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# Ivermectin Has Little Effect on Recovery Time From Covid, Study Finds

***A new clinical trial is the largest to date testing the antiparasitic drug on people with Covid.***

**By Carl Zimmer**

The antiparasite drug ivermectin does not meaningfully reduce the time needed to recover from Covid, according to a large study posted online Sunday. It is the largest of several clinical trials to show that the drug, popular since the early pandemic as an alternative treatment, is not effective against the virus.

The new trial, conducted by researchers at Duke University and Vanderbilt University, tested more than 1,500 people with Covid, about half getting the drug and the others a placebo. The study has not yet been published in a scientific journal.

"Given these results, there does not appear to be a role for ivermectin outside of a clinical trial setting, especially considering other available options with proven reduction in hospitalizations and death," Dr. Adrian Hernandez, the executive director of the Duke Clinical Research Institute who led the trial, said in a statement on Sunday night.

In 2020, laboratory experiments on cells suggested that ivermectin might block the coronavirus. The results triggered widespread excitement because ivermectin is an inexpensive drug that has been safely used in people for decades against parasitic worm infections.

The drug grew wildly popular, despite a lack of results from large randomized clinical trials. When those studies finally finished, they proved disappointing. In March, researchers published a study in which 679 people diagnosed with Covid received ivermectin. The drug did not significantly reduce their risk of going to a hospital for Covid compared with people who took a placebo.

The new study of ivermectin was part of a larger effort, organized by the National Institutes of Health, to identify existing drugs that might help treat Covid. Known as Accelerating COVID-19 Therapeutic Interventions and Vaccines-6, or ACTIV-6 for short, the program has also been testing an antidepressant and an antiasthma drug. Dr. Hernandez and his colleagues gave ivermectin to 877 volunteers who were diagnosed with Covid, while 774 others received a placebo. The researchers then observed how their cases progressed.

People on ivermectin felt unwell for an average of 10.96 days, while people on the placebo took 11.45 days — a difference of about 12 hours. There was no statistically significant difference in the risk each group faced of going to the hospital. One death was observed during the trial — of a volunteer who received ivermectin.

Almost half of the volunteers had been vaccinated, the researchers said. Their shots may have reduced the overall number of severe Covid cases, making it harder to detect a benefit.

Despite the negative results, the researchers did not entirely rule out the possibility that ivermectin might have a place in treating Covid. Among 90 people who were already suffering from severe Covid when they entered the trial, those who tried ivermectin appeared to fare better than did those on the placebo. But the small numbers made it impossible to draw any firm statistical conclusions about ivermectin's benefit. The effect might have been the result of chance.

To investigate that result further, the researchers will keep testing ivermectin at higher doses. A new set of volunteers will receive 50 percent more of the drug in each dose and for six days instead of three. "Given the favorable safety profile and continued public interest in ivermectin, the ACTIV-6 team will continue to study this higher dose to determine whether it will make enough of a difference to be considered for the treatment of mild-to-moderate COVID-19," Dr. Susanna Naggie, an infectious disease expert at

Duke University, said in the statement.

***https://bit.ly/3QFFIKX***

## Artificial intelligence may have unearthed one of the world's oldest campfires

***Human ancestors may have been cooking at site in Israel nearly 1 million years ago***

**By Michael Price**

It's not always easy to find clues to ancient campfires. Bits of charcoal, cracked bones, and discolored rocks often give a prehistoric blaze away. But not every blaze leaves such obvious traces, especially after hundreds of thousands of years.

Now, using artificial intelligence (AI) to detect the subtle ways in which extreme heat warps a material's atomic structure, scientists have discovered the potential presence of a nearly 1-million-year-old fire featuring dozens of purportedly burnt objects buried at an archaeological site in Israel. If the technique proves reliable, the findings could shed light on when, where, and why humans first learned to harness the flame.

Richard Wrangham, an anthropologist at Harvard University, is impressed with the new method. He has long advocated that our human ancestors evolved smaller guts and larger brains once they began to cook food, perhaps about 1.8 million years ago. "We need imaginative new methods" to pinpoint ancient fires, he says. "Now, we have one."

Most studies of fire rely on the obvious bits of charcoal and other clues. But Filipe Natalio, an archaeological biochemist at the Weizmann Institute of Science, wanted to find a way to identify the invisible evidence fire leaves behind. Previous work, led in part by forensic scientists, has shown that burning alters bone structure at the atomic level, so burnt and unburnt human bones absorb different wavelengths of the infrared spectrum. Researchers can detect a charred bone using a technique known as Fourier-transform infrared (FTIR) spectroscopy, which measures the absorption of different wavelengths of light.

Natalio and colleagues wondered whether a similar method might work for burnt stone tools, which are often more abundant than bones in very ancient sites—and are a clear sign of human presence. He and colleagues experimented by heating flint, a common toolmaking rock that can become easier to chip and shape after heating, to various temperatures in a fire, then applying spectroscopic techniques to see whether they could identify the signatures of burning. But because of natural variations in the flint, the patterns in the data were hopelessly complex.

"One peak would go up, another would go down … and the changes were so subtle that we couldn't rely on them," Natalio says. "That's when we turned to artificial intelligence."

The researchers devised a computer program to hunt for subtle patterns that would have taken ages for the scientists to find on their own, Natalio says. The AI worked. Using a technique called ultraviolet (UV) Raman spectroscopy, which measures the absorption of UV light, the AI could reliably differentiate burnt and unburnt pieces of modern flint and even reveal the temperatures at which they burned.

Next, the team applied its method to 26 flint tools, mostly small cutting edges, that had been excavated in the 1970s from Evron Quarry, a coastal site in northwestern Israel. A combination of dating methods suggested the site was between 800,000 and 1 million years old and was probably inhabited by the widespread, toolmaking human ancestor known as *Homo erectus*. Dozens of animal bones were found alongside the tools, but archaeologists had found no traditional evidence of fire such as charcoal or reddened sediment.

Using their new technique, Natalio and colleagues found most of the flint tools had been heated to a range of temperatures between

200°C and 600°C, they report today in the *Proceedings of the National Academy of Sciences*. (The average campfire burns at about 400°C.) The researchers also used FTIR spectroscopy to analyze 13 bits of tusk, from one of two elephantlike genuses known as *Stegodon* and *Elephas*, that had been found in the same sedimentary layer as the tools. The tusks, too, had been exposed to temperatures as high as 600°C.

That, Natalio says, may be evidence that the site's inhabitants cooked their kills. If so, that would make it—along with a potential 1-million-year-old hearth in South Africa's Wonderwerk Cave—among the oldest known cooking sites.

"It's well done," (the paper, not the roasted elephant) says Dennis Sandgathe, a paleoanthropologist at Simon Fraser University. "There are less than half a dozen sites in the world with [evidence for] fire that's older than 500,000 years old. It may be because hominins were not using fire very frequently, but it may also be that we are missing some of it. So, this is really important."

There's still no way to definitively say whether the tools and tusks at this site burned in a natural or humanmade fire, Natalio says. Based on vegetation, fires can burn at different temperatures even within a single location. But the sheer variability of temperatures among tools so closely situated at Evron Quarry suggests to Natalio a radical notion: that the toolmakers were experimenting, heating flint cores to different temperatures to see how it affected their workability.

Sarah Hlubik, a paleoanthropologist at George Washington University who studies the origins of fire, isn't so sure. "At the age of this site, I'd say that is unlikely but not impossible," she says. "We don't really see heat treatment until much later, and if the technology was being experimented with at nearly 1 million years, we would likely see it more widespread earlier than we do."

The new technique is promising, Hlubik says. But she'd like to see the work reproduced in a wider variety of settings—and for the team to rule out other possibilities, such as naturally burnt materials from different places and times washing into the site. Until then, Hlubik says, "It's important to take results like this with a grain of salt."

***https://bit.ly/3aWntjI***

## Research Shows That Robotic Surgery Is Safer and Improves Patient Recovery Time by 20%

***A new study has found that robotic surgery is less dangerous and has a faster recovery period for patients***

*Robotic surgery, also known as robot-assisted surgery, enables surgeons to conduct a variety of complicated operations with more precision, flexibility, and control than traditional approaches allow. Robotic surgery is often associated with minimally invasive surgery, which involves procedures carried out through small incisions. It's also occasionally employed in certain traditional open surgical procedures.*

*The most common clinical robotic surgical system consists of a camera arm and mechanical arms with surgical tools attached. While sitting at a computer station beside the operating table, the surgeon controls the arms. The console provides the surgeon with a magnified, high-definition 3D view of the operative site.*

A first-of-its-kind clinical trial led by scientists at University College London and the University of Sheffield found that using robot-assisted surgery to remove and rebuild bladder cancer allows patients to recover much faster and spend considerably (20%) less time in hospital.

The study, which was published in *JAMA* on May 15th and funded by The Urology Foundation with a grant from the Champniss Foundation, also discovered that robotic surgery cut the chance of readmission in half (52%) and revealed a "striking" four-fold (77%) reduction in the prevalence of blood clots (deep vein thrombus &

pulmonary emboli) – a significant cause of health decline and morbidity – when compared to patients who had open surgery.

Patients' stamina and quality of life also improved and their physical activity increased which was measured by daily steps recorded on a wearable smart sensor.

Unlike open surgery, which involves a surgeon working directly on a patient and large incisions in the skin and muscle, robot-assisted surgery enables doctors to remotely guide less invasive tools using a console and 3D view. It is currently only offered at a few UK hospitals.

Researchers say the findings provide the strongest evidence so far of the patient benefit of robot-assisted surgery and are now urging the National Institute of Clinical Excellence (NICE) to make it available as a clinical option across the UK for all major abdominal surgeries including colorectal, gastrointestinal, and gynecological.

Co-Chief Investigator, Professor John Kelly, Professor of Uro-Oncology at UCL's Division of Surgery & Interventional Science and consultant surgeon at University College London Hospitals, said: "Despite robot-assisted surgery becoming more widely available, there has been no significant clinical evaluation of its overall benefit to patients' recovery. In this study we wanted to establish if robot-assisted surgery when compared to open surgery, reduced time spent in hospital, reduced readmissions, and led to better levels of fitness and quality of life; on all counts, this was shown.

"An unexpected finding was the striking reduction in blood clots in patients receiving robotic surgery; this indicates a safe surgery with patients benefiting from far fewer complications, early mobilization and a quicker return to normal life."

Co-Chief Investigator Professor James Catto, Professor of Urological Surgery at the Department of Oncology and Metabolism, University of Sheffield, said: "This is an important finding. Time in hospital is reduced and recovery is faster when using this advanced surgery. Ultimately, this will reduce bed pressures on the NHS and allow patients to return home more quickly. We see fewer complications from improved mobility and less time spent in bed.

"The study also points to future trends in healthcare. Soon, we may be able to monitor recovery after discharge, to find those developing problems. It is possible that tracking walking levels would highlight those who need a district nurse visit or perhaps a check-up sooner in the hospital."

"Previous trials of robotic surgery have focused on longer-term outcomes. They have shown similar cancer cure rates and similar levels of long-term recovery after surgery. None have looked at differences in the immediate days and weeks after surgery."

Open surgery remains the NICE "gold standard" recommendation for highly complex surgeries, though the research team hopes this could change.

Professor Kelly added: "In light of the positive findings, the perception of open surgery as the gold standard for major surgeries is now being challenged for the first time.

"We hope that all eligible patients needing major abdominal operations can now be offered the option of having robotic surgery."

Rebecca Porta, CEO of The Urology Foundation said: "The Urology Foundation's mission is simple – to save lives and reduce the suffering caused by urological cancers and diseases. We do this through investing in cutting-edge research, leading education, and supporting the training of health care professionals to ensure that fewer lives will be devastated.

"We are proud to have been at the heart of the step change in the treatment and care for urology patients since our inception 27 years ago, and the outcomes of this trial will improve bladder cancer patients' treatment and care."

Bladder cancer is where a growth of abnormal tissue, known as a tumor, develops in the bladder lining. In some cases, the tumor spreads into the bladder muscle and can lead to secondary cancer in other parts of the body. About 10,000 people are diagnosed with bladder cancer in the UK every year and over 3,000 bladder removals and reconstructions are performed. It is one of the most expensive cancers to manage.

**Trial findings**

Across nine UK hospitals, 338 patients with non-metastatic bladder cancer were randomized into two groups: 169 patients had robot-assisted radical cystectomy (bladder removal) with intracorporeal reconstruction (the process of taking a section of bowel to make a new bladder), and 169 patients had open radical cystectomy.

The trial's primary end-point was the length of stay in the hospital post-surgery. On average, the robot-assisted group stayed eight days in the hospital, compared to 10 days for the open surgery group – so a 20% reduction. Readmittance to the hospital within 90 days of surgery was also significantly reduced – 21% for the robot-assisted group vs 32% for open.

A further 20 secondary outcomes were assessed at 90 days, six- and 12 months post-surgery. These included blood clot prevalence, wound complications, quality of life, disability, stamina, activity levels, and survival (morbidity). All secondary outcomes were improved by robot-assisted surgery or, if not improved, almost equal to open surgery.

This study, and previous studies, show both robot-assisted and open surgery are equally as effective in regard to cancer recurrence and length of survival.

**Next steps**

The research team is conducting a health economic analysis to establish the quality-adjusted life-year (QALY), which incorporates the impact on both the quantity and quality of life.

**Patient case studies**

John Hammond, retired, age 75, from Doncaster, said: "I left my symptoms too long, and found out that I had a tumor in the bladder. I was lucky to see Professor Catto and after being given options, I chose the operation to have my bladder removed and a stoma in place.

"I had the operation in August 2019 and was aware that it was robotic surgery in a trial and was keen to take part; in fact, I was pleased to be in a position to help anybody else in the future with this type of surgery. The operation was successful, and the whole team was hugely supportive.

"Amazingly, I was walking the next day and progressed excellently, improving my walking each day. I was in no pain and just had to adjust to the stoma bag. I have fully recovered from the operation and throughout I knew I was in professional hands. I was home about five days after surgery and am grateful to Professor Catto and his team that I did not have to stay in hospital for longer than necessary."

Frances Christensen Essendon, from Hertfordshire, said: "I was diagnosed with bladder cancer and after a course of chemotherapy it was suggested that I have my bladder removed. Under Professor John Kelly I underwent robotic surgery to remove my native bladder which was replaced with a new bladder made out of the bowel. The operation was a success, and I was up and walking soon after surgery. Having had the operation in April I was back to work and the gym in the middle of June. I have gone on to lead a normal active life and am eternally grateful to Prof Kelly and his team for their care and support."

*The trial took place from March 2017 to March 2020 and involved 29 surgeons at nine UK hospital trusts namely; University College London Hospitals NHS Foundation Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Guys and St Thomas' NHS Foundation Trust, NHS Greater Glasgow and Clyde, Royal Berkshire NHS Foundation Trust, St James University Hospital Leeds, Royal Liverpool and Broadgreen University*

*Hospitals NHS Trust, Royal Devon and Exeter NHS Trust, and North Bristol NHS Trust. Reference: "Effect of Robot-Assisted Radical Cystectomy With Intracorporeal Urinary Diversion vs Open Radical Cystectomy on 90-Day Morbidity and Mortality Among Patients With Bladder Cancer" by James W. F. Catto, Pramit Khetrapal, Federico Ricciardi, et al., 15 May 2022, JAMA.*
*DOI: 10.1001/jama.2022.7393*

***https://bit.ly/3O3OUH1***

# Years after finding it, archeologists enter chamber under a Peruvian temple

***The room was lost even to generations of people who lived and worshipped at the site.***

**Kiona N. Smith**

Today, the temples, canals, and plazas of Chavín de Huántar stand mostly in ruins. But the site (about 250 kilometers north of Lima, Peru) was once was the heart of the Chavín culture, a civilization that flourished in the central Andes centuries before the rise of the Inca Empire. Its oldest granite and limestone temples date back to about 1200 BCE, but people have lived at the site for much longer, since at least 3000 BCE.

Even after the Chavín culture's power faded, members of the Huaraz group used stones from the ancient temples to build a village in an abandoned plaza. People lived at Chavín de Huántar until the 1940s. The place has had a long enough life that, over thousands of years, even the people who lived there lost track of some of its secrets.

Archaeologists rediscovered one of those secrets by accident: a narrow duct leading to a small ritual chamber eight meters deep beneath one of the site's temple buildings. Based on the style of its architecture, the hidden chamber may be older than any other building or tunnel at the site.

"I put a date of 3,000 years, but I think I'm conservative, and it may be even older," Stanford University archaeologist John Rick, director of the Chavín de Huántar Archaeological Research and Conservation Program, told Peruvian newspaper El Comercio. Radiocarbon dating material from the chamber could provide a more definite answer, but that process could take about six months, according to Rick, who plans to do the work himself instead of sending samples to a lab, as is typically done.

**A secret chamber "frozen in time"**

Rick's first glimpse of the chamber—now nicknamed the Condor Gallery—came via a robotic camera that he had carefully lowered into the 40-centimeter-wide duct set in a passage between two temples. Archaeologists had been excavating the passage in 2012 when they found the duct, but they didn't get the chance to investigate with the robotic camera until 2019. In the video, Rick could just make out the dim outlines of a small room with a blurry object sitting in the center of the floor.

The duct probably once provided ventilation for the small chamber, according to Rick. He suggests that the chamber may originally have been a shallow, stone-lined pit where small groups of people could gather for rituals. Later renovations added a roof and walls. But eventually, later construction covered the chamber and its small ventilation shaft completely. "So the Condor Gallery, as we call it, was frozen in time—no more people entering," he said.

It took more than a year for the archaeologists to find a way to get inside without damaging the gallery or the temple above it. But earlier this month, Rick squeezed through a narrow opening and found himself standing, hunched over, inside a 1.5-meter-wide, two-meter-long room.

"There is enough space for a very small group to sit on stools, and we will probably also find a hearth because these early temples had a fire cult," said Rick.

In the center of the chamber sat the object he'd seen through the robotic camera: a heavy stone bowl. Its handles were carved into the shapes of an Andean condor's head and tail, while the bird's

wings curved along the sides of the bowl. The ornate bowl gave the chamber its name, the Condor Gallery, and it provided another clue about the room's age.

The carving's realistic style resembled earlier art from other sites, such as Caral, the 5,000-year-old seat of a city-building culture even older than the Chavín. Later art, including the animals and geometric designs that decorate the walls of Chavín de Huántar's temples, tended to be more stylized. That, along with the chamber's architecture—which didn't look like anything else at Chavín de Huántar—suggested that the room was older than anything else built at the site.

"All of this suggests we're talking about a connection to the past, with more original sites like Caral," said Rick.

**Subterranean secrets at Chavín de Huántar**

The Condor Gallery isn't the first underground architecture archaeologists unearthed at Chavín de Huántar. The network of subterranean passages under the temples inspired a 1997 hostage rescue operation, Operation Chavín de Huántar. Members of a rebel group called the Túpac Amaru Revolutionary Movement had taken several hundred hostages at the Japanese ambassador's residence in Lima. Peruvian special forces used tunnels dug from nearby buildings to access the ambassador's residence.

Two decades later, in 2018, Rick and his colleagues rediscovered 35 more tunnels beneath the site.

The construction project that finally cut the Condor Gallery off from the world probably happened well before 500 BCE. Around that time, the Chavín culture's political power waned, and the site fell into disuse—at least as a major religious center. Local people built a village in one of the great plazas, borrowing granite and limestone from temple walls to build their homes. They might have known about some of the tunnels and canals beneath their feet, but it's unlikely that they knew about the Condor Gallery.

***https://bit.ly/3zI2tYo***

# Giant Study Reveals Over 14% of The World Has Probably Had Lyme Disease

***More than 14 percent of the world's population has had Lyme disease, the most common tick-borne illness, according to a major review of the available research published on Tuesday.***

Central Europe had the highest rate of infection with 20 percent, while men over the age of 50 living in rural areas were most at risk, the study in the journal *BMJ Global Health* found.

The condition is rarely fatal, but people bitten by an infected tick often get a rash and suffer flu-like symptoms including muscle and joint ache, headache, nausea, and vomiting.

To find out how common Lyme disease is across the world, the researchers pooled data from 89 studies. The bacteria *Borrelia burgdorferi* (Bb), which causes the disease, was found in the blood of 14.5 percent of the nearly 160,000 total participants.

"This is the most comprehensive and up-to-date systematic review of the worldwide" prevalence of the disease, the researchers said.

After Central Europe, the regions with the highest antibody rates were Eastern Asia with 15.9 percent, Western Europe with 13.5 percent, and Eastern Europe with 10.4 percent.

The Caribbean meanwhile had the lowest rate, with just 2 percent.

Previous research has shown that the prevalence of tick-borne diseases has doubled in the last 12 years.

Reasons for the rise included longer, drier summers due to climate change, animal migration, habitat loss, and "increasingly frequent pet contact", the study said. Farmers and workers who regularly interact with host animals like dogs and sheep were most at risk of getting bitten by an infected tick, the study found.

It warned that the data could be skewed in regions where Lyme disease is endemic, because health workers are more likely to carry out regular antibody tests there compared to regions where it is less

common. The study also said that research using an analytic technique called western blotting was more reliable and that its use "could significantly improve the accuracy" of future studies.

***https://wb.md/3aVBTk7***

## Facing 'Extinction,' Doctors Urge AMA to Support Private Practices

***Fewer physicians today are in independent practice, a trend that some say could affect the cost and quality of healthcare.***

**Alison Sherwood**

CHICAGO — To help protect the viability of independent physician practice, the American Medical Association (AMA) decided Monday that it will issue a report at least every 2 years in collaboration with the Private Practice Physicians Section to communicate their efforts to support such medical practices.

The AMA, in considering the report at the annual meeting of its House of Delegates, noted that many physicians are not members of the association possibly because they are not satisfied with nor are aware of its activities to help physicians stay in private practice.

Howard Huang, MD, a physical medicine and rehabilitation doctor and delegate from New York, speaking on behalf of the Medical Society of the State of New York, said in a reference committee hearing that this is the right time to highlight this issue because the COVID-19 pandemic has accelerated the decline in the number of physicians in independent practice.

"As someone whose 65-year-old practice was forced by financial considerations to be acquired by a hospital, and some might say sell out to a hospital, we want to ensure the viability of independent medical practice as a counterweight to hospitals who might otherwise unilaterally try to influence our practice," he said.

Several doctors testified that the percentage of private practice physicians in their region or specialty has gone down significantly. Andrew Lazar, MD, said that when he began practicing dermatology in the early '80s, 75% of dermatology practices were one- and two-person practices, but now fewer than 10% are.

"The current macrosystem is accelerating the extinction of small practices by incentivizing mergers and big corporations," Lazar said. "Consolidation of the market will drive costs."

Carl Wehri, MD, a family medicine doctor in Ohio, speaking on behalf of the Great Lakes State Coalition, said that even more than a report, "we need bold and decisive action by our AMA in the support of the private practice of medicine."

Wehri said that without the AMA's efforts, independent practice will continue to dissolve and that the effects will result in "loss of high-quality, cost-effective medical care for millions of our patients. We must not allow this to happen."

He also said the AMA's actions could be helpful in recruitment of independent physicians into the AMA.

### "A Rare Dying Breed"

Internist Richard Frankenstein, MD, who spoke on behalf of the American College of Physicians, pointed out that despite their decline in numbers, private practices will be around for a long time, whether by a doctor's choice, subspecialty, or the reality of living in a rural community with few physicians.

"Small private practices will have to continue, and we need to support them so they can continue to provide high-quality care," Frankenstein said.

Florida internist Jason Goldman, MD, is one such doctor who described himself as "a rare dying breed of solo practice." He said with the support of the AMA, it's possible not only to survive but also to flourish in private practice.

"The survival of primary care and small independent practice is really the survival of medicine itself," Goldman said.

General surgeon Joseph Costabile, MD, an independent physician in New Jersey, said he has used the AMA's resources on

independent practice to educate and encourage his colleagues. He said he would like to see more information from the AMA, such as ideas on how to garnish referrals and sustain their practices.

Georgia cardiologist Ali Rahimi, MD, pushed for the AMA to commit to issuing a report at least every year rather than every 2 years. "This would be something equal to having a patient on the hospital wards and checking on them once a week," he said.

***https://bit.ly/3zGlv1r***

## 800-year-old graves pinpoint where the Black Death began

***Ancient DNA from cemeteries in today's Kyrgyzstan reveal earliest known victims of 14th century plague***

**By Ann Gibbons**

The Syriac engraving on the medieval tombstone was tantalizing: "This is the tomb of the believer Sanmaq. [He] died of pestilence." Sanmaq, who was buried in 1338 near Lake Issyk Kul in what is now northern Kyrgyzstan, was one of many victims of the unnamed plague. By scrutinizing field notes and more photos from the Russian team that had excavated the graves in the 1880s, historian Philip Slavin found that at least 118 people from Sanmaq's Central Asian trading community died in the epidemic.

Slavin was on the trail of the origin of the Black Death, which devastated Europe a decade after the Kyrgyzstan burials. But he knew the medieval diagnosis of "pestilence" encompassed many horrific diseases. "I was almost 100% certain it was the beginning of the Black Death," says Slavin, a medieval historian at the University of Stirling. "But there was no way to prove it without DNA."

Now, Slavin is senior author of a new study of ancient DNA from the "pestilence" victims showing they were indeed infected with the bacterium, *Yersinia pestis*, that caused the Black Death. The strain that killed them was ancestral to all the strains that rampaged across Europe a decade later and continued to kill for the next 500 years. The bacterium jumped from rodents to humans just before the Kyrgyzstan burials, perhaps after sudden changes in rainfall or temperature, the researchers propose this week in *Nature*.

"This is the place where it all started—the Wuhan of the Black Death," says senior author and paleogeneticist Johannes Krause of the Max Planck Institute for Evolutionary Anthropology.

***A headstone of a "pestilence" victim buried near Lake Issyk*** **KulA. S. Leybin**

The finding confirms some other researchers' hunches about Central Asia as a source for the Black Death strain, and pinpoints a precise time and place. "There's not much doubt about it—[the region is] where you have lots of reservoirs of the plague," says physical anthropologist Barbara Bramanti of the University of Ferrara.

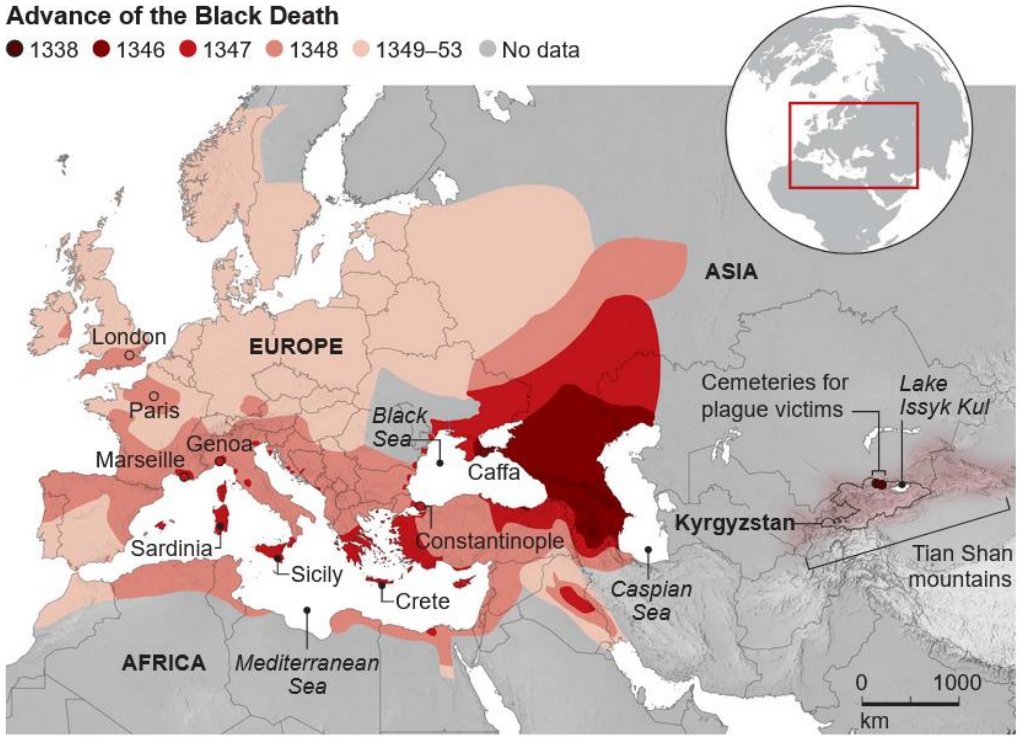
In European historical accounts, the Black Death appears first in 1346 at ports on the Black Sea. Within a year it was in Europe, where scholars estimate it killed more than half of the population by 1353. In 1894, microbiologists identified *Y. pestis* as the cause. Ever since, they have debated where and when the deadly strain was born, considering China, Central Asia, India, and Genghis Khan's armies marching from Mongolia.

In 2020, a new analysis of more than 1300 modern and ancient genomes of *Y. pestis* narrowed the options. A team led by microbiologist Mark Achtman of the University of Warwick used a new software tool to sort all known strains of *Y. pestis* from humans and host animals into a family tree showing their evolution over 5500 years, starting with strains that were not closely related to the Black Death strain.

One branch of the tree underwent a "big bang" explosion of

diversity at the time of the Black Death, creating a starlike pattern of four new lineages of *Y. pestis* whose descendant strains still persist in 40 species of rodents around the world. One of those lineages was the source of the Black Death and later outbreaks in Europe until the 18th century. The ancestral strain of this lineage was "literally the mother of them all," Krause says.

**Deadly spread**




***A new study pinpoints the first known cases of the plague that caused the Black Death, in people buried in 1338 near Lake Issyk Kul in today's Kyrgyzstan. A decade later, bubonic plague had devastated Europe.*** **(Map) K. Franklin/*Science*; (Data) Ole J. Benedictow, *The Complete History of the Black Death* (2021)**

Geneticists knew this mother strain did not arise in Europe, because the strains found in Black Death victims there differed by two mutations from the putative ancestral genome, says paleogeneticist Maria Spyrou of the University of Tübingen, who had been Krause's postdoc. "We knew the European genomes were very close to origins of the Black Death, but not quite there," she says. Several teams suspected the source was in Central Asia, where strains from rodents were the closest genetic match to the mother genome. But no one had DNA data on strains from human victims of the right time period.

Then Krause and Spyrou heard Slavin give a talk about the tombstones. When he reported that the people had died of "pestilence," they each immediately thought, "We should do DNA!" Krause recalls.

Working with Slavin and Russian collaborators including Valeri Khartanovich of the Peter the Great Museum of Anthropology and Ethnography, where the Issyk Kul skulls were stored, Spyrou extracted DNA from the pulp of seven individuals' teeth and found three were infected with *Y. pestis*. She was able to reconstruct a high-quality genome of the ancient strain that killed them. That strain "fell exactly on the origin point of that big bang event" in the evolution of *Y. pestis*, Spyrou says. "That was incredibly exciting."

The strain was closely related to ones found in rodents near Issyk Kul today. The authors suggest it spilled over to humans, perhaps from a marmot, which are abundant in the Tian Shan mountain region of northern Kyrgyzstan, southern Kazakhstan, and northwestern China.

Sudden changes in rainfall or temperature could have led to surges in local rodent populations and the fleas or other insects they harbor. More rodents and their pests meant more opportunities to hop to a new host—humans—and adapt to it, says population biologist Nils Christian-Stenseth of the University of Oslo, who has shown a correlation between outbreaks of plague and warm, wet weather in Central Asia. He adds: "There are many good possibilities for plague reservoirs; you have the great gerbils, marmots, voles."

The remaining mystery, he says, is how the Black Death traveled 3500 kilometers from Central Asia to the Black Sea, where historical accounts describe the Mongolian army hurling the bodies of plague victims into the besieged city of Caffa in Crimea in 1346 in an early form of biological warfare.

The meticulous archaeological records for each Kyrgyzstan grave offer hints, Slavin says. Many people were buried with pearls, coins, and other goods from the Indian Ocean, the Mediterranean, and Iran; some were apparently traders. As they traveled, their camel wagons may have harbored rats and fleas, long considered likely vectors for plague.

Another paper, in *Nature Communications* last month, suggests rats were perfectly positioned to help spread the Black Death. A team led by archaeologist David Orton of the University of York used the diversity of ancient DNA in rat bones to trace the ups and downs of black rat populations through history.

In Europe, one population collapsed with the fall of the Roman Empire but was replaced by another in the 13th century, when growing cities offered new food and shelter for the rodents. Black rats and their fleas were everywhere at that time, Krause says, especially aboard ships traveling between the Black Sea and Mediterranean ports—the route the Black Death evidently followed. Meanwhile, the Issyk Kul graveyard is giving names and identities to the first known victims of the Black Death. "To actually have *Y. pestis* from incredibly well dated burials is really exciting," says bioarchaeologist Sharon De Witte of the University of South Carolina, Columbia.

"We can clarify what other disease they were infected with and look at the biosocial factors that might have shaped risk of death in that first wave."

As for Slavin, he's still marveling at the discovery. "This was one of my dreams, to solve this outstanding puzzle."

***https://bit.ly/3MTZore***

# A $100 genome? New DNA sequencers could be a 'game changer' for biology, medicine

***"This is the year of the big shake-up."***

**By Elizabeth Pennisi**

For DNA sequencing, this "is the year of the big shake-up," says Michael Snyder, a systems biologist at Stanford University. Sequencing is crucial to fields from basic biology to virology to human evolution, and its importance keeps growing. Clinicians are clamoring to harness it for early detection of cancer and other diseases, and biologists are finding ever more ways to use genomics to study single cells. But for years, most sequencing has relied on machines from a single company, Illumina.

Last week, however, a young company called Ultima Genomics said at a meeting in Orlando, Florida, that with new twists on existing technologies, it could provide human genomes for $100 a pop, one-fifth the going rate. Several other companies also promised faster, cheaper sequencing at the same meeting, Advances in Genome Biology and Technology. This year, key patents protecting Illumina's sequencing technology will expire, paving the way for more competition, including from a Chinese company, MGI, which last week announced it would begin to sell its machines in the United States this summer. "We may be on the brink of the next revolution in sequencing," says Beth Shapiro, an evolutionary biologist at the University of California, Santa Cruz (UCSC).

Most sequencing companies, including Illumina, which has controlled 80% of the global market, depend on "sequencing by synthesis." The DNA to be deciphered is separated into single strands, which are usually chopped into short pieces and mounted on a surface—often a tiny bead—in a container called a flow cell. Each single strand fragment serves as a template to guide the

synthesis of a strand with complementary bases, supplied one at a time to channels of beads. Because each added base has been modified to glow, a camera can record where it attaches—and hence the identity of the corresponding base on the original strand. The steps are repeated until the new DNA strand is complete.

Ultima streamlined the process by spraying the DNA-laden beads by the billions onto round silicon wafers the size of dessert plates. Nozzles above each wafer gently squirt out bases and other reagents, which spread thinly and evenly across the wafer as it rotates, reducing the amount of these expensive materials needed. Instead of moving back and forth across under the camera, the disk moves in a spiral, akin to how a compact disk is played, which speeds up imaging. It's "clever engineering [that] avoids a lot of complex plumbing," says Mark Akeson, a molecular biologist at UCSC. A neural network program rapidly turns imaging data into a sequence.

The sequencing chemistry is different as well. Only a few bases carry fluorescent tags, reducing costs. Moreover, the bases lack the usual stop signal, which ensures no extra bases latch on. Without these "terminators," the growing chain can sometimes add multiple bases at once, speeding the process. "Many of these innovations are used elsewhere, but they seem to have come together very nicely here," says Jay Shendure, a geneticist and technology developer at the University of Washington (UW), Seattle.

Ultima CEO Gilad Almogy and his colleagues demonstrated the technology's potential in four preprints posted in late May on bioRxiv. In one, they and colleagues at the Broad Institute of MIT and Harvard used their machine to sequence more than 224 already-sequenced human genomes and found their results on par with previous work. The three other studies showed the technology can evaluate a single cell's repertoire of expressed genes, the effects of mutations, and epigenetics—chemical modifications of DNA that affect gene activity.

Until now, cost has limited such single-cell studies, causing a bottleneck in research. But Snyder found Ultima's low-cost approach enabled him to sequence multiple colon cancer cells to document how one DNA modification, methylation, changes as colon cancer develops.

In another preprint, Joshua Levin and his Broad Institute colleagues tested the ability of the Ultima technology to identify active genes in single blood cells as indicated by the genes' RNA transcripts. The team found Ultima's machine identified those genes about as well as Illumina's did. And, he adds, "It's a game changer due to the lower cost."

Florence Chardon, a UW genomics graduate student who modifies DNA with the genome editor CRISPR, is excited by that prospect. "The less expensive [sequencing] gets, the more accessible this kind of research is to more labs and more people," she says.

But Lior Pachter, a computational biologist at the California Institute of Technology, has reservations about the new technology. He and graduate student A. Sina Booeshaghi looked at one of the most active genes in blood cells from Levin's team, a possible cancer biomarker also known for producing a protein athletes sometimes inject to illegally enhance their performance. The Ultima technology sometimes missed the active gene, Pachter says. The "error rate was very high, and the performance was very poor."

The gene has a stretch in which the same base is repeated eight times, and Ultima admits long repeats can undermine the accuracy of its reads. Looking elsewhere in the Ultima sequence, Pachter found errors when one base was repeated just three times. He notes that a human genome contains at least 1.4 million of these so-called homopolymers. Still, he says, "For some applications, you don't need perfect sequences."

Pachter and others also take issue with the touted $100 cost. That figure only covers reagents, not the labor, pre- and postsequencing

steps, and initial outlay for the machine, the price of which has not been released. Even if the $100 figure is real, it may not be unique: Other companies are also promising $100 per human genome.

One is MGI, a subsidiary of Chinese sequencing giant BGI. MGI's technology is similar to Illumina's, but it increases accuracy by adding all four bases at once as it sequences DNA. To track which bases are incorporated, it uses antibodies, which are brighter and less expensive than fluorescent dyes. Illumina, too, is promising lower costs, and at the meeting it introduced new chemistries to increase accuracy and flexibility.

For this bargain rate to be realized, Ultima and MGI both require filling their sequencers to capacity with hundreds of genomes. But high-throughput sequencing "is not always good for clinical practice even if it is good economics," says Greg Elgar, a genome biologist at Genomics England, because sometimes a physician needs just one or a few people's genomes analyzed. Other companies with new flow cells and chemistries can economically sequence small numbers of genomes. At last week's meeting, Element Biosciences CEO Molly He reported the company is now shipping benchtop sequencers that can sequence three human genomes at a time, at a cost of $560 each. Another company, Singular Genomics, also promises benchtop technology that doesn't require high throughput for cost savings.

These machines, like those from Illumina, MGI, and Ultima, all decipher short fragments of DNA. But for the past 7 years, two companies, Pacific Biosciences and Oxford Nanopore Technologies, have worked on sequencing "long reads," thousands of bases long, which leave fewer partial sequences to piece together into a full genome. The technologies "can sequence the native DNA molecule, in all its glory," Elgar says. They have struggled with low accuracy and high cost, but he says they are on their way to becoming practical tools.

Don't count the sequencing giant Illumina out just yet. Its scientists "probably have kept a couple of cards in their back pocket" to keep their position in the market strong, says Albert Vilella, a bioinformatician and genomics consultant in Cambridge, England. Nonetheless, Illumina faces unprecedented competition, he adds. "It's time to look at the [DNA sequencing] landscape with fresh eyes."

***https://bit.ly/3xXZ46n***

## Catnip Turns Out to Have a Hidden Effect You Probably Don't Know About

***What appears to be an act of pure hedonism could also have a more medicinal purpose.***

**Mike McRae**

To many members of the feline family, perennial herb catnip (*Nepeta cataria*) is an irresistible psychoactive treat that induces short bouts of drooling, pawing, and writhing pleasure.

Not satisfied with merely rolling among its foliage, many kitties will tear and crumple the leaves, prompting researchers to investigate the purpose of this wanton destruction.

What appears to be an act of pure hedonism could also have a more medicinal purpose. According to a new study, the additional damage to the leaves releases significant amounts of insect-repelling compounds into the air, bathing the cat in a natural pesticide.

While *N. cataria* is the most commonly recognized cat intoxicant, a number of plants including valerian (*Valeriana officinalis*) and a species of kiwifruit called silver vine (*Actinidia polygama*) also contain compounds that induce odd behaviors in domestic and wild cats.

Two such chemicals are nepetalactol and nepetalactone – figure-eight-shaped molecules classed as iridoids, which are produced by plants like catnip and silver vine to ward off insect attacks.

Nepetalactone also happens to titillate a set of receptors inside feline nasal cavities, triggering a cascade of responses that make a quick roll in the leaves impossible to ignore.

Previous research joined the dots, demonstrating the cat's vigorous actions bruise the leaves of catnip and silver vine enough to release sufficient amounts of nepetalactone and nepetalactol to serve as a repellent against the mosquito, *Aedes albopictus*.

Now the same researchers wanted to know if the biting and chewing behaviors provided additional benefits, or were just a sign of the cat's exuberance while in the throes of pleasure.

Sixteen healthy lab cats participated in the study, which involved watching their behavior as samples of intact, crumpled, and torn catnip and silver vine leaves and cocktails of iridoids in petri dishes were placed in front of their cages.

The team also conducted a range of other tests on the efficiency of various plant extracts and iridoid mixtures as a mosquito repellent, and the concentrations of volatile compounds surrounding cat-damaged leaves.

Taken altogether, it was clear that the extra damage done by ripping at the leaves really helped get the party started a lot faster.

"We found that physical damage of silver vine by cats promoted the immediate emission of total iridoids, which was 10-fold higher than from intact leaves," says lead author Masao Miyazaki, an animal behavior researcher from Iwate University in Japan.

Not only was the total concentration higher in both plant types, the mix of iridoids was more complex in torn silver vine leaves, making for a more potent repellent at lower concentrations.

Cats who were exposed to these mixtures were also affected for a longer duration, suggesting their biology has been 'fine-tuned' to maximize the insect-repelling doses of silver vine.

"Nepetalactol accounts for over 90 percent of total iridoids in intact leaves, but this drops to about 45 percent in damaged leaves as other iridoids greatly increase," says Miyazaki.

"The altered iridoid mixture corresponding to damaged leaves promoted a much more prolonged response in cats."

Using naturally-occurring insecticides stolen from plants and even other arthropods isn't unknown in the animal kingdom.

Not only have we humans been waving *Chrysanthemum* extracts around for generations to keep the bugs at bay, lemurs have adapted to rubbing millipedes over their bodies as a form of parasite treatment, while other birds and animals have anointed themselves with citrus leaves for similar ends.

Still, few seem to derive quite the same pleasure from their protective body rubs. These cats seem to be onto something.

This research was published in *iScience*.

***https://nyti.ms/3N0yYEh***

## Unexplained hepatitis is not more common in U.S. children than before the pandemic, a C.D.C. study suggests.

***There have always been a subset of pediatric hepatitis cases with no clear cause***

**By Emily Anthes**

Officials have also been trying to determine whether the cases represent a new phenomenon or are simply a new recognition of one that has long existed; there have always been a subset of pediatric hepatitis cases with no clear cause.

Unexplained hepatitis does not appear to have become more common among American children than it was before the Covid-19 pandemic began, according to a new review of three large medical databases by researchers at the Centers for Disease Control and Prevention.

The results are part of an ongoing investigation into a puzzling cluster of cases of severe hepatitis, or liver inflammation, in previously healthy children, which date back to October 2021. As

of May 26, 650 probable cases had been reported in 33 countries, according to the World Health Organization. Although the cases are extremely rare, they can be severe, resulting in liver transplants or death.

Hepatitis has a wide variety of causes, including the hepatitis A through E viruses, toxins, and certain medications. In the recent cluster of cases, however, many of these common causes have been ruled out.

Researchers have been investigating a range of potential explanations, including the possibility that the cases might be linked to the pandemic or caused by an infection with an adenovirus, one of a family of common viruses that typically cause cold- and flu-like symptoms and have been detected in many of the affected children. (It is also possible that the two factors are working in concert. A previous coronavirus infection might leave children more vulnerable to a subsequent adenovirus infection, for instance.)

Officials have also been trying to determine whether the cases represent a new phenomenon or are simply a new recognition of one that has long existed; there have always been a subset of pediatric hepatitis cases with no clear cause.

In the new study, the researchers found that from October 2021 to March 2022, the number of weekly emergency room visits and monthly hospital admissions that were recorded as being associated with pediatric hepatitis of an unspecified cause was not significantly higher than prepandemic baselines, calculated as far back as 2017. The number of pediatric liver transplants per month did not increase significantly either, the study found.

To investigate the adenovirus hypothesis, the scientists reviewed data from the company Labcorp, which routinely tests pediatric stool samples for adenovirus type 40 and 41, which generally cause gastrointestinal symptoms. The share of samples testing positive was not significantly higher in recent months than in the years before the pandemic, the scientists found.

The findings diverge from reports from Britain, where officials have reported a small uptick in unexplained hepatitis among young children in 2022 compared to previous years, as well as an increase in adenovirus infections.

Because pediatric hepatitis remains rare, a modest increase would be difficult to detect, the researchers caution, and continued investigation and monitoring is needed. “Ongoing assessment of trends, in addition to enhanced epidemiologic investigations, will help contextualize reported cases of acute hepatitis of unknown etiology in U.S. children,” they write.

The new study has a number of limitations, the authors note. There is no comprehensive database of unexplained pediatric hepatitis cases in the United States so the true prevalence remains unknown. There are also lags between when hospital admissions and liver transplants occur and when these outcomes are reported, which means that more recent cases might be missing from the analysis.

***https://bit.ly/3OamBqv***

## New work upends understanding of how blood is formed

***The origins of our blood may not be quite what we thought.***

Using cellular "barcoding" in mice, a groundbreaking study finds that blood cells originate not from one type of mother cell, but two, with potential implications for blood cancers, bone marrow transplant, and immunology. Fernando Camargo, Ph.D., of the Stem Cell Program at Boston Children's Hospital led the study, published in *Nature* on June 15.

"Historically, people have believed that most of our blood comes from a very small number of cells that eventually become blood stem cells, also known as hematopoietic stem cells," says Camargo, who is also a member of the Harvard Stem Cell Institute and a

professor at Harvard University. "We were surprised to find another group of progenitor cells that do not come from stem cells. They make most of the blood in fetal life until young adulthood, and then gradually start decreasing."

The researchers are now following up to see if the findings also apply to humans. If so, these cells, known as embryonic multipotent progenitor cells (eMPPs), could potentially inform new treatments for boosting aging people's immune systems. They could also shed new light on blood cancers, especially those in children, and help make bone marrow transplants more effective.

**Cellular 'barcodes'**

Camargo's team applied a barcoding technique they developed several years ago and documented in *Cell*. Using either an enzyme known as transposase or CRISPR gene editing, they inserted unique genetic sequences into embryonic mouse cells in such a way that all the cells descended from them also carried those sequences. This enabled the team to track the emergence of all the different types of blood cells and where they came from, all the way to adulthood.

"Previously, people didn't have these tools," says Camargo. "Also, the idea that stem cells give rise to all the blood cells was so embedded in the field that no one attempted to question it. By tracking what happened in mice over time, we were able to see new biology."

**Understanding the aging immune system**

Through barcoding, the researchers found that eMPPs, as compared with blood stem cells, are a more abundant source of most lymphoid cells important to the immune responses, such as B cells and T cells. Camargo believes the decrease in eMPPs that they observed with age may explain why people's immunity weakens as they get older.

"We're now trying to understand why these cells peter out in middle age, which could potentially allow us to manipulate them with the goal of rejuvenating the immune system," says Camargo.

In theory, there could be two approaches: extending the life of eMPP cells, perhaps through growth factors or immune signaling molecules, or treating blood stem cells with gene therapy or other approaches to make them more like eMPPs.

**Unpacking blood cancers**

Camargo is also excited about the potential implications for better understanding and treatment of blood cancers. For example, myeloid leukemias, striking mostly older people, affect myeloid blood cells such as granulocytes and monocytes. Camargo thinks these leukemias may originate from blood stem cells, and that leukemias in children, which are mostly lymphoid leukemias, may originate from eMPPs.

"We are following up to try to understand the consequences of mutations that lead to leukemia by looking at their effects in both blood stem cells and eMPPs in mice," he says. "We want to see if the leukemias that arise from these different cells of origin are different—lymphoid-like or myeloid-like."

**Improving bone marrow transplant?**

Finally, the recognition that there are two types of mother cells in the blood could revolutionize bone marrow transplant.

"When we tried to do bone marrow transplants in mice, we found that the eMPPs didn't engraft well; they only lasted a few weeks," says Camargo. "If we could add a few genes to get eMPPs to engraft long term, they could potentially be a better source for a bone marrow transplant. They are more common in younger marrow donors than blood stem cells, and they are primed to produce lymphoid cells, which could lead to better reconstitution of the immune system and fewer infection complications after the graft."

***More information:*** *Fernando Camargo, Lifelong multilineage contribution by embryonic-born blood progenitors, Nature (2022). DOI: 10.1038/s41586-022-04804-z.*
*www.nature.com/articles/s41586-022-04804-z*

*Sarah Bowling et al, An Engineered CRISPR-Cas9 Mouse Line for Simultaneous Readout of Lineage Histories and Gene Expression Profiles in Single Cells, Cell (2020). DOI: 10.1016/j.cell.2020.04.048*

***https://bit.ly/3HAXo68***

# Japan's Upcoming Mission Will Use a Vacuum to Get its Sample From Phobos

***As soon as 2024, the mission called Martian Moons eXploration (MMX) will be sent to Phobos and use a pneumatic vacuum device to collect its samples***

**By Evan Gough**

***Much of Phobos' surface is covered with strange linear grooves. New research bolsters the idea that those iconic grooves were carved by boulders blasted free from Stickney crater (the large depression on the right).*** **Image Credit: NASA/JPL-Caltech/University of Arizona**

JAXA, the Japanese Aerospace Exploration Agency, is carving out a niche for itself in sample-return missions. Their Hayabusa mission was the first mission to sample an asteroid when it rought dust from the asteroid Itokawa to Earth in 2010. Then its successor, Hayabusa 2, brought back a sample from asteroid Ryugu in 2020.

Now JAXA has the Martian moon Phobos in its sights and will send a spacecraft to sample it as soon as 2024. The mission is called Martian Moons eXploration (MMX), and it'll use a pneumatic vacuum device to collect its samples.

Why go to Phobos and sample it? Because it's an unusual moon and understanding it better could answer questions about it and our Solar System. And we always want more answers.

Phobos is the larger of Mars' two moons, the other being Deimos. Both moons are irregularly shaped and look kind of like potatoes, especially Phobos. Phobos has a mean radius of only 11 km (7 mi). It's closer to Mars than Deimos and orbits only 6,000 km (3,700 mi) from the planet's surface. It moves rapidly, taking only 7 hours and 39 minutes to complete one orbit and completes three orbits each day.

Phobos is probably a captured rubble-pile asteroid, although astronomers still debate its nature. It has a lot in common with carbonaceous asteroids and is one of the least reflective objects in the Solar System.

The tiny moon is getting closer and closer to Mars. Every year it gets about 2 cm closer and will eventually be destroyed. In about 30 million to 50 million years, it will either smash into the surface of Mars and be utterly destroyed or be torn apart by tidal forces and form a debris ring around the planet. In fact, one hypothesis says that Mars' moons were formed from dust created by a giant impact on Mars. Dust to dust, as they say.

Japan leads the MMX mission, but NASA, the CNES (France), and the DLR (Germany) are also contributing. It has two broad goals: (1) determining the origin of the Martian moons and (2) observing processes in the circumplanetary environment of Mars, based on remote sensing, in situ observations, and laboratory analyses of returned samples of Phobos regolith. Scientists think that a better understanding of the Mars-Phobos-Deimos system will shed light on the planetary formation process in the Solar System.

Getting a sample from Phobos faces several obstacles. The moon is not massive enough for a spacecraft to enter orbit around it in the usual way. Instead, MMX will enter orbit around Mars and then perform quasi-satellite orbits. Those orbits become unstable over time but should allow for several months of operation near Phobos. This maneuver also enables the MMX lander to reach Phobos' surface.

JAXA designed the MMX mission with three components: a propulsion module, an exploration module, and the return module.

The French CNES space agency suggested that the mission should also deploy a tiny rover about the size of a microwave to the surface, built by France and Germany.

But the highlight of the MMX mission will be the sample return. We've made enormous progress in sending instruments on spacecraft, landers, and rovers to examine Solar System bodies. When it comes to Mars, the in-situ study of the planet has unleashed a flood of new evidence and insights. But the holy grail in space missions is still sample return. No matter how advanced the instruments we send on missions are, lab analysis back on Earth will always outstrip them.

MMX will gather samples in two ways. One is the Coring Sampler (C-SMP) developed by JAXA. The other is the Pneumatic Sampler (P-SMP), contributed by NASA and developed by Honeybee Robotics.

The pair of samplers will complement each other and partially account for the fact that we don't know what the surface is like. The Coring Sampler will be positioned on the lander's robotic arm. It will use a special shape memory alloy to gather a 10-gram sample from deeper than 2 cm under the regolith.

The Pneumatic Sampler will be positioned near the footpad on one of the lander's legs. It'll use pressurized nitrogen gas to gather the samples, and mission operators can manipulate the gas flow depending on requirements. It can be either continuous or pulsed.

The P-SMP has three sets of nozzles to perform the procedure. Two excavation nozzles point downward, two retro thrust nozzles point upward, and two transport nozzles point toward the sampling tube. The three pairs of nozzles fire simultaneously.

The excavation nozzles fire at the surface of Phobos and stir up material from the regolith. The transport nozzles direct material into the sampling head. The retro thrust nozzles fire to counteract the thrust on the spacecraft, so its position is stable during sampling.

Honeybee Robotics has tested its P-SMP extensively and is confident that it can handle any surprises on Phobos' surface. The company says its system can still gather a sample even if gravel covers the surface.

MMX won't be the only mission to use Honeybee's vacuum system. NASA plans to use it on the Moon to capture lunar regolith in Mare Crisium in 2023. The system is also being considered for a Europa Lander mission and several other missions still in the concept and design phase.

It's easy to see why.

"The purpose of this technology is to allow simple and inexpensive capture of planetary materials from largely unknown surfaces," said Honeybee project lead Kris Zacny. "Vacuum cleaners are designed to capture 'dirt,' hence a vacuum cleaner-like approach is ideal for working with planetary 'dirt.'"

***https://bit.ly/3n1qzww***

## Drug Treatment for Cataracts Might Soon Become a Reality

***Anglia Ruskin University expert leads work on an anti-cataract drug, which shows promising results in lab tests***

**By Anglia Ruskin University**

Currently, cataracts can only be cured with surgery. However, a groundbreaking new treatment for cataracts has had incredibly positive laboratory test results suggesting that the affliction might soon be able to be treated with drugs.

The study's results were published on May 2nd, 2022 in the peer-reviewed journal *Investigative Ophthalmology and Visual Science.*

A cataract is a clouding of the eye lens that develops over time and compromises the quality of vision. It is caused by a disorder of the proteins in the lens that leads to clumps of protein accumulating that scatter light and substantially limit transmission to the retina. The National Eye Institute estimates that cataracts impact an

estimated 24.4 million Americans age 40 or older.

Nuclear sclerotic, cortical, and posterior subcapsular cataracts are the three main types of cataracts.

A team of international scientists, led by Professor Barbara Pierscionek, Deputy Dean (Research and Innovation) in the Faculty of Health, Education, Medicine and Social Care at Anglia Ruskin University, have been carrying out advanced optical tests on an oxysterol compound that had been proposed as an anti-cataract drug.

In laboratory trials, treatment with the oxysterol compound VP1-001 showed an improvement in refractive index profiles – a key optical parameter that is needed to maintain high focusing capacity – in 61% of lenses. This means that the protein organization of the lens is being restored, resulting in the lens being better able to focus. This was supported by a reduction in lens opacity in 46% of cases.

Professor Pierscionek, who is also a member of the Medical Technology Research Centre at Anglia Ruskin University (ARU), said: “This study has shown the positive effects of a compound that had been proposed as an anti-cataract drug but never before tested on the optics of the lens. It is the first research of this kind in the world.

“It has shown that there is a remarkable difference and improvement in optics between eyes with the same type of cataract that was treated with the compound compared to those that were not. “Improvements occurred in some types of cataracts but not in all indicating that this may be a treatment for specific cataracts. This suggests distinctions may need to be made between cataract types when developing anti-cataract medications. It is a significant step forward towards treating this extremely common condition with drugs rather than surgery.”

*Reference: “Oxysterol Compounds in Mouse Mutant αA- and αB-Crystallin Lenses Can Improve the Optical Properties of the Lens” by Kehao Wang, Masato Hoshino, Kentaro Uesugi, Naoto Yagi, Barbara K Pierscionek and Usha P Andley, 2 May 2022, Investigative Ophthalmology & Visual Science. DOI: 10.1167/iovs.63.5.15*

***https://bit.ly/3HEqEzQ***

## Ingenious Technique Leads to Kids Having Kidney Transplants Without Immune Suppression

***Three successful kidney transplants used a new method that minimizes the risk of the new kidney getting rejected.***

**David Nield**

Organ transplants can quite literally save lives, but they also come with strings attached – often including a lifetime of immunosuppression drug treatments required to keep the immune system in check, lest it reject the transplanted organ as a foreign invader.

Now scientists are reporting on three successful kidney organ transplants, carried out in children in California, without the need for immune suppression. The transplants used a new method that minimizes the risk of the new kidney getting rejected.

This means freedom from immunosuppressants and the associated side effects, which aren't always pleasant (and include an increased risk of cancers and diabetes). It also reduces the chance of a second transplant being required due to rejection of the first one.

"Safely freeing patients from lifelong immunosuppression after a kidney transplant is possible," says Alice Bertaina, an associate professor of pediatrics at Stanford University in California.

The innovative technique works by safely transplanting the donor's immune system into the patient – via stem cells from bone marrow – before the kidney also moves over: dual immune/solid organ transplant or DISOT. This has been tried before, but with a limited amount of success.

Here, an extra process was added. The researchers performed an alpha-beta T cell and CD19 B-cell depletion, which meant removing the types of immune cells that cause graft-versus-host disease or GVHD – a potentially lethal complication that has been at risk of developing when similar techniques have been used in the

past.

With a reduced threat of GVHD, the process was much safer. The removal of the alpha-beta T cells is relatively 'gentle', making it suitable for medically vulnerable children, and it enables genetically half-matched transplants (from a parent). The removed cells recover naturally in the patient in 60-90 days, building up the immune system again.

Other tweaks were made, including a reduction in the toxicity of the chemotherapy and radiation treatment required before the transplant. Still, some pretty grueling preparation work is required to knock out the immune system of the patient and get the body prepared for receiving a new organ.

The three children given the kidney transplants in this way have an extremely rare genetic disease called Schimke immuno-osseous dysplasia (SIOD), which restricts the body's ability to fight off infection and can lead to kidney failure.

"This remarkable experience underscores the potential of combined or sequential hematopoietic stem-cell transplantation and kidney transplantation to correct disorders of hematopoiesis and immunodeficiency and to induce tolerance of the kidney allograft," write Thomas Spitzer and David Sachs from Massachusetts General Hospital in an accompanying editorial.

"SIOD is a rare disorder that involves immunodeficiency, which undoubtedly contributed to the achievement of successful donor HSCT engraftment."

While SIOD and all of its complications remains something the children have to deal with, they are now all the owners of kidneys that are working as they should be. The transplants have been successful for at least 22 and 34 months, the researchers report.

"These were unique patients in which we had to do the stem cell transplant and a kidney transplant," says Bertaina.

"They are doing everything: they go to school, they go on vacation, they are doing sports. They are having completely normal lives."

The next steps are to expand the number of patients and the number of conditions that this could work for, since for now it's only been demonstrated in patients with SIOD, making them especially suited to the procedure.

Of particular interest to the research team are patients who have already had a kidney transplant rejected by their bodies. That happens in up to half of all cases in children, leading to hypersensitized immune systems that most likely wouldn't accept a second kidney through a normal transplant procedure.

Children will be the first to benefit, then the researchers are going to work up to older ages. Eventually, the technique could even be adapted to cover transplants of organs other than kidneys, but it's going to take a while.

"That's a challenge, but it's not impossible," says Bertaina.

The research has been published in the *New England Journal of Medicine*.

***https://bit.ly/3xCQyIO***

## Tight budgeters beware: Skip the coffee before shopping

***If you're trying to scale back on impulse purchases, then you may want to hold off on drinking that coffee.***

An international study led by the University of South Florida (USF) found that caffeine impacts what you buy and how much you spend when shopping.

The research team ran three experiments in retail stores—an industry that's increasingly been adding coffee bars near their entrances. In their study published in the *Journal of Marketing*, they found that shoppers who drank a cup of complimentary caffeinated coffee prior to roaming the stores spent about 50% more money and bought nearly 30% more items than shoppers who drank decaf or water.

"Caffeine, as a powerful stimulant, releases dopamine in the brain, which excites the mind and the body. This leads to a higher energetic state, which in turn enhances impulsivity and decreases self-control," said lead author Dipayan Biswas, the Frank Harvey Endowed Professor of Marketing at USF. "As a result, caffeine intake leads to shopping impulsivity in terms of higher number of items purchased and greater spending."

The experiments consisted of setting up an espresso machine at the entrances of a retail chain and home goods store in France and a department store in Spain. Upon entry, more than 300 shoppers were provided a complimentary cup—with about half offered coffee that contained about 100 mg of caffeine and the others decaf or water. They then shared their receipts with the researchers as they exited the stores. The team found that caffeinated individuals purchased a significantly higher number of items and spent more money compared to those who had decaf or water.

Researchers found that caffeine also impacted what types of items they bought. Those who drank caffeinated coffee bought more non-essential items than the other shoppers, such as scented candles and fragrances. However, there was a minimal difference between the two groups when it came to utilitarian purchases, such as kitchen utensils and storage baskets.

They set up a fourth experiment in a lab and received similar results, this time regarding online shopping. They split the study pool of 200 business school students between individuals who consumed caffeinated and decaffeinated coffee and asked them to pick which items they'd purchase from a preselected list of 66 options. Those who consumed caffeine picked more items considered to be impulsive purchases, such as a massager, while others selected more practical items, such as a notebook.

"While moderate amounts of caffeine intake can have positive health benefits, there can be unintended consequences of being caffeinated while shopping. That is, consumers trying to control impulsive spending should avoid consuming caffeinated beverages before shopping," Biswas said.

***More information:*** *Dipayan Biswas et al, EXPRESS: Caffeine's Effects on Consumer Spending, Journal of Marketing (2022). DOI: 10.1177/00222429221109247*

***https://wb.md/3HBoGcC***

# What Are the Signs of Post-Acute Infection Syndromes?

***Clear definition and better understanding of post-acute infection symptoms is a necessary step toward developing a management approach***

**Paolo Spriano**

The long-term health consequences of COVID-19 have refocused our attention on post-acute infection syndromes (PAIS), starting a discussion on the need for a complete understanding of multisystemic pathophysiology, clinical indicators, and the epidemiology of these syndromes, representing a significant blind spot in the field of medicine. A better understanding of these persistent symptom profiles, not only for post-acute sequelae of SARS-CoV-2 infection (PASC), better known as long COVID, but also for other diseases with unexplainable post-acute sequelae, would allow doctors to fine tune the diagnostic criteria. Having a clear definition and better understanding of post-acute infection symptoms is a necessary step toward developing an evidence-based, multidisciplinary management approach.

## PAIS, PASC, or Long COVID

The observation of unexplained chronic sequelae after SARS-CoV-2 is known as PASC or long COVID.

Long COVID has been reported as a syndrome in survivors of serious and critical disease, but the effects also persist over time for subjects who experienced a mild infection that did not require admission to hospital. This means that PASC, especially when

occurring after a mild or moderate COVID-19 infection, shares many of the same characteristics as chronic diseases triggered by other pathogenic organisms, many of which have not been sufficiently clarified.

PAIS are characterized by a set of core symptoms centering on the following:

- ***Exertion intolerance***
- ***Disproportionate levels of fatigue***
- ***Neurocognitive and sensory impairment***
- ***Flu-like symptoms***
- ***Unrefreshing sleep***
- ***Myalgia/arthralgia***

A plethora of nonspecific symptoms are often present to various degrees. These similarities suggest a unifying pathophysiology that needs to be elucidated to properly understand and manage post-infectious chronic disability.

## Overview of PAIS

A detailed revision on what is currently known about PAIS was published in *Nature Medicine*. It provided various useful pieces of information to assist with the poor recognition of these conditions in clinical practice, a result of which is that patients might experience delayed or a complete lack of clinical care.

The following consolidated post-infection sequelae are mentioned:

- ***Q fever fatigue syndrome, which follows infection by the intracellular bacterium Coxiella burnetii***
- ***Post-dengue fatigue syndrome, which can follow infection by the mosquito-borne dengue virus***
- ***Fatiguing and rheumatic symptoms in a subset of individuals infected with chikungunya virus, a mosquito-borne virus that causes fever and joint pain in the acute phase***
- ***Post-polio syndrome, which can emerge as many as 15 to 40 years after an initial poliomyelitis attack (similarly, some other neurotropic microbes, such as West Nile virus, might lead to persistent effects)***
- ***Prolonged, debilitating, chronic symptoms have long been reported in a subset of patients after common and typically nonserious infections. For example, after mononucleosis, a condition generally caused by Epstein-Barr virus (EBV), and after an outbreak of Giardia lamblia, an intestinal parasite that usually causes acute intestinal illness. In fact, several studies identified the association of this outbreak of giardiasis with chronic fatigue, irritable bowel syndrome (IBS), and fibromyalgia persisting for many years.***
- ***Views expressed in the literature regarding the frequency and the validity of post-treatment Lyme disease syndrome (PTLDS) are divided. Although substantial evidence points to persistence of arthralgia, fatigue, and subjective neurocognitive impairments in a minority of patients with Lyme disease after the recommended antibiotic treatment, some of the early studies have failed to characterize the initial Lyme disease episode with sufficient rigor.***

## Symptoms and Signs

The symptoms and signs which, based on the evidence available, are seen more frequently in healthcare checks may be characterized as the following:

- ***Exertion intolerance, fatigue***
- ***Flu-like and 'sickness behavior' symptoms: fever, feverishness, muscle pain, feeling sick, malaise, sweating, irritability***
- ***Neurological/neurocognitive symptoms: brain fog, impaired concentration or memory, trouble finding words***
- ***Rheumatologic symptoms: chronic or recurrent joint pain***
- ***Trigger-specific symptoms: for example, eye problems post Ebola, IBS post Giardia, anosmia and ageusia post COVID-19, motor disturbances post polio and post West Nile virus***

## Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Patients with this disorder experience worsening of symptoms following physical, cognitive, or emotional exertion above their (very low) tolerated limit. Other prominent features frequently observed in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are neurocognitive impairments (colloquially referred to

as brain fog), unrefreshing sleep, pain, sensory disturbances, gastrointestinal issues, and various forms of dysautonomia. Up to 75% of ME/CFS cases report an infection-like episode preceding the onset of their illness. Post-infectious and post-viral fatigue syndromes were originally postulated as subsets of chronic fatigue syndrome. However, there appears to be no clear consensus at present about whether these terms should be considered synonymous to the ME/CFS label or any of its subsets, or include a wider range of post-infectious fatigue conditions.

**Practical Diagnostic Criteria**

From a revision of the available criteria, it emerges that the diagnostic criteria for a PAIS should include not only the presence of symptoms, but ideally also the intensity, course, and constellation of symptoms within an individual, as the individual symptoms and symptom trajectories of PAIS vary over time, rendering a mere comparison of symptom presence at a single time point misleading. Furthermore, when a diagnosis of ME/CFS is made, attention should be given to the choice of diagnostic criteria, with preference given to the more conservative criteria, so as not to run the risk of overestimating the syndrome.

Asthenia is the cornerstone symptom for most epidemiological studies on PAIS, but it would be reductive to concentrate only on this rather than the other characteristics, such as the exacerbation of symptoms following exertion, together with other characteristic symptoms and signs that may allow for better identification of the overall, observable clinical picture in these post-infection syndromes, which have significant impacts on a patient's quality of life.