information: *Kenneth Barnett Tankersley et al, The Hopewell airburst event, 1699–1567 years ago (252–383 CE), Scientific Reports (2022).* *DOI: 10.1038/s41598-022-05758-y*

https://go.nature.com/3qv4fkE

Last-resort cancer therapy holds back disease for more than a decade

Two of the first people treated with CAR-T-cell cancer therapies are still in remission 12 years on.

Heidi Ledford

A few weeks after receiving an experimental cancer therapy that turns immune cells into tumour-killing hunters, Doug Olson's doctor sat him down to give him news of his progress. "He said, 'Doug, we cannot find a single cancer cell in your body,'" Olson recalls. "I was pretty convinced that I was done with cancer."

Olson's doctors, however, weren't so sure. The year was 2010, and Olson was one of the first people with chronic lymphocytic leukaemia to receive the treatment, called CAR-T-cell therapy. When his doctors — including Carl June and David Porter at the University of Pennsylvania in Philadelphia — wrote the protocol for the clinical trial that Olson was involved in, they hoped that the genetically engineered cells might survive for a month in his body. They knew that cancer research could be heartbreaking; they didn't dare to expect a cure.

But more than ten years later, the immune cells continue to patrol Olson's blood and he remains in remission. June is finally ready to admit what Olson suspected all along. "We can now conclude that CAR T cells can actually cure patients with leukaemia," June told

reporters at a press briefing describing results that were published in *Nature* on 2 February[1].

Tumour destroyers

CAR-T-cell therapies involve removing immune cells called T cells from a person with cancer, and genetically altering them so that they produce proteins — called chimeric antigen receptors, or CARs — that recognize cancer cells. The cells are then reinfused into the person, in the hope that they will seek out and destroy tumours.

In the years since Olson's treatment, five CAR-T-cell therapies have been approved by the US Food and Drug Administration, to treat leukaemias, lymphomas and myelomas. June estimates that tens of thousands of people have received CAR-T cell treatment.

But the therapy is expensive, risky and technically demanding. It remains a last resort, to be used when all other treatments have failed. Despite the treatment's success for Olson, not everyone experiences durable remission of their cancer. In the beginning, only about 25–35% of CAR-T-cell recipients with chronic lymphocytic leukaemia experienced a complete remission of their cancer, says Porter. With refinement, that percentage has increased over the years, he says, but some of these initial successes still lead to relapse. Tracking the treatment long-term could reveal clues as to what factors are important for lasting CAR-T-cell success.

For more than ten years, Porter and his colleagues analysed the CAR T cells in Olson and one other person treated in 2010, tracing the cells' evolution and looking for any signs of safety concerns.

They found that the CAR T cells persisted, but the characteristics of the population shifted over time. Soon after infusion, a prominent population of T cells called $CD8^+$ cells emerged. These are sometimes called killer T cells, and can identify and destroy cells that display unusual proteins, such as cancer cells or cells that are infected with a virus.

But over the years, a different type of CAR T cell became dominant. $CD4^+$ T cells can take on a variety of functions in the immune system, but the researchers showed that both study participants had $CD4^+$ cells with characteristics suggesting that they would be capable of killing leukaemia cells.

Tremendous impact

Olson and the other participant now have no signs of leukaemia. It's unclear whether the CAR T cells killed all the leukaemia cells soon after they were introduced, or if the cells that continue to patrol are able to destroy any leukaemia cells before they reach detectable levels.

"The potential impact of CAR T is tremendous," says Nirali Shah, a paediatric haematologist at the US National Cancer Institute in Bethesda, Maryland. This study "gives you a proof of concept about the safety of having long-term persistence and integration of the T cells into your body".

It remains to be seen, she adds, how well the findings from these two individuals with chronic lymphocytic leukaemia will translate to other diseases. Efforts are under way to use CAR-T-cell approaches to treat solid tumours, such as prostate tumours and the devastating brain cancer glioblastoma. In January, researchers reported success in using the cells to destroy scar tissue in the heart — an approach that could one day be used to treat cardiac fibrosis[2].

In the years after his treatment, Olson returned to his career in medical diagnostics. He committed to staying healthy, and his son talked him into running half marathons. "If my cancer was gone, I certainly didn't want to die of a heart attack," he says. Eventually, he decided to go public with the story of his recovery, and serve as a mentor for other people with cancer.

He tries to give them hope, he says: "If there isn't a cure for their cancer today, there's a reasonable chance that around the corner, there's going to be one."

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https://bit.ly/3AWP2T7

Quick COVID breathalyzer could allow mass screening in public places

Prototype "breathalyzer" that can sensitively and accurately diagnose COVID-19

According to experts, bringing an end to the pandemic will require rapid screening of people attending large gatherings, such as conferences and weddings. Even those who are asymptomatic can still transmit COVID-19 to others, making it important to identify and isolate them until they are no longer contagious. Now, researchers reporting in *ACS Nano* have developed a prototype "breathalyzer" that can sensitively and accurately diagnose COVID-19, even in asymptomatic individuals, in less than five minutes.

A SERS-based breathalyzer can distinguish volatile organic compounds in the breath of COVID-positive people in less than five minutes. **Credit: Shi Xuan Leong and Yong Xiang Leong, Nanyang Technological University**

Currently, the "gold standard" for COVID-19 testing is a technique called reverse transcription-polymerase chain reaction (RT-PCR), which is slow, requires an uncomfortable nasopharyngeal swab for sample collection and must be performed in a lab. The rapid antigen test is much quicker but has a higher rate of false negatives and positives. Scientists have also developed breathalyzer-type tests for COVID-19, which rely on differences in concentrations of volatile organic compounds exhaled by those infected with the coronavirus, but most require bulky, nonportable instruments for analysis. Xing Yi Ling and colleagues wanted to develop a quick, convenient and accurate breathalyzer test that would be suitable for on-site screening of large numbers of people.

The researchers designed a handheld breathalyzer that contains a chip with three surface-enhanced Raman scattering (SERS) sensors attached to silver nanocubes. When a person exhales into the device for 10 seconds, compounds in their breath chemically interact with the sensors. Then, the researchers load the breathalyzer into a portable Raman spectrometer that characterizes the bound compounds based on changes to the molecular vibrations of the SERS sensors.

The team found that Raman spectra from COVID-positive and -negative people were different in regions responsive to ketones, alcohols and aldehydes, which they used to develop a statistical model for COVID diagnosis. They tested the breathalyzer on 501 people in hospitals and airports in Singapore, who were shown by RT-PCR to be negative (85.2 percent), positive and symptomatic (8.6 percent), or positive and asymptomatic (6.2 percent) for the coronavirus. The method had a 3.8 percent false-negative and 0.1 percent false-positive rate, comparable to RT-PCR tests, but it could be completed on-site in less than five minutes. The breathalyzer could someday be a new tool to reduce the silent spread of COVID-19 in communities, the researchers say.

More information: *Shi Xuan Leong et al, Noninvasive and Point-of-Care Surface-Enhanced Raman Scattering (SERS)-Based Breathalyzer for Mass Screening of Coronavirus Disease 2019 (COVID-19) under 5 min, ACS Nano (2022).* *DOI: 10.1021/acsnano.1c09371*

https://wb.md/3Gz752F

Patients Are Often the Best Instructors in Medical School

Often, the patient knows far more than the medical student

Yash B. Shah

As a medical student, you are constantly learning, certainly from

faculty and other healthcare professionals in the clinical setting, but also from the patients whom you are serving. Often, the patient knows far more than the medical student who may have never even heard of the medical topics in question. Many times, I have personally interacted with a patient who has done extensive research after their diagnosis and proceeds to teach me quite a bit about a condition with which I am entirely unfamiliar.

Patients can also educate students — and even seasoned physicians — about the experience of navigating a complicated healthcare system or the unending and oft-unrecognized challenges of living with a chronic condition. These are experiences that cannot be easily communicated via lecture or textbook and are frequently not well-understood by providers.

Although our coursework is valuable in teaching the science of underlying disease and therapeutics, many other factors can influence health. Real-life challenges arising from socioeconomics, such as access, affordability, transportation, and the psychological effects of a difficult diagnosis, have outsize impacts beyond the biological bases that are taught in class. An adage that has gained recent popularity is that an individual's zip code has larger effect on their health than their genetic code.

Through the Health Mentors Program, I teamed up with students from other healthcare training programs (such as nursing, physical therapy, social work, and nutrition) to learn from a local patient who lives with a chronic condition.

Because our group resembled a comprehensive healthcare team, we used our unique perspectives and specialized professional roles to gain a holistic understanding of our patient. It was enlightening to discern the hidden, nonmedical challenges that patients face after a life-changing diagnosis.

Our patient deals with a host of chronic conditions that necessitate numerous daily medications and pose extensive limits on her mobility. Hearing about the challenges that she faces in following complicated prescription regimens and attending frequent medical appointments, I learned that it is important for providers to consider these smaller, less obvious factors when partnering with patients to safeguard ease of adherence.

Affordability was the first challenge that came to mind for me, but there is a host of other issues that accompany chronic disease self-management.

Our patient discussed her gratitude for in-home nursing care for assistance with daily activities and emphasized her desire for an empathetic care team that not only assigns the optimal treatments but also shows humanity and teaches her how to advocate for her own health. These conversations helped our team understand how to best optimize a patient's experience and how to leverage each team member's role toward this end.

I believe that physicians of the future should work harder to collaborate with skilled nursing staff — whether via nursing homes or in-home care — to offer better preventive and patient-oriented services for our communities. This will reduce numerous issues that we face today, including high costs and the nursing home–to-hospital revolving door.

Moreover, our team learned how the COVID-19 pandemic has particularly affected patients like ours, compounding the loneliness and anxiety that many of us have faced during these past few years. Providers of the future will certainly have to account for the pandemic's resulting and everlasting stress, trauma, anxiety, and physical detriments on patients.

Perhaps, the most important lesson I learned is that prescribing a medication or performing a procedure is not the end goal. There are substantial germane nonmedical challenges that physicians must appreciate to ensure their patients' well-being. Whether that includes our evolving understanding of mental health or our new

realization of the profound effects of social determinants, it has become clear that biology alone cannot explain disease and treatment.

Many of these challenges are outside the control of the physician, who must partner with other specialists — and the patient themselves — to ensure longitudinal and comprehensive patient care. Medicine is truly a team sport, and physicians could not accomplish much without their coworkers.

Though a strong scientific knowledge serves as an excellent foundation to patient care, many other factors, including compassion, regard for social determinants, and partnership with other healthcare professionals, is vital to ensuring optimal patient experiences and is truly best learned by talking to patients.

https://go.nature.com/3Hy75l5

Breakthrough COVID powers up immune response to variants — including Omicron

Experiments suggest that SARS-CoV-2 infections after vaccination trigger antibody levels similar to those in people whose infections preceded their vaccination.

Ewen Callaway

Two studies suggest that 'breakthrough' SARS-CoV-2 infections result in improved immune protection against multiple variants of the virus, and data from one of the studies indicates that such infections also protect against Omicron[1,2].

Researchers have previously shown that people who have caught SARS-CoV-2 and are later vaccinated tend to make high levels of antibodies against the SARS-CoV-2 spike protein, one of the immune system's main targets when it is fending off the virus. These individuals' blood serum — which contains antibodies — blocks a diverse array of SARS-CoV-2 variants, and does so more effectively than serum from vaccinated people who were never infected and serum from people whose immunity comes from infection only.

But it has been unclear whether this powerful 'hybrid immunity' is also generated in people who were vaccinated before being infected. Microbiologist Fikadu Tafesse at Oregon Health & Science University in Portland and his colleagues analysed serum from three groups of health-care workers: some who'd had breakthrough infections, others who'd been infected before they were vaccinated, and vaccinated people with no history of infection. In laboratory assays, the sera from both groups with previous infections had higher levels of antibodies against the spike protein than did serum from people protected only by vaccines. The sera from infected people were also highly effective at protecting cells from infection by variants including Alpha, Beta and Delta, although the team has not yet looked at activity against Omicron. The researchers report their work in a 25 January study in *Science Immunology*[1].

Those results chime with a 19 January *Cell* study[2] led by structural biologists Alexandra Walls and David Veesler, both at the University of Washington in Seattle. This team looked at people who'd been infected and then received two doses of vaccine; people who had two doses of vaccine and then experienced breakthrough infections; and people who'd had a third, booster vaccine dose but no infection. Serum levels of antibodies that blocked variants including Omicron were higher, and persisted for longer, in all three groups than in people who'd had two doses of vaccine and hadn't been infected.

The maths of COVID-19 protection

The researchers suggest that the number of times people are exposed to SARS-CoV-2, whether through vaccination, infection or both, is a key factor in the quality of their antibody response. Confirming that idea, the group found that eight individuals whose immune systems had 'seen' the SARS-CoV-2 spike protein four times — once during a 2020 infection and again during three

separate vaccinations — had especially strong antibody responses against several variants, and even against the virus behind the 2002–04 epidemic of severe acute respiratory syndrome. "Those individuals are clearly doing the best," says Veesler.

Danny Altmann, an immunologist at Imperial College London, says it will be important to compare breakthrough infections caused by different variants. Current vaccines are based on the spike protein from the version of the virus first identified in Wuhan, China, in 2020, and vaccine-induced immune responses after a breakthrough infection will probably differ from variant to variant. Most of the breakthrough infections studied by Walls and Veesler's team were caused by Delta, but they also plan to analyse samples from people who have experienced a breakthrough infection caused by Omicron. With Omicron driving a global surge in cases, understanding the immunity that follows breakthrough infections is important, because it will affect many people, says Tafesse. "There is so much virus in circulation in the community. There is a high chance we'll all get a breakthrough infection."

doi: https://doi.org/10.1038/d41586-022-00328-8 ***References***

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https://bit.ly/3soMrqZ

Scientists Discover How To "Flavor" Your Food To Burn Excess Fat

Dietary intake of flavan-3-ols, type of dietary polyphenolics, could help prevent obesity by sympathetic nervous system-induced browning of fat tissue.

In cold conditions, brown adipose tissue (BAT) or brown fat generates heat to keep the body warm. Compared with white adipose tissue, BAT has more mitochondria—subcellular organelles associated with energy production—which allows it to burn calories and produce heat by activating the mitochondrial uncoupling protein 1 (Ucp-1). The stimulation of the sympathetic nervous system (SNS) after cold exposure, exercise, and calorie restriction is well known to induce fat browning. Dietary polyphenols may also activate BAT, causing heat to be dissipated from our bodies. BAT activation and white fat browning are thus both therapeutically significant in the fight against cardiovascular diseases and their comorbidities.

A group of scientists examined the browning of fat induced by dietary administration of flavan-3-ols (flavanols / FLs), a family of "catechin" containing polyphenols abundant in cocoa, apple, grapeseed, and red wine. In a new study published in the journal *Nutrients*, the team led by Professor Naomi Osakabe of Graduate School of Engineering and Science, Shibaura Institute of Technology, Japan proved that FLs enhance browning of adipose tissue by activating the SNS. The findings revealed a direct correlation between fat browning and FLs consumption, which could help researchers develop new treatments for obesity-related diseases.

The authors of this study had previously discovered that a single oral dose of FLs caused fat burning and increased skeletal muscle blood flow. Here, they investigated the effects of single and multiple dose administration of FLs in mouse adipose tissue and found that FLs activate fat browning via the SNS, which secretes "catecholamine" neurotransmitters such as adrenaline (AD) and noradrenaline (NA). They fed cocoa-derived FLs to distinct groups of mice in two independent sets of experiments. One group was given a single dose of FLs over the course of 24 hours, and their urine was collected for testing. The other group received repeated doses for 14 days before being dissected for the collection of brown and white fat. All adipose samples were tested for gene and protein markers that indicate fat browning, while the urine samples were

tested specifically for AD and NA levels.

Higher concentrations of AD and NA in the urine following a single dose of FL clearly demonstrated SNS activation. Although the use of urine samples to evaluate SNS activation is still controversial in clinical research, it has been validated in stressed rodents. "Oral administration of FLs likely activate the SNS because they are considered stressors in these models," explains Prof Osakabe.

The team then used the obtained adipose tissue to investigate the effects of long-term FL treatment. They were thrilled to discover that the white fat of mice who were fed FLs for 14 days eventually turned brown. Some of these cells also had notable structural changes, such as "multilocular phenotype," and appeared to be smaller than normal cells. Since BAT dissipates heat energy, does long-term FL consumption change the amounts of heat-related proteins? To answer this question, the scientists showed that Ucp-1 levels, as well as other high temperature-linked proteins, increased in mice fed repeated doses of FLs. Browning markers, referred to as "beige markers" in this study, were also abundant in these mice. "All of these proteins work together to induce the development of the BAT phenotype," exclaims Prof. Osakabe.

The team believes that the results of their study may contribute to the prevention of lifestyle-related diseases. Interestingly, this is not the first time FLs have worked wonders. Improvements in glucose and insulin tolerance have been seen after just one dose of FL-rich food administration. These findings taken together highlight the need of discussing both the acute and chronic aspects of the metabolic responses generated by FLs consumption.

It is evident from this research that the SNS activity in response to FLs intake caused the observed changes in mice fat. "Although the mechanism of adipose browning is not fully understood, it is possible that repeated administration of FLs may produce browning via catecholamines and its receptors," explains Prof. Osakabe. "Further studies will be required to understand how this process is induced by FL-rich foods," she concludes.

Reference: "Repeated Oral Administration of Flavan-3-ols Induces Browning in Mice Adipose Tissues through Sympathetic Nerve Activation" by Yuko Ishii, Orie Muta, Tomohiro Teshima, Nayuta Hirasima, Minayu Odaka, Taiki Fushimi, Yasuyuki Fujii and Naomi Osakabe, 24 November 2021, Nutrients. DOI: 10.3390/nu13124214

https://bit.ly/3Hy8xnx

A deadly bacteria has been infecting children for more than 1,400 years

The oldest known case of the disease was found in a 6-year-old boy who died around the year 550

By Amber Dance

The tragic death of a 6-year-old boy in early medieval England has given scientists the earliest direct clue to the history of the pathogen *Haemophilus influenzae* type b. Dated to about 550, it's the oldest case of this bacterial infection, called Hib, ever diagnosed, researchers report February 2 in *Genome Biology*.

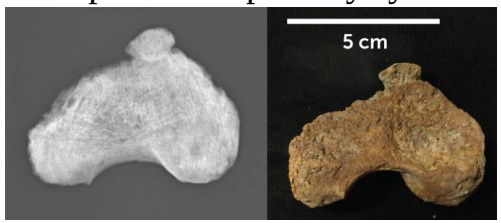
The next confirmed case occurred more than 1,300 years later in 1892, when *H. influenzae* was first identified. Despite the similar name and symptoms to influenza, the bacterium doesn't cause flu. But Hib can cause other serious illnesses such as pneumonia and meningitis — especially in young children (*SN: 1/9/02*). Since the late 1980s, a vaccine against Hib has largely sidelined the pathogen (*SN: 5/25/11*).

DNA in a tooth from the boy, who was buried in a plague cemetery in Cambridgeshire, indicates that Hib was infecting people at the same time as the first historically documented pandemic due to plague, caused by the bacterium *Yersinia pestis* (*SN: 12/2/19*). The relationship between *H. influenzae* and humans, the pathogen's only host, is probably much older than that, says Meriam Guellil, a paleogeneticist at the University of Tartu in Estonia.

Unsurprisingly, the boy's tooth also contained genetic remains of *Y.*

pestis. He probably contracted the Hib infection first, Guellil and colleagues say. While respiratory infections rarely leave marks, the boy's kneecaps had fused to the thighbones above them.

Such damage can happen when Hib escapes the respiratory system and infects joints, which would have taken weeks. This boy was already quite ill when he caught *Y. pestis*, but "plague, probably, was what killed him," Guellil says.



In medieval England, a 6-year-old boy's bout with a serious bacterial infection probably caused the fusion between this fragment of his thigh bone with the bit of his kneecap still present at the top (bone fragments, right; X-ray of the fragments, left). **Sarah Inskip and Sarah Morriss/University of Leicester**

This kind of research opens a window into how pathogens evolve to start pandemics or die out over thousands to millions of years. The work is a "great advance" for archaeology, history and the study of ancient diseases, says Pontus Skoglund, an expert in ancient genomics at the Francis Crick Institute in London who was not involved in the study. "The well-authenticated detection of *Haemophilus influenzae* in an early medieval child promises that it will be detectable in more cases in history, and potentially prehistory," he says.

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Left-handed nanoparticles are far better vaccine adjuvants than their mirror images

Left-handed gold more than 1000-fold more efficient as flu vaccine adjuvants in mice than their right-handed counterparts

By Katrina Krämer

Left-handed gold nanopropellers are more than 1000-fold more efficient as flu vaccine adjuvants in mice than their right-handed counterparts, scientists have discovered. This is the first time immune response has been shown to differ depending on nanoscale chirality.

As biological molecules are often chiral, they usually interact differently with each enantiomer of a chiral molecule. But nanoparticles are much larger than most molecules, so it was unclear whether proteins would be able to distinguish enantiomeric particles. Moreover, chiral nanoparticles often contain two types of chirality: one corresponding to chiral ligands and one corresponding to the whole particle's geometry.

Researchers have now confirmed that gold nanoparticle enantiomers are recognised differently by the immune system purely because of their propeller-shaped geometry. The team grew the gold propeller enantiomers using chiral dipeptides and circularly polarised light but removed the peptides before testing to ensure any effect was the result of nanoscale chirality.

Racemic inorganic nanoparticles can activate the immune system. But a left-handed propeller particle turned out to be twice as efficient as its mirror image when it came to being taken up by macrophages, white blood cells that are part of the immune system. In cell cultures, the macrophages exposed to the left-handed particles produced more than twice as much of certain inflammatory proteins. Similar results were seen in live mice injected with the nanoparticles.

Mice given an influenza vaccine containing left-handed particles produced a 1258-fold greater immune response, measured by their antibody titre, than those given the right-handed particles. Moreover, the former group did not develop abscesses in their lungs as they did when given alum, a common commercial adjuvant. The team suggests that immune responses could be tailored by fine-tuning nanoparticles' chirality.

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https://bit.ly/3quLHRP

Japanese squirrels can consume 'poisonous' mushrooms

Highly probable that these squirrels can safely consume poisonous mushrooms

Associate Professor Suetsugu Kenji (Kobe University Graduate School of Science) and independent photographer Gomi Koichi have observed a Japanese squirrel (Sciurus lis) routinely feeding on well-known species of poisonous toadstool mushroom, including fly agaric (Amanita muscaria) and panther cap (Amanita pantherina), in Nagano prefecture, Japan. The same individual squirrel returned a few days later to continue feeding on a panther cap mushroom, leading them to conclude that it is highly probable that these squirrels can safely consume poisonous mushrooms.

This discovery is an interesting phenomenon, since it is commonly believed that fungal toxins evolved to dissuade animals from eating these mushrooms. Conversely, being consumed by the squirrel may have an advantage for Amanita species. If the spores can survive being eaten and excreted, this suggests that animals may facilitate the dispersal of these fungi.

This discovery suggests that squirrels have adapted to safely eat Amanita fungi. On the other hand, it's possible that Amanita species also benefit from this arrangement as the squirrel may disperse their spores.

A Japanese squirrel feeding on a panther cap mushroom (Amanita pantherina). **Credit: Koichi Gomi**

Next, Associate Professor Suetsugu would like to determine if squirrels do act as a carrier for poisonous mushroom species by investigating whether living spores can be found in squirrel excrement. The research was published in *Frontiers in Ecology and the Environment*.

More information: *Kenji Suetsugu et al, Squirrel consuming "poisonous" mushrooms, Frontiers in Ecology and the Environment (2021). DOI: 10.1002/fee.2443*

https://nyti.ms/3usYJY9

Body Odor May Smell Worse to You Than Your Ancient Ancestors

Researchers worked out which receptors in your nose detect particular scent molecules, and found evidence of evolutionary change in some of these genes.

By Sam Jones

Sign up for Science Times Get stories that capture the wonders of nature, the cosmos and the human body. Get it sent to your inbox.

When you take a whiff of something, odor molecules sail inside your nose where they bind to proteins — called olfactory receptors — on cells that line your nasal cavity. These receptors trigger signals that your brain interprets as one or many smells.

A team of scientists has identified the olfactory receptors for two common odor molecules: a musk found in soaps and perfumes and a compound prominent in smelly underarm sweat. The research team also discovered that more recent evolutionary changes to these olfactory receptors alter people's sensitivities to those odors. The work was published in PLoS Genetics on Thursday.

Olfactory receptors can be traced back hundreds of millions of years and are believed to be present in all vertebrates. Humans have around 800 olfactory receptor genes, but only about half of them are functional, meaning they'll be translated into proteins that hang out in the nose and detect odor molecules. But within a functional gene, minor variations can cause changes in its corresponding receptor protein, and those changes can massively affect how an odor is perceived.

"There's a molecule called androstenone," said Joel Mainland, a neuroscientist at Monell Chemical Senses Center and an author of the new study. "And we know that some people smell that molecule

as urine, some people smell that molecule at sandalwood, and some people don't smell it at all."

With that said, genetic changes aren't the only thing underlying smell interpretation. "One is genetic and the other is experience, which includes things like the culture you grew up in," said Hiroaki Matsunami, a molecular biologist at Duke University who was not involved in the research but whose work is focused on olfaction.

The study by Dr. Mainland and colleagues was a collaborative effort between scientists in the United States and China. They sequenced the genomes of 1,000 people in Tangshan, China, who are members of the Han ethnic group. They did the same with an ethnically diverse cohort of 364 people in New York City. Participants were asked to rate, on a 100-point scale, the intensity and pleasantness of a range of common odors. The researchers then looked for associations between olfactory receptor genes and odors as well as variations within those genes and their potential impact on perception of the odor.

By sampling a large, diverse population of people the researchers were able to hone in on odors whose perception was based in genetic differences between people, rather than cultural or experiential factors. That led them to molecules including trans-3-methyl-2-hexenoic acid and galaxolide.

Trans-3-methyl-2-hexenoic acid is considered one of the most pungent compounds in underarm sweat. Galaxolide is a synthetic musk often described as having a floral, woody odor that's used in perfumes and cosmetics, but also things like kitty litter. The research team was able to identify olfactory receptor variants for those odors. In the case of the underarm odor, most people with the more evolutionarily recent gene variant found it more intense. The opposite was true for galaxolide.

The galaxolide findings were particularly striking, with some participants unable to smell the musk at all. "It's really rare to find an effect that's as large as what we saw for this one receptor on the perception of the musk odor," said Marissa Kamarck, a neuroscientist at the University of Pennsylvania who was an author of the study.

Dr. Matsunami views this work as another example of human olfaction being more complex than people initially thought. He said that, although the major findings in the study involved just two scents, they're adding to evidence that "odorant receptors as a group have extraordinary variety."

The authors think their findings support a hypothesis that has been criticized that the primate olfactory system has degenerated over evolutionary time. Kara Hoover, an anthropologist at the University of Alaska Fairbanks who was not involved in this research but who studies the evolution of human smell, is not convinced by that hypothesis in the first place.

"Why is reduced intensity assumed to be degradation?" she asked. "Maybe other things are becoming more intense or odor discrimination is improving. We know too little to make these conclusions."

For Dr. Hoover, these findings stirred up other evolutionary questions. "Our species is really young," she said. "Why this much variation in such a short period of time? Is there an adaptive significance?"

https://bit.ly/3J50xL2

A Man Declared Dead by Three Doctors Woke Up Shortly Before His Autopsy

His skin had been marked with scalpel guidelines in preparation for his imminent autopsy

Peter Dockrill

A few years ago, Spanish prison authorities were rather baffled after a prisoner who had been declared dead by three separate doctors woke up in the morgue – just hours before his own autopsy

was set to commence.

The prisoner, then-29-year-old Gonzalo Montoya Jiménez, was found unresponsive in his cell during a morning roll call on 7 January 2018 and had been transferred to a hospital mortuary in a body bag when pathologists heard something strange.

Snoring. Coming from inside the bag.

Jiménez, who was serving time for robbery in the maximum security wing of Asturias Central Penitentiary in northwest Spain, was first attended by two doctors on duty in the prison, after he was found sitting unconscious in a chair in his cell, with no signs of violence being evident.

Sensing no vital signs, the doctors declared him dead, and an hour later a forensic doctor inspected the body, concurred with the first evaluations, and issued a third death report. Only later in the morgue did physicians realize something was terribly wrong.

By this point, Jiménez had already spent time in a cold storage room to help preserve his body, and his skin had been marked with scalpel guidelines in preparation for his imminent autopsy – at which point the mistaken corpse suddenly stirred.

"Forensic doctors began to hear noises coming from inside the bag. Montoya was not dead. Quite the opposite," reported *El Español* at the time. "The forensic [pathologist] proceeded to open the bag and found the inmate still alive."

Jiménez was subsequently transferred under guard in an ambulance to another hospital to recover from his mystery episode, and was eventually reported to be in a stable condition – but as for how the mix-up could have occurred in the first place, prison authorities seemingly had no idea.

"I can't comment on what happened at the Institute of Legal Medicine," a spokesperson for the Spanish Prison Service told the media, "but three doctors have seen clinical signs of death so it's still not clear at the moment exactly why this occurred."

The day before Jiménez was found 'dead', he complained of feeling ill, and while it was unknown exactly what caused his condition, officials described his body as showing signs of cyanosis – a purplish discoloration of the skin caused by poor circulation or lack of oxygen – in addition to rigor mortis.

Hospital officials told Spanish media the faux fatality could be a case of catalepsy, in which the body enters a trance or seizure-like state, exhibiting a loss of consciousness and sensation, together with physical rigidity.

Just how Jiménez became cataleptic is unclear, although the prisoner experienced epilepsy, and takes medication for the condition – but his family said it wasn't always easy for Jiménez to adhere to his medication schedule in lock-up, so that might have had something to do with it.

In the hospital, it took 24 hours before Jiménez recovered consciousness in intensive care, and began to speak, which doctors said was a good sign.

When the 'dead man' woke up, he asked if he could see his wife.

https://bit.ly/3GweDU2

Newly discovered 'death receptor' could help drive type 1 diabetes

Scientists are studying potential treatments to block the receptor.

By Nicoletta Lanese

Insulin-producing cells in the pancreas carry a "death receptor" that, when activated, causes the cells to self-destruct. This cellular self-destruct button may in turn contribute to the development of type 1 diabetes, according to a new study in mice and human tissues.

The findings also suggest a potential way to rescue some of these cells from certain death — by locking those cellular doorways, according to a new study.

Type 1 diabetes is an autoimmune disorder where the immune system attacks the insulin-producing beta cells in the pancreas. A

hallmark of type 1 diabetes is the death of these beta cells, but exactly why those cells die isn't entirely clear; scientists suspect multiple mechanisms are at play, according to a 2016 report in The Journal of Autoimmunity.

The new study identifies the death receptor, called transmembrane protein 219 (TMEM219), which sits within the outer membrane of beta cells, as a key player in this process, according to a statement. A protein called insulin-like growth factor binding protein 3 (IGFBP3) binds to the portion of the death receptor that juts off the cell surface, and by doing so, it sets off a chain of events inside the cell. This chain of events spells certain doom for the beta cell — it triggers apoptosis, or cellular suicide, the new study found.

In several laboratory studies with mice, the researchers tried different ways of preventing this chain of events from unfolding; the mice used in the study were genetically modified such that they're prone to type 1 diabetes.

In one experiment, for example, the team deleted the death receptor altogether using genetic modification, and in another they blocked the receptor using a protein that had been modified for that purpose. The team found that, when they temporarily blocked the death receptor in mice, a larger number of beta cells survived than did in untreated mice, and insulin production increased. This, in turn, delayed or prevented the onset of diabetes in the mice. When the team blocked the death receptor for an extended period of time, the animals' beta cells increased in number.

The team also ran experiments with human beta cells. Applying IGFBP3 to the tissues triggered rampant beta cell death, but by blocking the death receptors on the cells, the researchers could stop this damage from occurring and allow the cells to keep producing insulin.

Supporting what they found in the laboratory, the team also found that people diagnosed with diabetes and those at high risk of diabetes both carried high levels of IGFBP3, as compared with those who did not have diabetes. This was also true of diabetic and prediabetic mice, compared with healthy mice, they found.

"We think that in disease, IGFBP3 production may be increased, so there is a loss of beta cells," Dr. Paolo Fiorina, a research associate and assistant professor at Harvard Medical School and Boston Children's Hospital, said in the statement. Fiorina is the founder of a biotechnology company, Enthera, that's developing treatments to block the beta cell death receptor. The first human trials of such a treatment could begin by fall 2022, according to the statement.

"The common thought for type 1 diabetes is that it [is] autoimmune," Fiorina said. "But immunotherapy doesn't completely cure diabetes." We think that IGFBP3 acts as a "betatoxin" and disrupts the normal function of beta cells, and thus also contributes to the development of diabetes, he said.

The new study was published Thursday (Feb. 3) in the journal Nature Communications.

https://bit.ly/3soYdaW

MIT Engineers Develop Biocompatible Surgical "Duct Tape" as an Alternative to Sutures

The sticky patch could be quickly applied to repair gut leaks and tears.

By Jennifer Chu, Massachusetts Institute of Technology

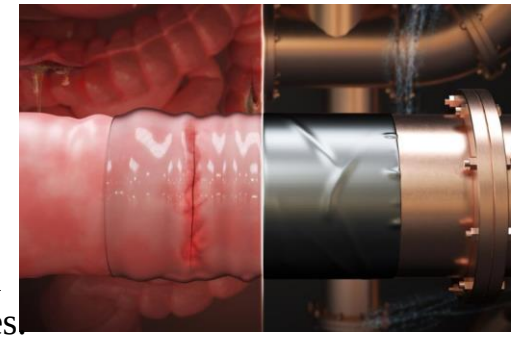
A staple on any engineer's workbench, duct tape is a quick and dependable fix for cracks and tears in many structural materials. MIT engineers have now developed a kind of surgical duct tape — a strong, flexible, and biocompatible sticky patch that can be easily and quickly applied to biological tissues and organs to help seal tears and wounds.

Like duct tape, the new patch is sticky on one side and smooth on the other. In its current formulation, the adhesive is targeted to seal defects in the gastrointestinal tract, which the engineers describe as

the body's own biological ductwork.

In numerous experiments, the team has shown the patch can be quickly stuck to large tears and punctures in the colon, stomach, and intestines of various animal models. The adhesive binds strongly to tissues within several seconds and holds for over a month. It is also flexible, able to expand and contract with a functioning organ as it heals. Once an injury is fully healed, the patch gradually degrades without causing inflammation or sticking to surrounding tissues.

The team envisions the surgical sticky patch could one day be stocked in operating rooms and used as a fast and safe alternative or reinforcement to hand-sewn sutures to repair leaks and tears in the gut and other biological tissues.



A new MIT-designed surgical sticky tape can be applied quickly and easily, like duct tape to a pipe, to repair leaks and tears in the gastrointestinal tract and other tissues and organs. **Credit: Courtesy of the researchers**

"We think this surgical tape is a good base technology to be made into an actual, off-the-shelf product," says Hyunwoo Yuk, a research scientist in MIT's Department of Mechanical Engineering. "Surgeons could use it as they use duct tape in the nonsurgical world. It doesn't need any preparation or prior step. Just take it out, open, and use."

Yuk, the study's co-lead and co-corresponding author, and his colleagues published their results on February 2, 2022, in the journal *Science Translational Medicine.* Other co-authors include MIT postdoc and lead author Jingjing Wu; project supervisor and co-corresponding author Xuanhe Zhao, who is a professor of mechanical engineering and of civil and environmental engineering at MIT; and collaborators from the Mayo Clinic and the Southern University of Science and Technology.

A gut instinct

The new surgical duct tape builds on the team's 2019 design for a double-sided tape. That early iteration comprised a single layer that was sticky on both sides and designed to join two wet surfaces together.

The adhesive was made from polyacrylic acid, an absorbent material found in diapers, which starts out dry and absorbs moisture when in contact with a wet surface or tissue, temporarily sticking to the tissue in the process. The researchers mixed into the material NHS esters, chemical compounds that can bind with proteins in the tissue to form stronger bonds. Finally, they reinforced the adhesive with gelatin or chitosan — natural ingredients that kept the tape's shape.

The researchers found the double-sided tape strongly bonded different tissues together. But when consulting with surgeons, they realized that a single-sided version might make a more practical impact. "In practical situations, it's not common to have to stick two tissues together —organs need to be separate from each other," Wu says. "One suggestion was to use this sticky element to repair leaks and defects in the gut."

Surgeons typically repair leaks and tears in the gastrointestinal tract with surgical sutures. But sewing the stitches requires precision and training, and following surgery the sutures can trigger scarring around the injury. The tissue between stitches could also tear, causing secondary leakages that could lead to sepsis.

"We thought, maybe we could turn our sticky element into a product to repair gut leaks, similar to sealing pipes with duct tape," Wu says. "That pushed us toward something more like single-sided tape."

Same tape, new tricks

The researchers first tuned their adhesive recipe, replacing gelatin

and chitosan with a longer-lasting hydrogel — in this case, polyvinyl alcohol. This swap kept the adhesive physically stable for over a month, long enough for a typical gut injury to heal. They also added a second, nonsticky top layer to keep the patch from sticking to surrounding tissue. This layer was made from a biodegradable polyurethane that has about the same stretch and stiffness of natural gut tissue.

"We don't want the patch to be weaker than tissue because otherwise it would risk bursting," Yuk says. "We also don't want it to be stiffer because it would restrict the peristaltic movement in guts that is essential for digestion."

In initial tests, the patch did stick to tissues, but it also swelled, just as a fully wet, hydrogel-based diaper would. This swelling stretched the tape and the underlying tear it was intended to seal.

"It was almost an impossible problem because hydrogel naturally swells," Yuk says. "But we did a simple trick: We prestretched the adhesive layer a bit, then introduced the nonadhesive layer, so that when applied to a tissue, that prestretching cancels out the swelling."

The team then carried out experiments to test the patch's properties and performance. When the patch was placed in a culture with human epithelial cells, the cells continued to grow, showing that the patch is biocompatible. When implanted under the skin of rats, the patch biodegraded after about 12 weeks, with no toxic effects.

The researchers also applied the patch to defects in the animals' colons and stomachs, and found it maintained a strong bond as the injuries fully healed. It also produced minimal scarring and inflammation compared with repairs made with conventional sutures.

Finally, the team applied the patch over colon defects in pigs, and observed that the animals continued to feed normally, with no fever, lethargy, or other adverse health effects. After four weeks, the defects fully healed, with no sign of secondary leakage.

Taken together, the experiments suggest that the surgical patch could potentially safely repair gastrointestinal injuries, and could be applied just as easily as commercial duct tape. Yuk and Zhao are further developing the adhesive through a new startup and hope to pursue FDA approval to test the patch in medical settings.

"We are studying a fundamental mechanics problem, adhesion, in an extremely challenging environment, inside the body. There are millions of surgeries worldwide a year to repair gastrointestinal defects, and the leakage rate is up to 20 percent in high-risk patients," Zhao says. "This tape could solve that problem, and potentially save thousands of lives."

Reference: "An off-the-shelf bioadhesive patch for sutureless repair of gastrointestinal defects" by Jingjing Wu, Hyunwoo Yuk, Tiffany L. Sarrafian, Chuan Fei Guo, Leigh G. Griffiths, Christoph S. Nabzdyk and Xuanhe Zhao, 2 February 2022, Science Translational Medicine. DOI: 10.1126/scitranslmed.abh2857

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https://bit.ly/34Dui6G

Mosquitoes are Attracted to Specific Colors, New Study Shows

Yellow fever mosquitoes (Aedes aegypti) fly toward specific colors, including red, orange, black and cyan, but they ignore other colors

Mosquitoes track odors, locate hosts, and find mates visually. The color of a food resource, such as a flower or warm-blooded host, can be dominated by long wavelengths of the visible light spectrum (green to red for humans) and is likely important for object recognition and localization. However, little is known about the hues that attract mosquitoes or how odor affects mosquito visual search behaviors. A new University of Washington-led study shows that after detecting a telltale gas that we exhale, yellow fever mosquitoes (*Aedes aegypti*) fly toward specific colors, including

red, orange, black and cyan, but they ignore other colors, such as green, purple, blue and white.

"Mosquitoes appear to use odors to help them distinguish what is nearby, like a host to bite," said Professor Jeffrey Riffell, a researcher in the Department of Biology at the University of Washington. "When they smell specific compounds, like carbon dioxide from our breath, that scent stimulates the eyes to scan for specific colors and other visual patterns, which are associated with a potential host, and head to them."

In the new experiments, Professor Riffell and his colleagues tracked behavior of female Aedes aegypti, when presented with different types of visual and scent cues. Like all mosquito species, only females drink blood, and bites from Aedes aegypti can transmit dengue, yellow fever, chikungunya and Zika.

The researchers tracked individual mosquitoes in miniature test chambers, into which they sprayed specific odors and presented different types of visual patterns — such as a colored dot or a tasty human hand. Without any odor stimulus, mosquitoes largely ignored a dot at the bottom of the chamber, regardless of color.

After a spritz of carbon dioxide into the chamber, mosquitos continued to ignore the dot if it was green, blue or purple in color. But if the dot was red, orange, black or cyan, mosquitoes would fly toward it.

Humans can't smell carbon dioxide, which is the gas we and other animals exhale with each breath. Mosquitoes can. Past research showed that smelling carbon dioxide boosts female mosquitoes' activity level — searching the space around them, presumably for a host.

The colored-dot experiments revealed that after smelling carbon dioxide, these mosquitoes' eyes prefer certain wavelengths in the visual spectrum. It's similar to what might happen when humans smell something good.

"Imagine you're on a sidewalk and you smell pie crust and cinnamon," Professor Riffell said. "That's probably a sign that there's a bakery nearby, and you might start looking around for it."

"Here, we started to learn what visual elements that mosquitoes are looking for after smelling their own version of a bakery."

Most humans have true color vision: We see different wavelengths of light as distinct colors: 650 nm shows up as red, while 450 nm wavelengths look blue, for example.

The scientists do not know whether mosquitoes perceive colors the same way that our eyes do. But most of the colors the mosquitoes prefer after smelling carbon dioxide — orange, red and black — correspond to longer wavelengths of light. Human skin, regardless of pigmentation, also gives off a long-wavelength signal in the red-orange range.

When the study authors repeated the chamber experiments with human skintone pigmentation cards — or a researcher's bare hand — mosquitoes again flew toward the visual stimulus only after carbon dioxide was sprayed into the chamber.

If the researchers used filters to remove long-wavelength signals, or had the researcher wear a green-colored glove, then carbon dioxide-primed mosquitoes no longer flew toward the stimulus.

Genes determine the preference of these females for red-orange colors. Mosquitoes with a mutant copy of a gene needed to smell carbon dioxide no longer showed a color preference in the test chamber. Another strain of mutant mosquitoes, with a change related to vision so they could no longer see long wavelengths of light, were more color-blind in the presence of carbon dioxide.

"These experiments lay out the first steps mosquitoes use to find hosts," Professor Riffell said.

The team's results were published in the journal Nature Communications.

D. Alonso San Alberto et al. 2022. The olfactory gating of visual preferences to human skin and visible spectra in mosquitoes. Nat Commun 13, 555; doi: 10.1038/s41467-022-28195-x

https://bit.ly/3J898N3

The Widely Available Low-Cost Drug That Could Fight COVID-19

A widely available and affordable drug, heparin, limits lung damage when inhaled by COVID-19 patients

A widely available and affordable drug, heparin, limits lung damage when inhaled by COVID-19 patients, according to world-first findings by researchers from The Australian National University (ANU).

The researchers are coordinating multiple studies tracking hospital patients infected with SARS-CoV-2 in 13 countries who were given doses of inhaled heparin. ANU study lead Professor Frank van Haren said initial results indicate the drug could be "a promising treatment" and also "a possible preventative against the virus."

Breathing and oxygen levels improved in 70 percent of the patients after they inhaled a course of heparin, and their symptoms improved according to the World Health Organization (WHO) COVID symptoms scale.

"There is still an urgent need for an effective treatment of COVID-19 and the early results of our trials show inhaled heparin is safe and effective," Professor van Haren said.

"This drug is already available in hospitals all over the world and it is a very inexpensive drug. If it is as effective as our early results suggest, it could have a major impact in our fight against COVID."

Heparin, which is normally administered via injection, is a blood thinner used to treat and prevent blood clots across the world and is said to be widely available.

Co-author Professor Clive Page, from King's College London, who is co-leading the global studies, said: "Inhaled heparin has antiviral properties which work by binding to the spike proteins the coronavirus uses to enter the cells of the body.

"Inhaled heparin effectively stops the virus infecting cells in the lungs and could also stop people from getting the virus from others.

"It also works as an anti-inflammatory drug — the medicine has the ability to calm everything down when the body is mounting an exaggerated response to the virus. We already know heparin can reduce lung damage caused by this inflammation and the immune response overdrive that we see in other lung diseases which could provide benefit to patients hospitalized with COVID-19.

"It's also a blood thinner. When COVID-19 patients get very sick they develop blood clots in the lungs and these can be lethal. Heparin stops these clots from forming. There is no other drug that has these three different effects — anti-viral, anti-inflammatory and anti-coagulant."

The researchers say because the drug has antiviral properties and calms the immune system down it could be used at different stages of treatment. When inhaled, heparin also shows promise as a preventative and could be used to boost vaccination efforts.

"Most COVID experts agree that vaccination alone is not going to stop the pandemic. This could really assist in poorer countries where vaccination is challenging and we think it could help front line workers who could use it as a preventative measure," Professor van Haren said.

"Inhaled heparin is a promising new possibility to provide a low-cost, safe and effective treatment for COVID-19 that is available and affordable to low and middle-income countries around the globe."

Professor van Haren said the team was now collecting more evidence that inhaled heparin works as a treatment and prevention for COVID-19. "Once we have this evidence, heparin via inhalation could be an option to treat COVID-19 patients, everywhere, within months," he said.

The findings from the first 98 patients in the studies are published in a new paper in the *British Journal of Clinical Pharmacology*.

Reference: "Inhaled nebulised unfractionated heparin for the treatment of hospitalised patients with COVID-19: A multicentre case series of 98 patients" by Frank M. P. van Haren, Lex M. van Loon, Anne Steins, Thomas L. Smoot, Caitlin Sas, Sabrina Staas, Alicia B. Vilaseca, Ruben A. Barbera, Gustavo Vidmar, Hugo Beccari, Frida Popilevsky, Eleonora Daribayeva, Bhuvaneshwari Venkatesan, Susan Mozes, Rachel Postel, Natalie Popilevski, Andrew Webb, Quentin Nunes, John G. Laffey, Antonio Artigas, Roger Smith, Barry Dixon, Alice Richardson, Hwan-Jin Yoon and Clive Page, 4 January 2022, British Journal of Clinical Pharmacology. DOI: 10.1111/bcp.15212