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Smokers, COPD Patients Have High Levels of Coronavirus 'Entry Point' Enzyme in Their Lungs

Higher levels of ACE2, the entry receptor for SARS-CoV-2, in their lungs may explain increased risk of severe COVID-19 in these subpopulations

According to a new study published in the *European Respiratory Journal*, smokers and individuals with chronic obstructive pulmonary disease (COPD) have higher levels of angiotensin converting enzyme II (ACE2), which is the entry receptor for the SARS-CoV-2 coronavirus, in their lungs; this may explain the increased risk of severe COVID-19 in these subpopulations and highlight importance of smoking cessation.

"The data emerging from China suggested that patients with COPD were at higher risk of having worse outcomes from COVID-19," said lead author Dr. Janice Leung, a researcher at the University of British Columbia and St. Paul's Hospital.

"We hypothesized that this could be because the levels of ACE2 in their airways might be increased compared to people without COPD, which could possibly make it easier for the virus to infect the airway."

Dr. Leung and colleagues studied samples taken from the lungs of 21 COPD patients and 21 people who did not have COPD.

They tested the samples to gauge the level of ACE2 and compared this with other factors, such whether they were from people who never smoked, were current smokers or former smokers.

Not only did they find higher levels of ACE2 in COPD patients, they also found higher levels in people who were smokers.

The study authors then checked their new findings against two existing study groups, which together contain data on a further 249 people — some non-smokers, some current smokers and some former smokers.

Again, they found levels of ACE2 were higher in current smokers but lower in non-smokers and in those who were former smokers.

"We found that patients with COPD and people who are still smoking have higher levels of ACE2 in their airways, which might put them at an increased risk of developing severe COVID-19 infections," Dr. Leung said.

"Patients with COPD should be counseled to strictly abide by social distancing and proper hand hygiene to prevent infection."

"We also found that former smokers had similar levels of ACE2 to people who had never smoked. This suggests that there has never been a better time to quit smoking to protect yourself from COVID-19."

Janice M. Leung et al. ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19. European Respiratory Journal, published online April 8, 2020; doi: 10.1183/13993003.00688-2020

https://go.nature.com/34AJ2PK

Enormous hailstones inspire a new scientific size category: 'gargantuan'

An ordinary storm generated extraordinary hail that pounded an Argentine city.

A thunderstorm that at first seemed unexceptional to scientists turned out to produce some of the biggest hailstones on record, which pummeled central Argentina in 2018.

Powerful thunderstorms moved across the city of Villa Carlos Paz in Córdoba province in February 2018.

Matthew Kumjian at Pennsylvania State University in University Park and his colleagues collected photographs, videos and stories from residents about the incredible hail.

'Victoria's hailstone', which fell on central Argentina in 2018, weighed nearly half a kilogram and is named for the teenager who scooped it out of her front garden. **Victoria Druetta**

The biggest hailstone measured an estimated 18.8–23.7 centimetres wide. That's potentially bigger than the 20-centimetre world record currently held by a hailstone that fell in South Dakota in 2010. The scientists propose that any hailstones measuring 15 centimetres — about the size of a honeydew melon — or more should be categorized as gargantuan.

As the storm developed, weather-radar images showed nothing in it that hinted that it might yield such enormous hailstones. The authors say that meteorologists should work closely with the public to document gargantuan hail, to understand the conditions that lead to it. *Bull. Am. Meterol. Soc.* (2020)

https://bit.ly/3ahjwQV

How the first visitor to our Solar System may have formed—no alien technology required

Using computer simulations to understand how 'Oumuamua got its strange shape and trajectory

By Sid Perkins

When 'Oumuamua swooped into our Solar System in 2017, the object stirred up excitement. The strange shape and trajectory of this first known visitor from interstellar space prompted even some serious scientists to suggest it might be an alien probe. But a new study arrives at a much more mundane explanation.

'Oumuamua, which entered our Solar System from interstellar space in 2017, may be one of many remnants of a comet, asteroid, or small planet ripped apart by another star. **ESO/M. Kornmesser**

'Oumuamua—"scout" or "messenger" in Hawaiian—is about 100 meters long, or slightly longer than a U.S. football field, and at least six times longer than it is wide. The object also didn't follow a path shaped only by the Sun's gravitational attraction, which suggests 'Oumuamua was releasing gas as a comet might, even though observations hint that the object doesn't have the icy surface expected of a comet.

In a new study, Yun Zhang, an astrophysicist at the Cote d'Azur Observatory, and a colleague used computer simulations to understand how 'Oumuamua got its strange shape and trajectory by looking at what happens to various orbiting objects if they strayed, Icarus-like, too close to their own sun. For example, if an asteroid, a small rocky body that in our Solar System is often nothing more than a loosely packed pile of rubble, passed within 60,000 kilometers of its parent star, it would be stretched and then pulled apart by strong tides, creating a large number of tumbling, elongated fragments. Some of these would be ejected from the solar system into interstellar space, the researchers report today in *Nature Astronomy*.

If 'Oumuamua's parent body was instead a comet, it would suffer a similar fate. Strong gravitational tides would rip the comet apart, and much of the ice on its surface would be baked away by the close call, Zhang says. But some volatile ices, including water and carbon dioxide, would survive at depths of 10 to 50 centimeters below the object's rocky surface.

If such an object later swooped past a larger and warmer star such as our Sun, those ices could evaporate and slowly but steadily spew into space. If those emissions were uneven, they would act as tiny booster rockets and cause the sort of trajectory anomalies that astronomers have observed for 'Oumuamua. And if the remnants of an asteroid carried small amounts of water beneath its surface, its emissions also could result in a weird trajectory like 'Oumuamua has, Zhang notes.

Even a planet 10 times larger than Earth could be torn apart if it passed within 40,000 kilometers of a red dwarf, the team's simulations show. About half of the oddly shaped, water-bearing

shrapnel from such an event could escape the star and eventually pass through other solar systems.

Zhang and her colleague have put together "a compelling analysis," says Matthew Knight, an astronomer at the United States Naval Academy. Several of these general scenarios to explain 'Oumuamua's origins have been floating around for a while, he notes, "but these guys are the first to have actually run the numbers."

***Correction, 13 April, 4:20 p.m.:** Two erroneous distances mentioned in the original story have been corrected. Posted in: Space doi:10.1126/science.abc2271*

https://bit.ly/2xnxfIx

Longevity Gene May Protect against a Notorious Alzheimer's Risk Gene

Some nominally high-risk individuals may have a lower chance of developing dementia than once thought

By Gary Stix

Consumer genetic tests can sometimes result in a terrible surprise appearing in the same report that divulges whether one has a cilantro aversion or wet or dry earwax. Test takers may receive the devastating news that they have a version of a gene—*apolipoprotein E* epsilon 4 (*APOE* e4)—that greatly increases their chances of getting Alzheimer's disease. The shock can be so great that some will seek solace in a support group to help them adjust to the possibility that they could run into cognitive problems beginning in their 50s or 60s.

One thing that makes the information so difficult to absorb is that there is no certainty about it. A person with one copy of the *APOE* e4 gene is more than three times as likely to wind up with Alzheimer's (one copy can be inherited from each parent). A hit of two copies increases the risk by 10 times or more. *APOE* e4 may also reduce the age of the disease's onset by up to a decade.

Still, not everyone who is an *APOE* e4 carrier will ultimately receive a diagnosis for Alzheimer's, the most common form of dementia. Given the ambiguities, scientists have long wondered whether other genes might counterbalance *APOE* e4's effects. A new paper may have found a candidate for just such a gene.

An analysis across multiple studies—with results from more than 20,000 individuals—found that *APOE* e4 carriers between the ages of 60 and 80 who also had a particular variant of a gene called *klotho* (named for Clotho, one of the Greek Fates, who spins the thread of life) were 30 percent less likely to receive an Alzheimer's diagnosis than carriers without it. People in their late 70s with a single copy of the *klotho* variant were also less apt to experience the initial cognitive losses (mild cognitive impairments) that often precede an Alzheimer's diagnosis. Study participants with the relevant variant also had reduced signs of the hallmark clumps of beta-amyloid protein that turn up in the brain before symptoms arise.

The new study was published on Monday in *JAMA Neurology*. Two smaller investigations conducted in recent years had looked at whether *klotho,* a purported longevity gene, might provide some benefit for *APOE* e4 carriers. One of those studies affirmed that the gene variant did so, and the other suggested the opposite. Michael Greicius—senior author of the *JAMA Neurology* paper, an associate professor of neurology at Stanford University and medical director of the Stanford Center for Memory Disorders—had been considering doing research on *klotho* when he learned of the study with negative results. "I was kind of prepared to throw in the towel," he says. "But Michael Belloy [of Stanford], the first author on the [new] paper, had already gotten his teeth into this, thankfully. And we got all of these data sets about these *APOE* e4 interactions. And [they are] really quite strong and consistent."

The *klotho* variant studied by Greicius and his Stanford colleagues is not rare. Of the 10,000 subjects with at least one copy of *APOE* e4 examined by the researchers within the larger data compilation, there were 2,700 who carried the advantageous variant. *APOE* e4 is not uncommon either: the gene turns up in at least 15 to 20 percent of the population. It is present, however, in about half of the more than five million Alzheimer's cases in the U.S.

The new finding may add precision to the design of clinical trials and could potentially provide ideas for therapeutics. *APOE* e4 carriers are sometimes recruited for studies of drugs to prevent Alzheimer's because of the likelihood that they will get the disease. Excluding carriers who have the *klotho* variant might ensure that the pool of study participants is truly at high risk, as intended. Greicius and his colleagues' conclusions might also lead to new drug targets. "The whole pathway of proteins that involve *klotho* and its interaction with *APOE* e4 is now worth pursuing," he says.

Other scientists who were not involved with the research agree that the new results warrant taking a closer look at *klotho*. "I think these are important findings, and this genetic variant should be considered for incorporation into ongoing and future clinical research related to [Alzheimer's]," says David M. Holtzman, a professor and chair of the department of neurology at Washington University School of Medicine in St. Louis. He says that human-, animal- and cell-based research should now investigate why the *klotho* variant may partially protect *APOE* e4 carriers—and whether it might help early or late in the course of the disease. New studies must also focus on people who are not of northwestern European descent, as were those in the Stanford paper.

"I think this is an exciting finding," says Guojun Bu, who researches the *APOE* gene and is a professor and chair of the department of neuroscience at the Mayo Clinic. He points out that whereas *klotho* is considered a longevity gene, *APOE* e4 has been found to shorten life spans in humans—even when its link to Alzheimer's was discounted. But scientists have suspected that there are other genes that protect against its ill effects. In the case of *klotho,* a longevity gene may be countering an antilongevity one.

The Stanford study, Bu says, needs support from other research that examines *klotho* levels in both blood and cerebrospinal fluid and compares them with various measures of Alzheimer's biomarkers and pathology. Mice carrying a human version of the *APOE* e4 gene might also be used to look for relevant biological pathways that could explain these findings. And even some behavioral factors could be scrutinized. "As several lifestyle factors, including exercise and diet, are known to protect against *APOE* e4–related risk," Bu says, "it would also be interesting to examine whether they alter the levels of *klotho* as a potential underlying mechanism."

Dena Dubal, a *klotho* researcher who is an associate professor at the University of California, San Francisco, and an associate editor for *JAMA Neurology*, co-authored an accompanying commentary that called for further research on questions such as whether the gene could diminish *APOE* e4's disruption of cellular and brain-network activity. "The study carries exciting implications for future therapies," she says. "One wonders whether giving a boost of the *klotho* hormone itself, which drops in aging and Alzheimer's disease, could be a new treatment for individuals in preventing or treating Alzheimer's disease."

https://bit.ly/3ciyTd4

Loss of smell and taste validated as COVID-19 symptoms in patients with high recovery rate

Study suggests clinicians should include sensory impairment as standard screening measure

Loss of smell and taste has been anecdotally linked to COVID-19 infections. In a study published April 12, 2020 in the journal *International Forum of Allergy & Rhinology*, researchers at UC San

Diego Health report the first empirical findings that strongly associate sensory loss with COVID-19, the respiratory disease caused by the novel coronavirus.

"Based on our study, if you have smell and taste loss, you are more than 10 times more likely to have COVID-19 infection than other causes of infection. The most common first sign of a COVID-19 infection remains fever, but fatigue and loss of smell and taste follow as other very common initial symptoms," said Carol Yan, MD, an otolaryngologist and head and neck surgeon at UC San Diego Health. "We know COVID-19 is an extremely contagious virus. This study supports the need to be aware of smell and taste loss as early signs of COVID-19."

Yan and colleagues surveyed 1,480 patients with flu-like symptoms and concerns regarding potential COVID-19 infection who underwent testing at UC San Diego Health from March 3 through March 29, 2020. Within that total, 102 patients tested positive for the virus and 1,378 tested negative. The study included responses from 59 COVID-19-positive patients and 203 COVID-19-negative patients.

Yan said the study demonstrated the high prevalence and unique presentation of certain sensory impairments in patients positive with COVID-19. Of those who reported loss of smell and taste, the loss was typically profound, not mild. But encouragingly, the rate of recovery of smell and taste was high and occurred usually within two to four weeks of infection.

"Our study not only showed that the high incidence of smell and taste is specific to COVID-19 infection, but we fortunately also found that for the majority of people sensory recovery was generally rapid," said Yan. "Among the Covid-19 patients with smell loss, more than 70 percent had reported improvement of smell at the time of survey and of those who hadn't reported improvement, many had only been diagnosed recently."

Sensory return typically matched the timing of disease recovery. ***Interestingly, the researchers found that persons who reported experiencing a sore throat more often tested negative for COVID-19.*** ***(Italics mine)***

In an effort to decrease risk of virus transmission, UC San Diego Health now includes loss of smell and taste as a screening requirement for visitors and staff, as well as a marker for testing patients who may be positive for the virus.

Other known symptoms of COVID-19 include fever, fatigue, cough and difficulty breathing. Respondents in Yan's study were most often persons with milder forms of COVID-19 infection who did not require hospitalization or intubation. The findings, she said, underline the importance of identifying early or subtle symptoms of COVID-19 infection in people who may be at risk of transmitting the disease as they recuperate within the community.

"It is our hope that with these findings other institutions will follow suit and not only list smell and taste loss as a symptom of COVID-19, but use it as a screening measure for the virus across the world," Yan said.

Co-authors include: Farhoud Faraji, Divya P. Prajapti, Christine E. Boone and Adam S. DeConde, all at UC San Diego.

https://bit.ly/2RV5IFp

Tumors hijack the cell death pathway to live

Manipulating cell death signaling after radiation could offer a new way to treat cancers, new UT Southwestern study suggests

DALLAS - Cancer cells avoid an immune system attack after radiation by commandeering a cell signaling pathway that helps dying cells avoid triggering an immune response, a new study led by UTSW scientists suggests. The findings, published in a recent issue of *Nature Immunology*, could eventually lead to new ways to augment existing treatments to fight this disease.

Researchers have long known that radiation - a mainstay of treatment protocols for many types of cancerous tumors - kills cancer cells in two different ways: The high-energy beams smite some cells directly, and these dead cells leak DNA that triggers a tumor-fighting immune response through proteins known as interferons (IFNs).

But even though cancerous cells make up the vast majority of a tumor, explains study leader *Yang-Xin Fu, Ph.D.*, studies have shown that these cells secrete very little IFN themselves, muting the immune response that could eradicate them.

"We figured that tumor cells must have some mechanism to escape interferon production," Fu says.

To figure out what that mechanism might be, he and his colleagues tested 42 FDA-approved drugs that block various parts of cell signaling on mouse colon cancer cells growing in petri dishes, searching for any that might be able to prompt these cells to secrete abundant interferons after radiation. Their search identified a drug known as emricasan, often prescribed to liver transplant recipients to help prevent rejection. This drug broadly inhibits production of a family of enzymes known as caspases, which not only help trigger cell death but also muffle the immune system's response to dying cells.

Further experiments indicated that one particular member of this family known as caspase-9 (CASP9) was key for preventing the cancer cells from secreting IFN. When the researchers genetically manipulated cancer cells to turn off CASP9 production, radiation increased their IFN production thousands-fold compared with "wild type" cancer cells that hadn't been modified.

When the researchers placed these CASP9-deficient cancer cells into mice, their tumors completely regressed after radiation, compared with those carrying tumors made of wild type cells. Additional experiments showed that a particular population of immune cells, known as CD8+ T cells, were recruited by the secreted interferon and were responsible for this dramatic regression.

Peering deeper into the mechanism behind how CASP9 helps protect tumor cells from the immune system, the researchers looked for the molecular trigger behind the production of this enzyme. Because cells secrete DNA from the nucleus only after they're dead, the researchers looked to an event that occurs earlier after radiation damage: the secretion of DNA from mitochondria, the cell's power-generating organelles. When the researchers removed mitochondrial DNA from cancer cells, they no longer produced IFN when they were irradiated, suggesting that this was the triggering event.

Although blocking CASP9 production appears to be a promising way to boost the anti-tumor immune response, it comes with a significant drawback: When tumors in animal models lost CASP9 signaling, these masses found a new way to evade immune attack by stepping up production of a protein called programmed death-ligand 1 (PD-L1), which shields cancer cells from immune discovery.

However, when the researchers administered an antibody that blocked PD-L1, the tumors regressed again. Using a combination of CASP9 inhibitors with anti-PD-L1 could offer a new strategy for boosting the effects of radiation, Fu says.

"This approach could eventually give doctors the confidence that they're irradiating the tumor that they can see and using the immune system to knock out other tumor cells that they can't see," he adds. "Together, this may be able to give some patients long-lasting survival that's not yet achievable."

Other UTSW researchers who contributed to this study include Chuanhui Han, Zhida Liu, Yunjia Zhang, Aijun Shen, Chunbo Dong, Anli Zhang, Casey Moore, Zhenhua Ren, Changzheng Lu, Xuezhi Cao, Chun-Li Zhang, and Jian Qiao.

This study was supported by Texas CPRIT grants RR150072 and RR180725.

Dr. Fu holds the Mary Nell and Ralph B. Rogers Professor in Immunology.

https://bit.ly/2VaITzq

Could a 100-year-old vaccine protect against COVID-19?

Several clinical trials around the world are now examining whether this vaccine could protect against this new foe.

By Yasemin Saplakoglu - Staff Writer 3 days ago

Scientists around the world are racing to find ways out of the new coronavirus pandemic. Some are working to develop new drugs and vaccines, while others are looking to see whether therapies we already have may help against COVID-19.

In the latter category, researchers have dusted off one intriguing compound in our collective medicine cabinet — a century-old vaccine to fight tuberculosis, a bacterial disease that affects the lungs. A couple of early analyses, which have yet to be peer-reviewed, have found that countries that require this vaccine, called Bacillus Calmette–Guérin (BCG), seemed to have been hit less severely, in terms of both number and severity, by the coronavirus that causes the disease COVID-19.

Could this vaccine be protecting people from COVID-19? The short answer is: We don't know. But several clinical trials around the world are now examining whether this vaccine could protect against this new foe.

Related: 13 coronavirus myths busted by science

"I was originally quite skeptical" that the studies could tease apart all of the other factors that could be causing some countries to be hit harder with COVID-19 than others," said Paula Cannon, a distinguished professor of molecular microbiology and immunology at the University of Southern California's Keck School of Medicine, who is not a part of any of these studies. Among those factors are the quality of the healthcare system, measures put in place to fight the disease and testing capacity. Still, it is a "provocative idea" and the "data is tantalizing," Cannon said.

Dozens of countries, including Japan and China, require children — typically newborns — to receive the BCG vaccine as protection against tuberculosis, an infection that is typically more common in lower-income countries. Other countries, such as Spain, France and Switzerland, used to require the vaccine but stopped because the risk of catching the disease in those countries lessened, according to one of the preprint studies published in medRxiv on March 28. Other countries, such as the U.S., Italy and the Netherlands never had such a universal vaccine policy for the BCG vaccine.

But scientists have long known that "almost by lucky accident," the BCG vaccine doesn't just protect against tuberculosis, it also helps fight other viruses, respiratory infections in particular, Cannon said. The vaccine, "in some sort of unexpected and magical way, is like a broad immune booster," she said.

For example, one study conducted in Guinea-Bissau in West Africa found that children who were vaccinated with BCG had about a 50% reduction in overall mortality, largely because the vaccine reduced respiratory infections and sepsis, or blood poisoning, according to the medRxiv study. Other studies, mostly conducted in animals, have found similar broad-spectrum protections from the BCG vaccine.

Weakened, live bacteria vaccine

The BCG vaccine is made up of weakened forms of live Mycobacterium bovis, closely related to the bacteria that causes tuberculosis. It was first developed in the 1920s in Paris and later shipped all over the world.

Now, countries from Japan to Denmark have their own BCG vaccines, made using different formulations of live bacteria — and each one has varying degrees of immune boosting ability, said Dr. Ofer Levy, the director of the precision vaccines program at Boston Children's hospital and a professor at Harvard Medical School.

Typically, live vaccines provide a "strong and long-lasting immune response" and sometimes even "lifelong protection" against the germ, whereas inactivated forms of vaccines, such as those in flu shots don't provide immunity that's "as strong," according to the U.S. Department of Health and Human Services.

While most vaccines prompt one arm of the immune system — the adaptive immune system — to create antibodies that target very specific pathogens, the BCG vaccine taps into the other arm, the innate immune system. This system doesn't discriminate against pathogens and releases immune cells rather quickly to fight any foreign substance. The BCG vaccine thus boosts the body's production of non-specific immune cells.

The medRxiv study and another preliminary study recently published in Research Gate came to similar conclusions: there seemed to be a correlation between countries that require BCG vaccines and a reduced spread and severity of COVID-19 cases. For example, Portugal — which has required BCG vaccines for infants — has over 16,000 cases of COVID-19 but only 535 deaths whereas neighboring Spain has over 169,000 cases and over 17,000 deaths.

Similarly, Ireland, with 9,655 cases and only 334 deaths, requires the BCG vaccination, whereas the U.K. with 89,554 cases and 11,346 deaths no longer does. Based on these numbers, Ireland has a fatality rate 3.5% whereas the U.K. has a fatality rate of 12.7%.

Of course, there are big population number differences across these countries, along with other variables that could affect death and infection rates.

These preliminary studies are "very flawed," because many factors such as differences in wealth and testing ability, can affect the outcomes Levy told Live Science. But the authors are "doing the best they can in a very difficult situation." While there's no direct evidence that BCG vaccines will reduce people's risk of developing COVID-19, "I'm enthusiastic about the hypotheses," Levy said.

It's difficult to draw firm conclusions, but there's enough scientific evidence to prompt clinical trials, and his team is looking into starting one in the U.S, he said. Clinical trials analyzing the protective effects of the vaccine against COVID-19 are already underway in other countries, including Australia and the Netherlands.

CLOSE

Vaccination or revaccination?

"I'm kind of puzzled," by the implication that the BCG vaccine might be able to protect for such a long period of time once someone has received it as a baby, Cannon said. Indeed, it's not clear how long the BCG vaccine effects can last.

The second study, which also has not been peer-reviewed, analyzed how countries with re-vaccination policies — or booster shots — fared in the COVID-19 pandemic. That study found that countries without re-vaccination policies had a 5.2% case fatality rate, versus a0.6% case fatality rate in countries that required re-vaccination.

"The big kind of asterisk, if you like, against all of these studies, is that they are really dealing with massively incomplete information," Cannon said. "We're all guessing what the true infection rates and the case fatality rates are because there isn't widespread uniform testing in every country."

Still, "I applaud the authors for at least, you know, doing what they could with the available data and providing some very provocative hypotheses," she said. "The good news is they're very testable."

In another world, we would be doing animal experiments to test this hypothesis. In this world, amid the coronavirus pandemic, we don't have time for that, she said. But the BCG vaccine has a "very safe track record," and likely can be tried in those who aren't old and who don't have weakened immune systems (since this is a live

vaccine, it can potentially cause more side effects for older people or those with weakened immune systems), she added.

The human immune system is like an orchestra, "it's massively interconnected and what the BCG vaccine seems to do is maybe it gives like a little bit of extra control to the conductor," Cannon said. "So in the symphony of immune attack against respiratory viruses, the orchestra is able to go full blast, straightaway, all together, in sync, rather than kind of playing catch up."

https://bit.ly/34DK1Pf

'A bad time to be alive': Study links ocean deoxygenation to ancient die-off

Oxygen deficit in Earth's oceans contributed to a devastating die-off approximately 444 million years ago

In a new study, Stanford researchers have strongly bolstered the theory that a lack of oxygen in Earth's oceans contributed to a devastating die-off approximately 444 million years ago. The new results further indicate that these anoxic (little- to no-oxygen) conditions lasted over 3 million years - significantly longer than similar biodiversity-crushing spells in our planet's history.

Laminated black shales and cherts exposed on the Peel River, Yukon, Canada, that were deposited during the late Ordovician and earliest Silurian. These sediments show no evidence of organisms living on the seafloor due to anoxic conditions at the seabed. Researchers estimated the global extent of low-oxygen conditions during this time period using new trace metal isotope data and uncertainty modeling. **Erik Sperling**

Beyond deepening understandings of ancient mass extinction events, the findings have relevance for today: Global climate change is contributing to declining oxygen levels in the open ocean and coastal waters, a process that likely spells doom for a variety of species.

"Our study has squeezed out a lot of the remaining uncertainty over the extent and intensity of the anoxic conditions during a mass die-off that occurred hundreds of millions of years ago," said lead author Richard George Stockey, a graduate student in the lab of study co-author Erik Sperling, an assistant professor of geological sciences at Stanford's School of Earth, Energy & Environmental Sciences (Stanford Earth). "But the findings are not limited to that one biological cataclysm."

The study, published in *Nature Communications* April 14, centered on an event known as the Late Ordovician Mass Extinction. It is recognized as one of the "Big Five" great dyings in Earth's history, with the most famous being the Cretaceous-Paleogene event that wiped out all non-avian dinosaurs some 65 million years ago.

Water world

At the outset of the Late Ordovician event about 450 million years ago, the world was a very different place than it is today or was even in the age of the dinosaurs. The vast majority of life occurred exclusively in the oceans, with plants having just begun to appear on land. Most of the modern-day continents were jammed together as a single super-continent, dubbed Gondwana.

An initial pulse of extinctions began due to global cooling that gripped much of Gondwana under glaciers. By approximately 444 million year ago, a second pulse of extinction then set in at the boundary between the Hirnantian and Rhuddanian geological stages largely - albeit inconclusively - attributed to ocean anoxia. Around 85 percent of marine species vanished from the fossil record by the time the Late Ordovician event ultimately passed.

The Stanford researchers and their study colleagues looked specifically at the second pulse of extinction. The team sought to constrain uncertainty regarding where in Earth's seas a dearth of

dissolved oxygen - as critical for oceanic biology then as it is now - occurred, as well as to what extent and for how long. Prior studies have inferred ocean oxygen concentrations through analyses of ancient sediments containing isotopes of metals such as uranium and molybdenum, which undergo different chemical reactions in anoxic versus well-oxygenated conditions.

Elemental evidence

Stockey led the construction of a novel model that incorporated previously published metal isotope data, as well as new data from samples of black shale hailing from the Murzuq Basin in Libya, deposited in the geological record during the mass extinction. The model cast a wide net, taking into account 31 different variables related to the metals, including the amounts of uranium and molybdenum that leach off land and reach the oceans via rivers to settle into the seafloor.

The model's conclusion: In any reasonable scenario, severe and prolonged ocean anoxia must have occurred across large volumes of Earth's ocean bottoms. "Thanks to this model, we can confidently say a long and profound global anoxic event is linked to the second pulse of mass extinction in the Late Ordovician," Sperling said. "For most ocean life, the Hirnantian-Rhuddanian boundary was indeed a really bad time to be alive."

Effects on biodiversity

The lessons of the past suggest that the deoxygenation increasingly documented in the modern oceans, particularly in the upper slopes of the continental shelves that bracket major landmasses, will put strain on many organism types - possibly to the brink of extinction. "There is no way that low oxygen conditions are not going to have a severe effect on diversity," Stockey said.

In this way, in addition to shedding light on Earth of a distant yester-eon, the study's findings could help researchers better model the planet as it is now.

"We actually have a big problem modeling oxygenation in the modern ocean," Sperling said. "And by expanding our thinking of how oceans have behaved in the past, we could gain some insights into the oceans today."

Co-authors on the study are with the Georgia Institute of Technology, Yale University, University of Portsmouth and Czech University of Life Sciences Prague.

The research was supported by the Alfred P. Sloan Foundation, National Science Foundation, Packard Foundation and NASA.

https://bit.ly/2XEsqoL

Copper's Virus-Killing Powers Were Known Even to the Ancients

The SARS-CoV-2 virus endures for days on plastic or metal but disintegrates soon after landing on copper surfaces. Here's why

By Jim Morrison smithsonianmag.com

When researchers reported last month that the novel coronavirus causing the COVID-19 pandemic survives for days on glass and stainless steel but dies within hours after landing on copper, the only thing that surprised Bill Keevil was that the pathogen lasted so long on copper.

Keevil, a microbiology researcher at the University of Southampton (U.K.), has studied the antimicrobial effects of copper for more than two decades. He has watched in his laboratory as the simple metal slew one bad bug after another. He began with the bacteria that causes Legionnaire's Disease and then turned to drug-resistant killer infections like Methicillin-resistant Staphylococcus aureus (MRSA). He tested viruses that caused worldwide health scares such as Middle East Respiratory Syndrome (MERS) and the Swine Flu (H1N1) pandemic of 2009. In each case, copper contact killed the pathogen within minutes. "It just blew it apart," he says.

In 2015, Keevil turned his attention to Coronavirus 229E, a relative of the COVID-19 virus that causes the common cold and pneumonia. Once again, copper zapped the virus within minutes

while it remained infectious for five days on surfaces such as stainless steel or glass.

“One of the ironies is, people [install] stainless steel because it seems clean and in a way, it is,” he says, noting the material’s ubiquity in public places. “But then the argument is how often do you clean? We don’t clean often enough.” Copper, by contrast, disinfects merely by being there.

Ancient Knowledge

Keevil’s work is a modern confirmation of an ancient remedy. For thousands of years, long before they knew about germs or viruses, people have known of copper’s disinfectant powers. "Copper is truly a gift from Mother Nature in that the human race has been using it for over eight millennia," says Michael G. Schmidt, a professor of microbiology and immunology at the Medical University of South Carolina who researches copper in healthcare settings.

The first recorded use of copper as an infection-killing agent comes from Smith's Papyrus, the oldest-known medical document in history. The information therein has been ascribed to an Egyptian doctor circa 1700 B.C. but is based on information that dates back as far as 3200 B.C. Egyptians designated the ankh symbol, representing eternal life, to denote copper in hieroglyphs.

As far back as 1,600 B.C., the Chinese used copper coins as medication to treat heart and stomach pain as well as bladder diseases. The sea-faring Phoenicians inserted shavings from their bronze swords into battle wounds to prevent infection. For thousands of years, women have known that their children didn't get diarrhea as frequently when they drank from copper vessels and passed on this knowledge to subsequent generations. "You don't need a medical degree to diagnose diarrhea," Schmidt says.

And copper’s power lasts. Keevil’s team checked the old railings at New York City’s Grand Central Terminal a few years ago. "The copper is still working just like it did the day it was put in over 100 years ago," he says. "This stuff is durable and the anti-microbial effect doesn't go away."

Long-Lasting Power

What the ancients knew, modern scientists and organizations such as the Environmental Protection Agency have confirmed. The EPA has registered about 400 copper surfaces as antimicrobial. But how exactly does it work?

Heavy metals including gold and silver are antibacterial, but copper’s specific atomic makeup gives it extra killing power, Keevil says. Copper has a free electron in its outer orbital shell of electrons that easily takes part in oxidation-reduction reactions (which also makes the metal a good conductor). As a result, Schmidt says, it becomes a “molecular oxygen grenade.” Silver and gold don’t have the free electron, so they are less reactive.

Copper kills in other ways as well, according to Keevil, who has published papers on the effect. When a microbe lands on copper, ions blast the pathogen like an onslaught of missiles, preventing cell respiration and punching holes in the cell membrane or viral coating and creating free radicals that accelerate the kill, especially on dry surfaces. Most importantly, the ions seek and destroy the DNA and RNA inside a bacteria or virus, preventing the mutations that create drug-resistant superbugs. “The properties never wear off, even if it tarnishes,” Schmidt says.

Schmidt has focused his research on the question of whether using copper alloys in often-touched surfaces reduces hospital infections. On any given day, about one in 31 hospital patients has at least one healthcare-associated infection, according to the Centers for Disease Control, costing as much as $50,000 per patient. Schmidt’s landmark study, funded by the Department of Defense, looked at copper alloys on surfaces including bedside rails, tray tables, intravenous poles, and chair armrests at three hospitals around the

country. That 43-month investigation revealed a 58 percent infection reduction compared to routine infection protocols.

Further research stalled when the DOD focused on the Zika epidemic, so Schmidt turned his attention to working with a manufacturer that created a copper hospital bed. A two-year study published earlier this year compared beds in an intensive care unit with plastic surfaces and those with copper. Bed rails on the plastic surfaces exceeded the accepted risk standards in nearly 90 percent of the samples, while the rails on the copper bed exceeded those standards on only 9 percent. "We again demonstrated in spades that copper can keep the built environment clean from microorganisms," he says.

Schmidt is also a co-author of an 18-month study led by Shannon Hinsa-Leasure, an environmental microbiologist at Grinnell College, that compared the bacterial abundance in occupied and unoccupied rooms at Grinnell Regional Medical Center's 49-bed rural hospital. Again, copper reduced bacterial numbers. "If you're using a copper alloy that's always working," Hinsa-Leasure says, "you still need to clean the environment, but you have something in place that's working all the time (to disinfect) as well."

Harnessing Copper

Keevil and Schmidt have found that installing copper on just 10 percent of surfaces would prevent infections and save $1,176 a day (comparing the reduced cost of treating infections to the cost of installing copper). Yet hospitals have been slow to respond. "I've been surprised how slow it has been to be taken up by hospitals," Hinsa-Leasure adds. "A lot of it has to do with our healthcare system and funding to hospitals, which is very tight. When our hospital redid our emergency room, we installed copper alloys in key places. So it makes a lot of sense when you're doing a renovation or building something that's new. It's more expensive if you're just changing something that you already have."

The Sentara Hospital system in North Carolina and Virginia made copper-impregnated surfaces the standard across 13 hospitals in 2017 for overbed tables and bed rails after a 2016 clinical trial at a Virginia Beach hospital reported a 78 percent reduction in drug-resistant organisms. Using technology pioneered in Israel, the hospital has also moved to copper-infused bedding. Keevil says France and Poland are beginning to put copper alloys in hospitals. In Peru and Chile, which produce copper, it's being used in hospitals and the public transit systems. "So it's going around the world, but it still hasn't taken off," he says.

If copper kills COVID-19, should you periodically roll a few pennies and nickels around in your hands? Stick with water, soap, and sanitizer. "You never know how many viruses are affiliated with the hand, so it may not completely get them all," Schmidt says. "It will only be a guess if copper will completely protect."

https://nyti.ms/2RGaS80

Despite Qualms, Arthritis Drug to Be Tested in Coronavirus Study

Even though it can make infections worse, it also may be able to keep the immune system from overreacting.

By Gina Kolata

An Eli Lilly drug for rheumatoid arthritis carries a warning on its label saying patients with infections should not take it because it can make infections worse. Yet the National Institutes of Health is about to test it in people hospitalized with coronavirus infections.

The study, whose innovative design is meant to find out — fast — what works, began at the end of February with the antiviral drug remdesivir made by Gilead Sciences. Four hundred patients have been treated either with remdesivir or a placebo. The results are now being analyzed and will be known within a few weeks.

Then the study will move on to baricitinib, made by Eli Lilly and Company, the company said.

Jennifer Routh, a spokeswoman at the National Institute of Allergy and Infectious Diseases, confirmed that the drug would now be tested in the federal trial but said the institute could offer no further comment.

Dan Skovronsky, chief scientific officer at Lilly, explained how and why baricitinib was chosen.

In February, when the new coronavirus was emerging as a pandemic threat, a company in the United Kingdom called Benevolent AI began using its artificial intelligence system to look for approved drugs that could possibly help people with coronavirus infections. It pointed toward baricitinib precisely because it suppresses the immune system. That, the company suggested, might allow it to quell a cytokine storm, a disastrous immune system response that kills patients.

As a coronavirus infection progresses, the amount of the virus infecting cells does not appear to be extremely high. But the immune system in some people goes into overdrive, sending out vast amounts of small proteins — cytokines — that trigger inflammation. Cytokine storms can kill patients with other diseases, including flu. This immune overreaction, some scientists think, could explain why some people infected with coronavirus have only mild symptoms while others have severe or fatal illnesses.

Benevolent AI also noted another potential advantage of baricitinib, said Dr. Vincent Marconi of Emory University, a key investigator in the federal trial. The drug might have anti-viral activity. That, plus the chance of subduing cytokine storms, Dr. Marconi said, "made a compelling case for baricitinib to be explored further in a clinical trial."

At Lilly, executives were a bit skeptical. "Our initial reaction was, 'Does it make sense to immunosuppress when patients are trying to fight off an infection?'" Dr. Skovronsky said. The warning label on the drug, he added, "tempered our enthusiasm."

As Covid-19 spread, some doctors started giving patients the drug anyway. It is a pill and there is a huge supply, making it easy for doctors to prescribe it off-label.

Dr. Skovronsky and his colleagues at Lilly were concerned.

"We are extremely cautious," said Patrik Jonsson, Lilly's president of biomedicines. "We cannot encourage use."

But such warnings were not enough.

"In desperate times, doctors are trying everything," Dr. Skovronsky said. "Various drugs are just being tried on patients in clinical trials without a control. It is really hard to interpret those kinds of data."

The company realized it had to accept the offer to contribute its drug for the federal trial.

Dr. Andre Kalil, a principal investigator in the federal trial, urged doctors and patients to refrain from using baricitinib until the results of the federal trial are known, which should be in a matter of months.

"This is a drug that has never been used before in this situation," he said. "That is why it needs to be tested in a randomized clinical trial. We don't know if it will help or harm. We have so much uncertainty."

The final design of the next phase of the federal trial is still being worked out, but the expectation is that it will include 600 to 800 patients, Dr. Marconi said. If the first phase of the study finds that remdesivir seems to help patients, half of the patients in the second phase will take remdesivir plus a placebo pill, and half will get remdesivir plus baricitinib.

If remdesivir is no better than or even worse than placebo — a very real possibility given the progress so far of a company-sponsored study in China — one group of patients will get a placebo pill and the other group will get baricitinib.

"We are looking for a strong effect," Dr. Skovronsky said. "If it works, it will be big. If it doesn't, we will move on."

https://bit.ly/34HmnS0

Aspirin linked to reduction in risk of several cancers of the digestive tract

Aspirin is associated with a reduction in the risk of developing several cancers of the digestive tract, including some that are almost invariably fatal, such as pancreatic and liver cancers.

The largest and most comprehensive analysis to date of the link between aspirin and digestive tract cancers, published in the leading cancer journal *Annals of Oncology* [1] today (Thursday), found reductions in the risk of these cancers of between 22% and 38%.

Aspirin has been linked to a reduction in the risk of bowel cancer for some time, and other, smaller analyses have found associations with cancers of the oesophagus (the food pipe or gullet) and stomach.

This analysis looked at evidence from 113 observational studies investigating cancers in the general population published up to 2019, of which 45 studies were on bowel cancer and included 156,000 cases. In addition to bowel cancer, the cancers investigated included those of the head and neck, oesophagus, stomach, the part of the stomach that connects to the oesophagus (gastric cardia), liver, gallbladder and bile ducts (hepato-biliary) and pancreas.

The researchers, led by Dr Cristina Bosetti (PhD), head of the Unit of Cancer Epidemiology at the Mario Negri Department of Oncology, Milan (Italy), found that regular use of aspirin, defined as taking at least one or two tablets a week, was associated with a significant reduction in the risk of developing all these cancers, apart from head and neck cancer.

Specifically, aspirin use was linked to 27% reduced risk of bowel cancer (45 studies), 33% reduced risk of oesophageal cancer (13 studies), 39% reduced risk of gastric cardia (ten studies), 36% reduced risk of stomach cancer (14 studies), 38% reduced risk of hepato-biliary cancers (five studies), and 22% reduced risk of pancreatic cancer (15 studies). Ten studies of head and neck cancer did not show a significant reduction in risk.

The senior author of the paper, Carlo La Vecchia (MD), Professor of Epidemiology at the School of Medicine, University of Milan, said: "There are about 175,000 deaths from bowel cancer predicted for 2020 in the EU, of which about 100,000 will be in people aged between 50 and 74. If we assume that regular use of aspirin increases from 25% to 50% in this age group, this would mean that between 5,000 to 7,000 deaths from bowel cancer and between 12,000 and 18,000 new cases could be avoided if further studies show that aspirin does indeed cause the reduction in cancer risk.

"Corresponding figures would be approximately 3,000 deaths each for oesophageal, stomach and pancreatic cancer, and 2,000 deaths from cancer of the liver. Given the unfavourable prognoses for these cancers, the number of new cases would be only slightly greater."

The researchers also analysed the effect of aspirin dose and duration on bowel cancer. They looked at low dose (100mg), regular (325mg) and high dose (500mg), combined with how many times a day, week or month it was taken.

Dr Bosetti said: "We found that the risk of cancer was reduced with increased dose; an aspirin dose between 75 and 100mg a day was associated with a 10% reduction in a person's risk of developing cancer compared to people not taking aspirin; a dose of 325mg a day was associated with a 35% reduction, and a dose of 500mg a day was associated with a 50% reduction in risk. However, the estimate for high dose aspirin was based on just a few studies and should be interpreted cautiously.

"Our findings on bowel cancer support the concept that higher aspirin doses are associated with a larger reduction in risk of the disease. However, the choice of dose should also take into

consideration the potential risk of stomach bleeds, which increases with higher aspirin doses.

"Compared to people who did not take aspirin regularly, the risk of bowel cancer declined in regular aspirin users up to ten years. The risk was reduced by 4% after one year, 11% after three years, 19% after five years and 29% after ten years."

Prof Carlo La Vecchia said: "These findings suggest there's a beneficial effect of aspirin in the prevention of bowel and other cancers of the digestive tract. The results for bowel, oesophageal and pancreatic cancers are consistent with evidence from clinical trials on aspirin in the prevention of heart and blood vessel diseases.

"The findings for pancreatic and other digestive tract cancers may have implications for the prevention of these highly lethal diseases. For pancreatic cancer, we found that risk of the disease declined by 25% after five years among people who took aspirin regularly compared to those who did not.

"Taking aspirin for the prevention of bowel cancer, or any other cancers, should only be done in consultation with a doctor, who can take account of the person's individual risk. This includes factors such as sex, age, a family history of a first-degree relative with the disease, and other risk factors. People who are at high risk of the disease are most likely to gain the greatest benefits from aspirin."

In addition to stomach bleeds, the side effects of aspirin include bleeding in other parts of the body and, occasionally, haemorrhages.

As the study is based on observational studies, it can only show that aspirin is associated with a reduced risk, and biases or confounding factors may partly explain its results. Other limitations include the fact that in some studies information may not reflect changes in aspirin use over time; the people in the studies might not remember or report their aspirin use accurately; and most studies did not have data on other medications that might affect the association between aspirin and the risk of cancer.

[1] *"Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis up to 2019", by C. Bosetti et al. Annals of Oncology. doi: https://doi.org/10.1016/j.annonc.2020.02.012*

https://bit.ly/2KlEWSp

We could soon be harvesting anti-viral antibodies from tobacco plants

"Plantibodies" represent a new avenue for treatments against fast moving viruses like influenza or coronavirus

Marnie Willman

With infectious disease outbreaks such as COVID-19 remaining a continual threat, and cancer rates on the rise, we rely on modern medical treatments like antibodies more than ever before. Antibody production is a major source of research animal use. Scientists use what are called "humanized mice," which are mice that have immune machinery to make human antibodies, to create antibodies to human medical treatments. Antibodies function by tagging "foreign bodies" like cancer cells, bacteria, viruses, or anything that isn't human, marking them for destruction by the immune system.

if anti-flu plantibodies can make people less infectious if they *do* become infected, that can limit viral spread on its own

Antibodies produced by mice are used for treating a wide variety of conditions, including cancer, Crohn's Disease, asthma, septicemia, and viral infections. However, obtaining these life-saving antibodies from the blood of mice is expensive, not to mention lethal for the animals themselves.

"Plantibodies" offer a new solution to this problem. These are antibodies made from plants that have been genetically engineered to express human antibodies. They've been in use, under the radar, for a while. Perhaps the most notable plantibody cocktail is the ZMapp Ebola vaccine that was used to try and stem the outbreak in the Dominican Republic of the Congo (though ultimately found to be less effective than other therapies).

Jun-Gyu Park and colleagues from University of Rochester Medical Center recently showed that human antibodies produced in tobacco plants can lower influenza infection rates in guinea pigs. When sick guinea pigs were treated with plantibodies and housed with healthy guinea pigs, they were less likely to transmit the virus to their unprotected cage-mates. The researchers concluded that these particular plantibodies have the ability to protect the animals from catching and transmitting influenza, even when they only took the plantibodies 6 hours before infection (compared to influenza vaccination, which requires 2 weeks or more to become effective).

The same researchers previously isolated an antibody that effectively killed the influenza virus in several cell and animal models. Building on this exciting finding, this research ported the same antibody to be produced in tobacco plants instead in a lab. Given the antibody worked as well against influenza virus in guinea pigs when produced in tobacco plants compared to cell culture methods, this provides an alternative with a much lower manufacturing cost.

There are concerns about plantibodies being allergenic in animals and humans. Because of the slightly different ways that plants produce proteins in comparison to animals, plantibodies may be recognized by a patient's body as being foreign, triggering an allergy-like immune response. In addition, plantibodies cannot be produced in all plants, further limiting options for production.

The current influenza vaccine is great, but it comes with a number of problems

Crop researchers produce plantibodies by genetically altering corn, alfalfa, tobacco, and a variety of other crops. However, scientists and politicians agreed it would be safest to reduce contamination potential by restricting plantibody production and research to "non-consumptive crops." This would ensure food crops wouldn't be accidentally contaminated with antibody-producing genes.

While it rarely makes headlines, seasonal influenza continues to cause 12,000-61,000 deaths and millions of cases of illness each year. The current influenza vaccine is great, but it comes with a number of problems, like the low number of people who get the vaccine each year, and the ever-changing nature of seasonal influenza varieties circulating. With ever-growing resistance to antivirals, influenza remains a great threat for a future pandemic.

Plantibodies could be an alternative to vaccination, which is often skipped entirely because it's seen as being unnecessary or ineffective, and antivirals, which are resulting in resistance. Plantibody-based vaccines are more stable at a greater range of temperatures compared to standard vaccines, which must be kept at a specific temperature and have a short life. Another fear regarding influenza vaccination is how vaccines are made: using a lot of eggs. This is a problem for those allergic to eggs, and for avian influenza, which can wipe out egg supplies, creating a shortage for vaccine creation come flu season. A plantibody treatment does not face these same crises, and tobacco plants are extremely hearty, non-consumptive crops, making them an ideal plantibody source.

The finding that guinea pigs not only transmit viruses less efficiently to their cage-mates, but also become less sickened shows another benefit to using plantibodies. Vaccines are intended to prevent us from getting diseases by giving our immune system a chance to build immunity against a dead or pseudo-virus before we come in contact with the real virus. However, being vaccinated against influenza doesn't necessarily mean you won't catch the flu. Mismatches between the vaccine strain and the strain circulating during that particular season, lack of herd immunity from low vaccination, and a host of other problems can still lead to infection. However, if anti-flu plantibodies can make people less infectious if they *do* become infected, that can limit viral spread on its own.

Plantibody research is of great interest to the medical system, animal ethics groups, and the economy. For ethical reasons, they are better than using mice, ferrets, rabbits, or other animals that traditionally have been used for antibody production. They are also more inexpensive than traditional antibody production because of the limited processing required compared to harvesting antibodies from animals like mice. They can be scaled up and produced in high quantities for clinical use, as was done for the ZMapp Vaccine, making their use a feasible medical treatment.

Plantibodies have the potential to increase accessibility to medical treatments for a variety of ailments which previously required expensive or difficult-to-transport medications — for example, vaccines often have to be kept at a low temperature during transport, which can be difficult in hot or developing countries. From influenza to Ebola, coronavirus to cancer, this new treatment is sweeping the pharmaceutical field, even claiming a line in the $7.2 million Euros Horizon 2020 project, which was awarded to the John Innes Center to fund their research on plantibody development.

https://bit.ly/2RGU40B

Harvard Study Says We Could Need Bouts of Social Distancing Until 2022

Repeated periods of social distancing may be required into 2022 to prevent hospitals from being overwhelmed.

A one-off lockdown won't halt the novel coronavirus and repeated periods of social distancing may be required into 2022 to prevent hospitals from being overwhelmed, Harvard scientists who modelled the pandemic's trajectory said Tuesday.

The study comes as the US enters the peak of its COVID-19 caseload and states eye an eventual easing of tough lockdown measures.

The Harvard team's computer simulation, which was published in a paper in the journal *Science*, assumed that COVID-19 will become seasonal, like closely related coronaviruses that cause the common cold, with higher transmission rates in colder months.

But much remains unknown, including the level of immunity acquired by previous infection and how long it lasts, the authors said.

"We found that one-time social distancing measures are likely to be insufficient to maintain the incidence of SARS-CoV-2 within the limits of critical care capacity in the United States," lead author Stephen Kissler said in a call with reporters.

"What seems to be necessary in the absence of other sorts of treatments are intermittent social distancing periods," he added.

Widespread viral testing would be required in order to determine when the thresholds to re-trigger distancing have been crossed, said the authors.

The duration and intensity of lockdowns can be relaxed as treatments and vaccines become available.

But in their absence, on and then off distancing would give hospitals time to increase critical care capacity to cater for the surge in cases that would occur when the measures are eased.

"By permitting periods of transmission that reach higher prevalence than otherwise would be possible, they allow an accelerated acquisition of herd immunity," said co-author Marc Lipsitch.

Conversely, too much social distancing without respite can be a bad thing. Under one modelled scenario "the social distancing was so effective that virtually no population immunity is built," the paper said, hence the need for an intermittent approach.

The authors acknowledged a major drawback in their model is how little we currently know about how strong a previously infected person's immunity is and how long it lasts.

At present the best guesses based on closely-related coronaviruses are that it will confer some immunity, for up to about a year. There

might also be some cross-protective immunity against COVID-19 if a person is infected by a common cold-causing coronavirus.

One thing however is almost certain: the virus is here to stay. The team said it was highly unlikely that immunity will be strong enough and last long enough that COVID-19 will die out after an initial wave, as was the case with the SARS outbreak of 2002-2003. Antibody tests that have just entered the market and look for whether a person has been previously infected will be crucial in answering these vital questions about immunity, they argued, and a vaccine remains the ultimate weapon.

https://bit.ly/2K90H7J

A Safe Alternative to Opioid Painkillers Could Come From Tarantula Venom

Painkiller that rivals opioids in effectiveness, but without the damaging side-effects

Michelle Starr

Many people have no love for spiders. But some of the venomous arthropods could hold the key to unlocking a painkiller that rivals opioids in effectiveness, but without the damaging side-effects, such as addiction.

(Edgar Stich/iNaturalist, CC-BY-NC)

Scientists have modified the neurotoxic venom of a tarantula called the Chinese bird spider (*Cyriopagopus schmidti*) to produce a protein that acts as a powerful painkiller. So far, it's proven effective in mice.

"Our findings could potentially lead to an alternative method of treating pain without the side-effects and reduce many individuals' reliance on opioids for pain relief," said chemical biologist Christina Schroeder of the University of Queensland in Australia.

Opioids - drugs derived from the latex of opium poppies, as well as synthetic and semi-synthetic versions - are among the best tools we have for treating various types of pain. But they're also hugely addictive, and overdose can be deadly. In 2018, opioids were involved in 46,802 overdose deaths; the White House has called it "the worst drug crisis in US history".

Even when these drugs are used as prescribed, it's not always smooth sailing. Common side effects include dizziness, nausea, drowsiness, constipation, and difficulty breathing.

The myriad problems with opioids have driven researchers to hunt for alternatives, leading to the exploration of the neurotoxic venom of snakes, arachnids, and even sea snails. These venoms affect the nervous system, and their numbing and paralytic properties can be exploited to relieve pain once the deadly part has been extracted or neutralised.

The venom of Chinese bird spiders contains a peptide that has also been explored in this context. It's called Huwentoxin-IV, and it works by inhibiting activation of the voltage-gated sodium channels required for the flow of sodium ions that can trigger pain receptors in the nervous system.

Previous work showed that this peptide can be exploited to dull pain in rats. But - aside from the effect on the sodium channels - Schroeder and colleagues later showed the importance of the cell membrane in this interaction, too.

Now, they have manipulated Huwentoxin-IV to improve its affinity for the cell membrane, to promising effect.

"Our study found that a mini-protein in tarantula venom from the Chinese bird spider, known as Huwentoxin-IV, binds to pain receptors in the body," Schroeder explained.

"By using a three-pronged approach in our drug design that incorporates the mini-protein, its receptor and the surrounding membrane from the spider venom, we've altered this mini-protein resulting in greater potency and specificity for specific pain receptors."

This ensures, she said, that the correct amount of Huwentoxin-IV attaches to the cell and cell membrane. And, when tested in mice, the most potent of the analogues the team developed resulted in a significant decrease in pain response compared to the control.

It's far from close to being ready, but each step in investigating how venoms work to dull pain brings us a little closer. And the team hopes that soon, we will be able to get closer still.

"We anticipate that new technologies, including cryogenic electron microscopy, will help us to overcome current limitations and allow future studies to focus on investigating the three components simultaneously, providing a complete picture of the different interactions," they wrote in their paper. The research has been published in the *Journal of Biological Chemistry*.

https://go.nature.com/3craP7O

Neutrinos could shed light on why the Universe has so much more matter than antimatter

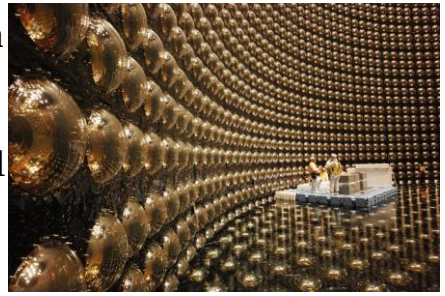
A major finding in particle physics reminds us of the importance of robust preliminary results — and paves the way for more exciting discoveries.

Nuclear-weapons physicists Clyde Cowan and Frederick Reines considered the neutrino “the smallest bit of material reality ever conceived of by man” [sic].

That was in a commentary[1] for *Nature* in 1956, published a few months after they published a paper in *Science*[2] reporting the experimental discovery of neutrinos. These subatomic particles lack an electrical charge and are extremely hard to detect, because they have very little interaction with other forms of matter. The pair wondered about the relationship between neutrinos and their counterparts, antineutrinos. With the benefit of hindsight, that turned out to be a rather important question.

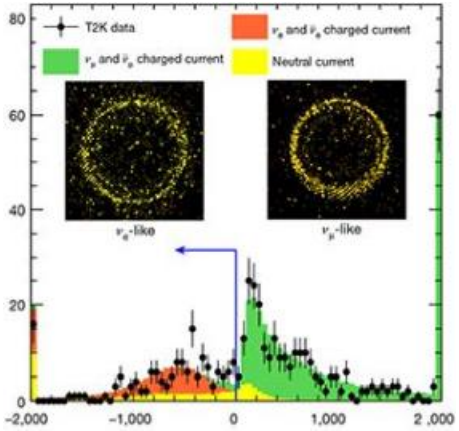
In this week’s *Nature*, researchers — directly following in the footsteps of Cowan and Reines — suggest that differences between neutrinos and antineutrinos might help to explain one of the Universe’s biggest mysteries[3].

Some 13.8 billion years ago, at the time of the Big Bang, every particle of matter in the early Universe should have been created together with a counterpart called antimatter. Antimatter is precisely the same as matter but with some opposite physical property, such as electrical charge. That, at least, is what current theories propose.



Inside the Super-Kamiokande neutrino detector during work on the detectors.
Kamioka Observatory, ICRR, Univ. Tokyo

The great mystery for physicists is why there seems to be so much more matter than antimatter in the current Universe. This, however, is just as well — if there had been equal quantities of both, each particle would have cancelled each other out in a blaze of energy, leaving the Universe full of just photons and dark matter.



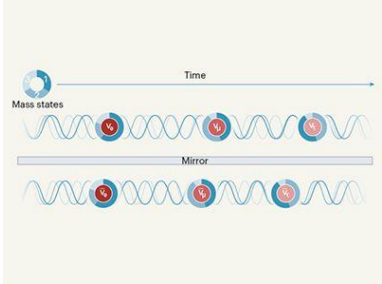
Read the paper: Constraint on the matter–antimatter symmetry-violating phase in neutrino oscillations

Ten years after Cowan and Reines discovered the neutrino, the Russian physicist and human-rights campaigner Andrei Sakharov proposed a mechanism for how the balance — or symmetry — between matter and antimatter might have come to be violated. One of Sakharov’s suggested reasons was that their symmetry was not perfect, and that each exhibited slightly different properties. This difference might have led to a surplus of matter during the cooling

that took place soon after the Big Bang. But was Sakharov right? A particle-physics experiment called Tokai to Kamioka, or T2K, run by an international collaboration of hundreds of physicists, is now offering a hint that he might have been.

In the T2K experiment, neutrinos are generated at the Japan Proton Accelerator Research Complex (J-PARC) at Tokai, on Japan's east coast. From there, they are fired underground and travel 295 kilometres towards a neutrino observatory called Super-Kamiokande on the west coast. The centrepiece of the observatory is a giant water tank lined with thousands of detectors ready to capture the light emitted as neutrinos interact with the water. Because neutrinos have an extremely small chance of interaction, these kinds of experiment take years to gather enough data for scientists to draw meaningful conclusions. It took T2K a decade to detect just 90 neutrinos and 15 antineutrinos — from around 10^{20} potential neutrino-generating collisions at J-PARC.

Using these data, the T2K collaboration measured the probability that a neutrino would oscillate between different physical properties that physicists call 'flavours' during its journey. The team then ran the same experiment with antineutrinos, and compared the numbers. If matter and antimatter are perfectly symmetrical, the probabilities should be the same.



Matter–antimatter symmetry violated

The results, however, suggest they are not. T2K detected a higher probability that neutrinos would change flavour during their 300-km journey — and a correspondingly lower probability for antineutrinos — than would be expected if they behaved identically.

Trust but verify

Such a finding, if it can be confirmed, lends weight to Sakharov's explanation from 1967 that matter and antimatter have different properties[4]. But there's a caveat: the current finding does not satisfy the required level of confidence — known as 5-sigma (5σ) — that particle physicists would typically demand to consider the result a discovery. The present T2K results are at a 3σ level of statistical significance — and this drops to 2σ if matter–antimatter symmetry is to be ruled out entirely.

Even so, it's important to publish such fundamental work as it progresses. Experiments in particle physics can take decades to be planned and built, so results that are not yet at the 5σ significance have a crucial role in informing the community's decisions on future investments.

The researchers could have waited longer. But even if they had, the T2K experiment is unlikely to have provided the additional data required to cross the 5σ finishing line. To get to 5σ, physicists will need results from the next generation of neutrino detectors. Fortunately, there are three such detectors due to come on stream: Hyper-Kamiokande, located near Super-Kamiokande, expected to start in 2027; DUNE in the United States, due to start in 2025; and JUNO in China, which aims to be the first of the three to go live, in 2022.

Time will tell if these preliminary observations hold. But at a time when big investments in high-energy physics are coming under increased scrutiny, this result reinforces the importance of continuing to search for answers to some of the Universe's deepest mysteries.

Nature ***580***, *305 (2020) doi: 10.1038/d41586-020-01022-3* ***References***

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https://bit.ly/34JCiim

Improving the treatment of periodontitis

Amoeba linked to severe gum disease

For the first time, researchers from Charité - Universitätsmedizin Berlin have shown that a unicellular parasite commonly found in the mouth plays a role in both severe tissue inflammation and tissue destruction. Most patients with severe and recurrent periodontitis (gum disease) showed an increased presence of the amoeba *Entamoeba gingivalis* inside their oral cavities. The effect of this amoeba is similar to that of Entamoeba histolytica, the parasite responsible for causing amebiasis. Once the parasite has invaded the gingival tissue, it feeds on its cells and causes tissue destruction. According to the researchers' findings, which have been published in the *Journal of Dental Research**, the two amoebae show similar mechanisms of tissue invasion and elicit a similar immune response in the host.

Periodontitis, or gum disease, is an inflammation of the gums and supporting structures of the teeth. It is one of the most common chronic diseases in the world. In Germany, approximately 15 percent of people are affected by a particularly severe form of this disease. If left untreated, periodontitis will lead to tooth loss. The disease also increases the risk of arthritis, cardiovascular disease and cancer. In patients with periodontitis, a decrease in the diversity of the oral flora coincides with an increase in the frequency of *E. gingivalis*. A team of researchers, led by Prof. Dr. Arne Schäfer, Head of the Periodontology Research Unit at Charité's Institute of Dental and Craniofacial Sciences, was able to show that oral inflammation is associated with colonization by the oral parasite *E. gingivalis*.

Scientists have long been aware of the virulence potential of this genus of amoebae. The gastrointestinal parasite E. histolytica, for instance, causes a disease known as amebiasis, one of the most common causes of death from parasitic diseases worldwide. "We have shown that an amoeba like *E. gingivalis*, which colonizes the oral cavity, will invade the oral mucosa and destroy gingival tissue. This enables increased numbers of bacteria to invade the host tissue, which further exacerbates inflammation and tissue destruction," says Prof. Schäfer. The international team of researchers was the first to describe precise roles of *E. gingivalis* in the pathogenesis of inflammation. During their analysis of inflamed periodontal pockets, the researchers detected evidence of the amoeba in approximately 80 percent of patients with periodontitis, but in only 15 percent of healthy subjects. Their observations revealed that, after invading the gums, the parasites move within the tissue, feeding on and killing host cells. Cell culture experiments showed that infection with *E. gingivalis* slows the rate at which cells grow, eventually leading to cell death.

The researchers concluded that the amoeba's role in inflammation shows distinct parallels to the pathogenesis of amebiasis. "*E. gingivalis* actively contributes to cell destruction inside the gingival tissue and stimulates the same host immune response mechanisms as E. histolytica during its invasion of the intestinal mucosa," explains Prof. Schäfer. "This parasite, which is transmitted by simple droplet infection, is one potential cause of severe oral inflammation."

Treatment success is often short-lived in patients with periodontitis. This might be due to the high virulence potential of this previously unnoticed, yet extremely common amoeba. Summing up the results of the research, Prof. Schäfer says: "We identified one infectious parasite whose elimination could improve treatment effectiveness and long-term outcomes in patients with gum disease." He adds: "Current treatment concepts for periodontitis fail to consider the possibility of infection by this parasite or its successful elimination." A clinical trial is underway to determine the extent to

which the elimination of this amoeba might improve treatment outcomes in patients with periodontitis.

**Bao X et al. Entamoeba gingivalis causes oral inflammation and tissue destruction. J Dent Res (2020), DOI: 10.1177/0022034520901738*

https://bit.ly/34JDwKu

Australia's Centre for Digestive Diseases cures Crohn's disease in new study

The Centre for Digestive Disease headed by Professor Thomas Borody has cured Crohn's disease as reported today by Dr Gaurav Agrawal in Gut Pathogens

The Centre for Digestive Disease (CDD) headed by Professor Thomas Borody has cured Crohn's Disease as reported today by Dr Gaurav Agrawal in *Gut Pathogens*.

Professor Borody is internationally recognised for curing stomach ulcers caused by *H. Pylori*, and is currently researching the infection connection associated with heart disease. He is also a leader in Faecal Microbiota Transfer (FMT) and pioneered the innovative treatment process in Australia.

Crohn's Disease was until today an incurable and debilitating gut disease that affects 75,000 people in Australia and almost 3 million globally. Curing Crohn's Disease has been a global priority with 1,455 Crohn's Disease clinical research studies currently listed on ClinicalTrials.Gov.

***Professor Thomas Borody* Credit: CDD**

According to *Gut Pathogens:*

"Prolonged remission has been achieved for 3-23 years with individualised treatments," patients being off all Crohn's therapies.

Professor Borody and his team devised a treatment of specific antibiotics combinations and doses, and/or FMT.

FMT is where the gut microbiome bacteria from a healthy donor is transferred to the gut of a patient with a damaged gut ecosystem, to repopulate the gut with healthy and balanced microbiome.

Each year, Crohn's Disease results in frequent hosptialisations and surgical procedures and is life threatening. The research study was funded by the CDD and involved 10 Australian patients. The team was led by Professor Borody and included Dr Gaurav Agrawal, Dr Annabel Clancy and Dr Roy Huynh.

Professor Borody has overseen more than 37,000 FMT processes at the CDD, making him the most experienced FMT specialist in the world. He and his world-class team use FMT to treat and manage a range of gut health conditions.

According to the report in *Gut Pathogens:*

"Crohn's disease (CD) is a chronic inflammatory process of the digestive tract characterized by deep ulcerations, skip lesions, transmural inflammation, fistulae and granulomas, with no known cure. It has a negative impact on many aspects of quality of life, including physical, social, psychological, and sexual functioning."

"Crohn's disease (CD) is rising in incidence and has a high morbidity and increased mortality. Current treatment use immunosuppressives but e cacy is suboptimal, and relapse is common. It has been shown that there is an imbalance present in the gut microbiome (dysbiosis) in CD with a possible infective aetiology--Mycobacterium avium subsp. paratuberculosis (MAP) being the most proposed. Antibacterial therapy and Faecal Microbiota Transplan- tation (FMT) are emerging treatments which can result in clinical and endoscopic remission, if employed correctly. The objective of this study was to report on the treatment and clinical outcomes of patients with CD in prolonged remission. "

Professor Borody said this breakthrough opens the way for Crohn's treatments using the antibiotic combination and a "crapsule" - an oral capsule of freeze dried donor faecal microbiota for FMT.

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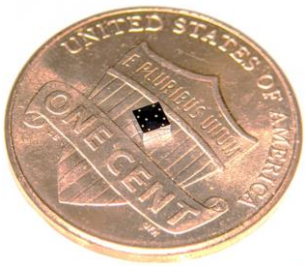
Lung-heart super sensor on a chip tinier than a ladybug

The future of socially distanced lung and heart health monitoring could lie in an inconspicuous yet incredibly sensitive MEMS chip

During a stroll, a woman's breathing becomes a slight bit shallower, and a monitor in her clothing alerts her to get a telemedicine check-up. A new study details how a sensor chip smaller than a ladybug records multiple lung and heart signals along with body movements and could enable such a future socially distanced health monitor.



A square black dot with mammoth abilities to record lung and heart data.
Georgia Tech / Ayazi lab

The core mechanism of the chip developed by researchers at the Georgia Institute of Technology involves two finely manufactured layers of silicon, which overlay each other separated by the space of 270 nanometers - about 0.005 the width of a human hair. They carry a minute voltage.

Vibrations from bodily motions and sounds put part of the chip in flux, making the voltage flux, too, thus creating readable electronic outputs. In human testing, the chip has recorded a variety of signals from the mechanical workings of the lungs and the heart with clarity, signals that often escape meaningful detection by current medical technology.

"Right now, medicine looks to EKGs (electrocardiograms) for information on the heart, but EKGs only measure electrical impulses. The heart is a mechanical system with muscles pumping and valves opening and shutting, and it sends out a signature of sounds and motions, which an EKG does not detect. EKGs also say nothing about lung function," said Farrokh Ayazi, Ken Byers Professor in Georgia Tech's School of Electrical and Computer Engineering.

Stethoscope-accelerometer combo

The chip, which acts as an advanced electronic stethoscope and accelerometer in one, is aptly called an accelerometer contact microphone. It detects vibrations that enter the chip from inside the body while keeping out distracting noise from outside the body's core like airborne sounds

"If it rubs on my skin or shirt, it doesn't hear the friction, but the device is very sensitive to sounds coming at it from inside the body, so it picks up useful vibrations even through clothing," Ayazi said.

The detection bandwidth is enormous - from broad, sweeping motions to inaudibly high-pitched tones. Thus, the sensor chip records all at once fine details of the heartbeat, pulse waves traversing the body's tissues, respiration rates, and lung sounds. It even tracks the wearer's physical activities such as walking.

The signals are recorded in sync, potentially offering the big picture of a patient's heart and lung health. For the study, the researchers successfully recorded a "gallop," a faint third sound after the "lub-dub" of the heartbeat. Gallops are normally elusive clues of heart failure.

The researchers published their results in the journal *npj Digital Medicine* on February 12, 2020. The research was funded by the Georgia Research Alliance, the Defense Advanced Research Projects Agency (DARPA), the National Science Foundation, and the National Institutes of Health. Study coauthor Divya Gupta, M.D., a cardiologist at Emory University, collaborated in testing the chip on human participants.

Hermetically sealed vacuum

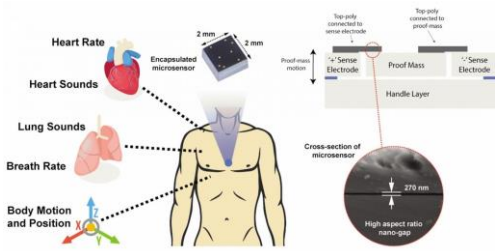
Medical research has tried to make better use of the body's mechanical signals for decades but recording some - like waves traversing multiple tissues - has proven inconsistent, while others -

like gallops - have relied upon clinician skills influenced by human error. The new chip produces high-resolution, quantified data that future research could match to pathologies in order to identify them.

"We are working already to collect significantly more data matched with pathologies. We envision algorithms in the future that may enable a broad array of clinical readings," Ayazi said.

Though the chip's main engineering principle is simple, making it work and then manufacturable took Ayazi's lab ten years, mainly because of the Lilliputian scale of the gap between the silicon layers, i.e. electrodes. If the 2-millimeter by 2-millimeter sensor chip were expanded to the size of a football field, that air gap would be about an inch wide.

"That very thin gap separating the two electrodes cannot have any contact, not even by forces in the air in between the layers, so the whole sensor is hermetically sealed inside a vacuum cavity," Ayazi said. "This makes for that ultralow signal noise and breadth of bandwidth that are unique."



On the right, the minuscule gap that allows the Lilliputian chip to collect high-resolution signals from the broad array of sound and motion sources on the left. **Georgia Tech / Ayazi lab**

Detects through clothing

The researchers used a manufacturing process developed in Ayazi's lab called the HARPSS+ platform (High Aspect Ratio Poly and Single Crystalline Silicon) for mass production, running off hand-sized sheets that were then cut into the tiny sensor chips. HARPSS+ is the first reported mass manufacturing process that achieves such consistently thin gaps, and it has enabled high-throughput manufacturing of many such advanced MEMS, or microelectromechanical systems.

The experimental device is currently battery-powered and uses a second chip called a signal-conditioning circuit to translate the sensor chip's signals into patterned read-outs.

Three sensors or more could be inserted into a chest band that would triangulate health signals to locate their sources. Someday a device may pinpoint an emerging heart valve flaw by turbulence it produces in the bloodstream or identify a cancerous lesion by faint crackling sounds in a lung.

These researchers co-authored the study: Pranav Gupta (first author), Mohammad Moghimi, Yaesuk Jeong and Omer Inan from Georgia Tech. The research was funded by the Georgia Research Alliance, the Defense Advanced Research Projects Agency (DARPA) Technology Office's Advanced Inertial Micro Sensors program (contract # N66001-16-1-4064), and by the National Science Foundation/National Institutes of Health Smart and Connected Health Program (grant # R01 EB023808). The team's work with human subjects was approved by Emory University and Georgia Institute of Technology Institutional Review Boards (IRB# H18248). Any findings, conclusions or recommendations are those of the authors and not necessarily of the sponsors.

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DNA Could Hold Clues to Varying Severity of COVID-19

Hundreds of scientists around the globe are launching studies in search of genes that could explain why some people fall victim to coronavirus infection while others escape relatively unscathed.

Marla Broadfoot

Among the many mysteries that remain about COVID-19, the disease caused by the new coronavirus, is why it hits some people harder than others. Millions of people have been infected, but many never get sick. Those who do can experience an ever-expanding array of symptoms, including loss of smell or taste, pink eye, digestive issues, fever, cough, and difficulty breathing. Although the elderly, those with pre-existing conditions such as heart disease, and men are most likely to suffer severe complications, hundreds of young and previously healthy people have died from the disease in the US alone.

In recent weeks, researchers have begun asking whether genetics could influence the severity of symptoms.

So far, they know "basically nothing," Wendy Chung, a clinical geneticist and physician at Columbia University, tells *The Scientist*. She is one of hundreds of scientists launching studies to interrogate the human genome for answers. Chung and her team are racing to "recycle" and bank nasal swabs and other clinical samples from COVID-19 patients across the New York-Presbyterian Hospital System, currently in the epicenter of the coronavirus pandemic.

The researchers plan to extract the patients' DNA and scan the genomes for tiny sequence variations associated with symptoms listed in their electronic health records.

Prior research has uncovered gene variants that can alter a person's chances of contracting an infectious disease. The most famous example is a mutation in the *CCR5* gene, which offers protection against HIV.

Other variants can affect what happens once the virus is inside the human body, leading to strikingly disparate outcomes from one person to the next, says Priya Duggal, a geneticist at Johns Hopkins University. Duggal has previously shown that variants in the *human leukocyte antigen* (*HLA*) genes, which influence the body's immune response, may explain why some people spontaneously clear hepatitis C infection whereas others are left with chronic disease.

Duggal says understanding how genetic background affects people's responses to infection may give scientists proteins or pathways to target to boost the immune response with a vaccine. That's the reason she recently expanded her lab's research from HIV, hepatitis, and other pathogens to look at the SARS-CoV-2 coronavirus. She is planning a study of younger people who have been hospitalized after contracting the virus to see if there is a genetic basis for their more serious disease, though she hesitates to guess what might come up in her search.

"I think we're so bad at predicting [which genes matter]. We've been terrible in the past and I think a lot of it is because we don't fully understand everything that's going on in the immune system," she says. One of the reasons COVID-19 can be so fatal to some people is because of their bodies elicit an overzealous immune response called a cytokine storm, which may originate in their DNA. A small study of patients who died from the 2009 H1N1 flu outbreak found that many carried mutations that triggered this self-destructive flood of cytokine molecules.

Results from studies on the genetics of COVID-19 susceptibility and severity are beginning to trickle in. One study suggests that variants in the *HLA* genes likely play a role. Others point to differences in the ABO blood type, as well as variants in the *ACE2* gene, which codes for the protein SARS-CoV-2 latches onto to infect human cells. But the findings are all preliminary, and require follow-up with larger datasets.

Andrea Ganna, a biostatistician at the University of Helsinki, is leading a major effort to pool data from genomics projects around the globe. The COVID-19 Host Genetics Initiative includes 117 studies on its website, and more than 439 scientists on its Slack channel. Ganna says several big biobanks have agreed to share the DNA data they have been gathering since before the pandemic, including the Penn Medicine Biobank, which has 60,000 participants; FinnGen, which has collected DNA from 5 percent of Finland's entire population; and the UK Biobank, one of the world's largest with samples from 500,000 volunteers.

"I'm quite confident when these big players come on board, we can grow our databases exponentially in the next month and that we will find something," says Ganna, who is hoping to identify gene variants associated with COVID-19 outcomes.

Earlier this month, the personal genomics company 23andMe announced it would be tapping its database of more than

10 million customers for clues. Joyce Tung, 23andMe's vice president of research, says her group plans to roll out surveys to the more than 80 percent of customers who have consented to be part of research. They hope to get hundreds of thousands of volunteers to enroll in the study, which will ask questions about their social distancing measures, symptoms, and COVID-19 test results.

Unique challenges of collecting genomic data during the pandemic

Every new positive case of COVID-19 provides another valuable data point for genomic studies. But if the pandemic wanes significantly, it is possible some studies may never be completed. "In some ways we're playing a weird game, because the best scenario would be if we can't get enough data because there weren't enough cases," says Tung.

For now, the rapidly moving nature of the pandemic, and the infection itself, poses unique challenges. For their study, Chung's and her colleagues have already identified thousands of positive cases, which they are consenting remotely. Several times, coordinators have called potential study subjects after they've been discharged, only to find out they've died.

Chung, who pivoted her own work on rare diseases to contribute to COVID-19 research, says she feels a tremendous sense of urgency. "We think about what we can learn in two weeks, not what we can learn in two years," says Chung. "Literally, my teams are working seven days a week, 16 hours a day."

The same issue that has hampered efforts to stem the spread of the coronavirus—the lack of widespread testing—is also complicating research to understand its biology. For instance, just this week, New York City added more than 3,700 people to its death toll who were presumed to have died of the coronavirus but had never tested positive. "If we don't have widespread testing, then I can't rely on that to tell me that someone was positive or not," says Duggal.

If scientists are successful in identifying genes that presage the infection's most devastating effects, they could more effectively triage the patients who need medical attention. If they get lucky, they might even uncover genes that make some people resistant, granting them the return to normalcy that so many people crave. So far, there's no evidence for this.

"I'm not convinced this is going to be the last one of these infectious disease crises," Chung says. "I think what we're trying to do is learn what we can for this one condition . . . and gain a better understanding of the immune response and generally how we fight infections."

https://wb.md/2wOa5KS

Unusual Presentations of COVID-19: 'Our Ignorance Is Profound'

The take-home message from a growing number of recent COVID-19 case reports is that the infection might be far more than a respiratory disease.

M. Alexander Otto

Although a cause-and-effect relationship is unknown, people with the virus have presented with or developed heart disease, acute liver injury, ongoing GI issues, skin manifestations, neurologic damage, and other problems, especially among sicker people.

For example, French physicians described an association with encephalopathy, agitation, confusion, and corticospinal tract signs among 58 people hospitalized with acute respiratory distress (N Engl J Med. 2020 Apr 15. doi: 10.1056/NEJMc2008597).

In particular, Yale New Haven (Conn.) Hospital is dealing with unexpected complications up close. Almost half of the beds there are occupied by COVID-19 patients. Over 100 people are in the ICU, and almost 70 intubated. Of the more than 750 COVID admissions so far, only about 350 have been discharged.

"Even in a bad flu season, you never see something like this; it's just unheard of," said Harlan Krumholz, MD, a Yale cardiologist and professor of medicine helping lead the efforts there.

Kidney Injuries Prominent

"When they get to the ICU, we are seeing lots of people with acute kidney injuries; lots of people developing endocrine problems; people having blood sugar control issues, coagulation issues, blood clots. We are just waking up to the wide range of ways this virus can affect people. Our ignorance is profound," Dr. Krumholz said, but physicians "recognize that this thing has the capability of attacking almost every single organ system, and it may or may not present with respiratory symptoms."

It's a similar story at Mt. Sinai South Nassau, a hospital in Oceanside, N.Y. "We've seen a lot of renal injury in people having complications, a lot of acute dialysis," but it's unclear how much is caused by the virus and how much is simply because people are so sick, said Aaron Glatt, MD, infectious disease professor and chair of medicine at the hospital. However, he said things are looking brighter than at Yale.

"We are not seeing the same level of increase in cases that we had previously, and we are starting to see extubations and discharges. We've treated a number of patients with plasma therapy, and hopefully that will be of benefit. We've seen some response to" the immunosuppressive "tocilizumab [Actemra], and a lot of response to very good respiratory therapy. I think we are starting to flatten the curve," Dr. Glatt said.

"Look for Tricky Symptoms"

The growing awareness of COVID's protean manifestations is evident in Medscape's Consult forum, an online community where physicians and medical students share information and seek advice; there's been over 200 COVID-19 cases and questions since January. Early on, traffic was mostly about typical pulmonary presentations, but lately it's shifted to nonrespiratory involvement. Physicians want to know if what they are seeing is related to the virus, and if other people are seeing the same things.

There's a case on Consult of a 37-year-old man with stomach pain, vomiting, and diarrhea, but no respiratory symptoms and a positive COVID test. A chest CT incidental to his abdominal scan revealed significant bilateral lung involvement.

A 69-year-old woman with a history of laparotomy and new onset intestinal subocclusion had only adhesions on a subsequent exploratory laparotomy, and was doing okay otherwise. She suddenly went into respiratory failure with progressive bradycardia and died 3 days later. Aspiration pneumonia, pulmonary embolism, and MI had been ruled out. "The pattern of cardiovascular failure was in favor of myocarditis, but we don't have any other clue," the physician said after describing a second similar case.

Another doctor on the forum reported elevated cardiac enzymes without coronary artery obstruction in a positive patient who went into shock, with an ejection fraction of 40% and markedly increased heart wall thickness, but no lung involvement. There are also two cases of idiopathic thrombocytopenia without fever of hypoxia.

An Italian gastroenterologist said: "Look for tricky symptoms." Expand "patient history, asking about the sudden occurrence of dysgeusia and/or anosmia. These symptoms have become my guiding diagnostic light" in Verona. "Most patients become nauseated, [and] the taste of any food is unbearable. When I find these symptoms by history, the patient is COVID positive 100%."

"Make Sure That They Didn't Die in Vain"

There was interest in those and other reports on Consult, and comments from physicians who have theories, but no certain answers about what is, and is not, caused by the virus.

Direct viral attack is likely a part of it, said Stanley Perlman, MD, PhD, a professor of microbiology and immunology at the University of Iowa, Iowa City.

The ACE2 receptor the virus uses to enter cells is common in many organs, plus there were extrapulmonary manifestations with severe acute respiratory syndrome (SARS), another pandemic caused by a zoonotic coronavirus almost 20 years ago. At least with SARS, "many organs were infected when examined at autopsy," he said.

The body's inflammatory response is almost certainly also in play. Progressive derangements in inflammatory markers – C-reactive protein, D-dimer, ferritin – correlate with worse prognosis, and "the cytokine storm that occurs in these patients can lead to a degree of encephalopathy, myocarditis, liver impairment, and kidney impairment; multiorgan dysfunction, in other words," said William Shaffner, MD, a professor of preventive medicine and infectious diseases at Vanderbilt University Medical Center, Nashville, Tenn.

But in some cases, the virus might simply be a bystander to an unrelated disease process; in others, the experimental treatments being used might cause problems. Indeed, cardiology groups recently warned of torsade de pointes — a dangerously abnormal heart rhythm — with hydroxychloroquine and azithromycin.

"We think it's some combination," but don't really know, Dr. Krumholz said. In the meantime, "we are forced to treat patients by instinct and first principles," and long-term sequelae are unknown. "We don't want to be in this position for long."

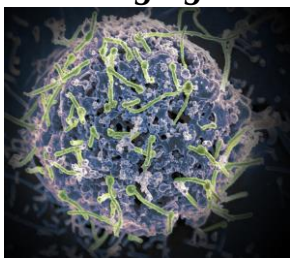
To that end, he said, "this is the time for us all to hold hands and be together because we need to learn rapidly from each other. Our job is both to care for the people in front of us and make sure that they didn't die in vain, that the experience they had is funneled into a larger set of data to make sure the next person is better off."

This story originally appeared on MDedge.com.

https://bit.ly/2XLUR4f

New universal Ebola vaccine may fight all four virus species that infect humans

Early preclinical tests in lab models are encouraging



CINCINNATI - Infectious disease scientists report early development of a potential universal vaccine for Ebola viruses that preclinical tests show might neutralize all four species of these deadly viruses infecting people in recent outbreaks, mainly in Africa.

The highly infectious and deadly Ebola virus is shown in this research photo from the National Institute of Allergy and Infectious Diseases. Ebola virus disease has an average fatality rate of about 50%, although rates in certain recent outbreaks have reached close to 90%, according to the World Health Organization. Researchers report in the Journal of Virology early development of a potential universal vaccine for Ebola. Preclinical tests show it may neutralize all four species of the virus infecting people. **NIAID**

Scientists at Cincinnati Children's Hospital Medical Center report their preclinical results in the *Journal of Virology*, published by the American Society for Microbiology.

Although still in early preclinical testing, researchers report that their data indicate that the prospective vaccine has potential to be a stand-alone protection from Ebola. It also could broaden and extend the durability of protective immunity induced by current live vaccines already being tested in clinical trials against individual Ebola virus species, said Karnail Singh, PhD, the study's co-principal investigator in the Division of Infectious Diseases.

"This could be a significant advancement in the global effort to prevent or manage Ebola outbreaks, especially if this vaccine used alone or in combination with another Ebola vaccine results in long-term and durable protective immunity against different Ebola viruses," Singh said.

A deadly Ebola outbreak in West Africa between 2013 and 2016 accelerated international efforts to develop vaccines for these highly infectious and harmful viruses. This led to development of recombinant Ebola vaccines in which glycoprotein from Zaire Ebola virus is engineered into another modified live viral vector. When administered, these live vaccines induce immune responses against the Ebola glycoprotein that, in turn, protect against any subsequent attack by the Ebola virus.

Singh and colleagues report that while the live-vector vaccines are producing encouraging results in clinical trials, until the current study none of the new vaccines under development have been shown to induce immune responses that cross-react against multiple Ebola virus species that cause the deadly disease in humans.

A Different Approach

The new vaccine takes a novel approach, according to the study. The researchers designed a bivalent, spherical Ebola virus-like particle (VLP) that incorporates two genetically diverse glycoproteins (one each from the Zaire Ebola virus and Sudan Ebola virus) on a spherical core.

This approach will not cause illness in the recipient as the VLPs lack the genetic material and do not multiply. The vaccine works by stimulating immune responses against Ebola that generate virus-fighting antibodies to attack the different virus species.

When the researchers administered their new Ebola VLP vaccine to appropriate animal models, it produced robust immune responses against Ebola virus species known to be pathogenic in humans.

Although the new vaccine uses glycoproteins from two Ebola virus species, Singh said it might work against all four known pathogenic Ebola viruses as responses to one of the glycoproteins generates cross-reactive responses against two other Ebola virus species.

More Testing Needed

The researchers emphasize that extensive additional preclinical testing of the prospective Ebola VLP vaccine is needed before it could potentially be tested in clinical trials.

A key collaborator on the multi-institutional study -- which included the University of Cincinnati College of Medicine, the Emory University School of Medicine, and the University of Louisiana's New Iberia Research Center - was Paul Spearman, MD, Division Director of Infectious Diseases at Cincinnati Children's.

Spearman said at the moment, vaccine challenge experiments are in the planning stages. They will involve working in collaboration with an institution that has Level 4 biosafety facilities and will require additional external funding to move this promising research forward.

"If the data from those studies is equally encouraging, the vaccine should be ready to progress to generation of clinical grade material for human trials," he said.

The study was funded in part by a pilot grant to Singh and Spearman by Innovation Ventures, the technology commercialization arm of Cincinnati Children's, the Cincinnati Children's Research Foundation and support from the New Iberia Research Center, University of Louisiana at Lafayette. Partial support for the study's use of virus-like-particle (VLP) platforms to conduct Ebola vaccine research was provided by the National Institutes of Health.

https://bit.ly/2z7tuXW

Influenza: researchers show that new treatment reduces spread of virus

The antiviral drug, baloxavir (tradename Xofluza), is the first treatment for influenza with a new mode of "action" to be licensed in nearly 20 years.

It was approved in Australia in February 2020 by the Therapeutic Goods Administration (TGA) and has been used to treat influenza in Japan, the USA, and several other countries since 2018.

Researchers at the WHO Collaborating Centre for Reference and Research on Influenza at the Peter Doherty Institute for Infection

and Immunity (Doherty Institute - a joint venture between the University of Melbourne and Royal Melbourne Hospital) and Imperial College London tested whether baloxavir could prevent the spread of influenza virus in an animal model in conditions that mimicked household settings, including direct and indirect contact. They also compared the treatment to oseltamivir (tradename Tamiflu), a widely prescribed influenza antiviral.

Published today in *PLoS Pathogens* is a detailed report of the study, which was conducted in ferrets - considered the gold standard animal model for evaluating influenza - detailing how baloxavir reduced the transmission of influenza across all settings, and did so immediately. Conversely, oseltamivir did not reduce the transmission of influenza to other ferrets.

First author Leo Yi Yang Lee, a medical scientist at the WHO Collaborating Centre for Reference and Research on Influenza, believes the results are an important breakthrough in our understanding of managing the influenza virus.

"Our research provides evidence that baloxavir can have a dramatic dual effect: a single dose reduces the length of influenza illness, while simultaneously reducing the chance of passing it on to others," Mr Lee said.

"This is very important, because current antiviral drugs only treat influenza illness in the infected patient. If you want to reduce the spread of influenza to others, people in close contact need to take antiviral drugs themselves to stave off infection."

Senior author Professor Wendy Barclay, head of the Department of Infectious Disease at Imperial College London, said if the results of the study were replicated in humans, the discovery could be a game changer in stemming outbreaks of influenza, particularly amongst vulnerable groups.

"We know that influenza can have serious and devastating outcomes for people with compromised immune systems, such as those in care facilities and hospitals, where finding more ways to reduce transmission is essential," Professor Barclay said.

A first-of-its-kind clinical trial is currently underway to test the effectiveness of baloxavir in reducing transmission amongst human household contacts by treating individuals infected with influenza and monitoring for infection in household members.

"If further trials prove successful, baloxavir could dramatically change how we manage seasonal influenza outbreaks and pandemic influenza in the future," Professor Barclay said.

https://wb.md/3bqOqCG

COVID-19 Pneumonia: Only Some Cases Are Like Severe ARDS

Italian clinicians warn that protocol-driven ventilator use could be doing more harm than good in some patients.

Liam Davenport

More details on the "remarkable combination" of distinctive features seen in patients with COVID-19 pneumonia are outlined by the Italian clinicians who warned that protocol-driven ventilator use could be doing more harm than good in some patients.

Luciano Gattinoni, MD, from Medical University of Göttingen, Germany, and colleagues first raised these concerns in a letter to the *American Journal of Respiratory and Critical Care Medicine.*

Now they have taken their observations further, writing in an editorial in *Intensive Care Medicine* on April 14. They argue that although COVID-19 pneumonia may fall under the definition of adult respiratory distress syndrome (ARDS), it is a "specific disease" with distinctive features.

They report that, in their series of 150 patients, only 20% to 30% showed disease that was similar to severe ARDS.

They also identified two distinct phenotypes (Type L and Type H), which they argue require different treatment approaches.

This runs counter to current guidance. The European Society of Intensive Care Medicine, which issued one of the first international guidelines on the management of critically ill patients with the disease, states that patients with COVID-19 receiving mechanical ventilation "should be managed similarly to other patients with acute respiratory failure in the intensive care unit (ICU)".

Other groups have also questioned this guidance and the current protocols for mechanical ventilation in COVID-19 pneumonia patients.

In a Medscape commentary, Barbara A. McLean, MN, RN, CCRN, a critical care clinical specialist at Grady Health System, Atlanta, Georgia, said that their experience also points to COVID-19 pneumonia as having two different lung pathologies, which need two separate ventilator protocols.

A frontline clinician in New York has also questioned current ventilator protocols, pointing out that some patients were presenting with symptoms that looked like high-altitude sickness, with hypoxia, but were still able to talk.

This was echoed in comments made recently by Massimiliano Sorbello, MD, AOU Policlinico San Marco University Hospital, Catania, Italy, who has observed a "dissociation" between clinical signs and laboratory results in COVID-19 patients.

Speaking in a webinar hosted by the European Society of Anaesthesiology (ESA) April 9, he noted that, based on what the numbers say, one would think the patient would be "gasping or almost in a coma." "But when you go and see the patient, he is awake, he is speaking to you, he doesn't look as bad" as his data would suggest, and "you are really starting to ask yourself why you should intubate such a patient," Massimiliano said.

He added that that, "at least at the beginning, it is not the ARDS we used to know...it's a different respiratory failure." But he warned that COVID-19 patients can "suddenly deteriorate."

Report on 150 Patients With COVID-19

In their latest study, Gattinoni and colleagues report on 150 patients with COVID-19 pneumonia. More than half of these patients had near-normal respiratory system compliance despite having severe hypoxemia, a finding that was corroborated by other colleagues working in Northern Italy.

Analyzing the cases further, they determined that there were different patterns of COVID-19, depending on the interaction of three factors:

- ***The severity of the infection, the host response, the physiologic reserve, and comorbidities***
- ***The ventilatory responsiveness to hypoxemia***
- ***The length of time between symptom onset and presenting to the hospital***

Gattinoni and collegues say that consideration of these factors led them to develop the view that there are two distinct COVID-19 phenotypes, Type L and Type H.

Type L was characterized by:

- ***Low elastane (high compliance)***
- ***A low ventilation-to-perfusion ratio, with a near-normal pulmonary artery pressure***
- ***A low lung weight on computed tomography (CT)***
- ***Low lung recruitability, with a very low proportion of non-aerated lung tissue***

These Type L patients may stay in this phenotype for a period of time and then either improve or worsen, in which case they shift to the opposite end of the phenotypic spectrum and develop Type H disease, the team notes.

Type H patients were found to have:

- ***High elastane, linked to increased edema***
- ***High right-to-left shunt***
- ***High lung weight, with a >1.5 kg increase on CT***
- ***High lung recruitability***

"The transition from Type L to Type H may be due to the evolution of the COVID-19 pneumonia," the authors write, but they suggest that this transition could also be a result of the "the injury attributable to high-stress ventilation." In other words, the mechanical ventilation may be doing more harm than good in these cases.

They set out a series of recommendations that emphasize the need to take into account the patient's clinical condition and minimize the risk of lung injury while they have Type L disease. The authors add that Type H COVID-19 pneumonia accounts for 20% to 30% of patients in their series, and "fully fits" the criteria for severe ARDS.

These Type H patients "should be treated as severe ARDS," including mechanical ventilation with higher positive end-expiratory pressure.

The researchers conclude that, while CT scan is the best way to distinguish patients with the two phenotypes, if that is not available, "signs which are implicit in Type L and Type H definition could be used as surrogates: respiratory system elastance and recruitability."

"Understanding the correct pathophysiology is crucial to establishing the basis for appropriate treatment," the authors stress. They have previously outlined the different treatment approaches for the distinct physiologies.

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

Am J Respir Crit Care Med. Published online March 30, 2020. Letter

Intensive Care Med. Published online April 14, 2020. Editorial

https://wb.md/3amy69J

Obesity Link to Severe COVID-19, Especially in the Under 60s

It is becoming increasingly clear that obesity is one of the biggest risk factors for severe COVID-19 disease, particularly among younger patients.

Liam Davenport and Lisa Nainggolan

Newly published data from New York show that among those under 60, obesity was twice as likely to result in hospitalization for COVID-19 and also significantly increased the likelihood that a person would end up in intensive care.

"Obesity [in people < 60 years] appears to be a previously unrecognized risk factor for hospital admission and need for critical care. This has important and practical implications when nearly 40% of adults in the US are obese with a body mass index [BMI] of ≥ 30," write Jennifer Lighter, MD, NYU School of Medicine/NYU Langone Health, and colleagues in their research letter published online April 9 in *Clinical Infectious Diseases*.

Similar findings in a preprint publication, yet to be peer reviewed, from another New York hospital show that, with the exception of older age, obesity (BMI > 40 kg/m^2) had the strongest association with hospitalization for COVID-19, increasing the risk more than sixfold.

Meanwhile, a new French study shows a high frequency of obesity among patients admitted to one intensive care unit for COVID-19; furthermore, disease severity increased with increasing BMI.

One of the authors told *Medscape Medical News* that many of the presenting patients were younger, with their only risk factor being obesity.

"Patients with obesity should avoid any COVID-19 contamination by enforcing all prevention measures during the current pandemic," say the authors, led by Arthur Simonnet, MD, Centre Hospitalier Universitaire de Lille, France. They also stress COVID-19 patients "with severe obesity should be monitored more closely."

Those With Obesity Are Young and Become Very Sick, Very Quickly

Coauthor of the French article, published online April 9 in *Obesity*, François Pattou, MD, PhD, told *Medscape Medical News* that when patients with COVID-19 began to arrive at their intensive care unit

in Lille there were young patients who did not have any other comorbidities.

"They were just obese," he observed, adding that they seemed "to have a very specific disease, something different" from that seen before, with patients becoming very sick, very quickly.

In their study, they examined 124 consecutive patients admitted to intensive care with COVID-19 between February 25 and April 5, 2020, and compared them with a historical control group of 306 patients admitted to the ICU at the same hospital for non-COVID-19-related severe acute respiratory disease in 2019.

By April 6, 60 patients with COVID-19 had been discharged from intensive care, 18 had died, and 46 remained in the unit. The majority (73%) were male, and their median age was 60 years.

Obesity and severe obesity were significantly more prevalent among the patients with COVID-19, at 47.6% and 28.2%, versus 25.2% and 10.8% among historical controls ($P < .001$ for trend).

A key finding was that those with a BMI > 35 kg/m^2 had a more than sevenfold increased risk of requiring mechanical ventilation (odds ratio [OR], 7.36; $P = .021$), compared to those with a BMI < 25 kg/m^2, even after adjusting for age, diabetes, and hypertension.

Obesity in Under 60s at Least Doubles Risk of Admission in US

The studies out of New York, one of which was stratified by age, paint a similar picture.

Lighter and colleagues found that of the 3615 individuals who tested positive for COVID-19 in their series, 775 (21%) had a BMI 30-34 kg/m^2 and 595 (16%) had a BMI ≥ 35 kg/m^2. Obesity wasn't a predictor of admission to hospital or the ICU in those over the age of 60 years, but in those younger than 60 years, it was.

Those under age 60 with a BMI 30-34 kg/m^2 were twice as likely to be admitted to hospital (hazard ratio [HR], 2.0; $P < .0001$) and critical care (HR, 1.8; $P = .006$) compared to those under age 60 with a BMI < 30 kg/m^2. Likewise, those under age 60 with a BMI ≥ 35 kg/m^2 were 2.2 ($P < .0001$) and 3.6 ($P < .0001$) times more likely to be admitted to acute and critical care. "Unfortunately, obesity in people < 60 years is a newly identified epidemiologic risk factor which may contribute to increased morbidity rates [with COVID-19] experienced in the US," they conclude.

And in the other US study, Christopher M. Petrilli, MD, NYU Grossman School of Medicine, and colleagues looked at 4103 patients with COVID-19 treated between March 1 and April 2, 2020, and followed to April 7. Just under half of patients (48.7%) were hospitalized, of whom 22.3% required mechanical ventilation and 14.6% died or were discharged to hospice. The research was posted April 11 on *medRxiv*. It showed that, apart from age, the strongest predictors of hospitalization were BMI > 40 kg/m^2 (OR, 6.2) and heart failure (OR, 4.3).

"It is notable that the chronic condition with the strongest association with critical illness was obesity, with a substantially higher odds ratio than any cardiovascular or pulmonary disease," they note.

Is Inflammation the Culprit?

Pattou believes that the culprit behind the increased risk of disease severity seen with obesity in COVID-19 is inflammation, mediated by fibrin deposits in the circulation, which his colleagues have seen on autopsy, and which "block oxygen passage through the blood."

This may help explain why mechanical ventilation can be less successful in these patients. "The answer is to get rid of this inflammation," Pattou observed.

Petrilli and colleagues also observe that obesity "is well-recognized to be a proinflammatory condition." And their findings show "the importance of inflammatory markers in distinguishing future critical from noncritical illness," they say, noting that, among these markers, early elevations in C-reactive protein and D-dimer "had the strongest association with mechanical ventilation or mortality."

Livio Luzi, MD, of IRCCS MultiMedica, Milan, Italy, has previously written on the relationship between influenza and obesity, and discussed with Medscape Medical News the potential lessons for the COVID-19 pandemic.

"Obesity is characterized by an impairment of immune response and by a low-grade chronic inflammation. Furthermore, obese subjects have an altered dynamic of pulmonary ventilation, with reduced diaphragmatic excursion," Luzi said.

These factors, alongside others, "may help to explain" the current results, and stress the importance of close monitoring of those with obesity and COVID-19, he concluded.

No relevant financial relationships were declared.

Clin Infect Dis. Published online April 9, 2020. Letter
medRxiv. Published online April 11, 2020. Full text
Obesity. Published online April 9, 2020. Full text

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'Silent Hypoxemia' and Other Curious Clinical Observations in COVID-19

Some of the unusual clinical features of patients with suspected or confirmed COVID-19

Gary S. Ferenchick, MD, MS; Hannah R.B. Ferenchick, MD

This transcript has been edited for clarity.

Gary S. Ferenchick, MD, MS, a professor of medicine at Michigan State University, interviewed his daughter, Hannah R.B. Ferenchick, MD, an emergency and critical care physician working on the frontline in a busy Detroit hospital, about some of the unusual clinical features of patients with suspected or confirmed COVID-19.

Gary S. Ferenchick, MD, MS: I'm Gary Ferenchick with Hannah Ferenchick, who has agreed to join us to talk about what's going on in Detroit, and also about PPE and decontamination processes. Why don't you introduce yourself?

Hannah R.B. Ferenchick, MD: I am Hannah Ferenchick. I'm an ER physician and medical intensivist. I split my time between the medical ICU and the emergency department at Detroit Medical Center.

Dr Gary Ferenchick: We were talking earlier about some of the not-well-described clinical scenarios that patients with definitive COVID might present with. One of these was the idea of "silent hypoxemia." Could you describe that?

Dr Hannah Ferenchick: Silent hypoxemia is being described in many of these COVID patients. That means the patient is very hypoxemic—they may have an oxygen saturation of about 85% on room air, but clinically they look very comfortable—they are not dyspneic or tachypneic and may not even verbalize a significant sense of shortness of breath. It's not every patient, but it has been interesting to see patients sitting there looking fairly normal, with a resting oxygen saturation much lower than you would expect for someone who doesn't have underlying pulmonary disease or other symptoms.

Dr Gary Ferenchick: What abnormalities are you seeing on standard or not-so-standard lab tests?

Dr Hannah Ferenchick: Some of the characteristic lab findings we are seeing are lymphopenia and elevated inflammatory markers (eg, CRP). A couple of other atypical findings seem to be specific for COVID—elevated LDH, ferritin, CPK, and procalcitonin levels. Some of the hematologic markers that we look at—the coagulation profile studies—are also abnormal, showing thrombocytopenia and elevated D-dimer levels.

That constellation of symptoms represents more of a clinical picture. A lot of times we have only a very high clinical suspicion, because in many parts of the country it still takes days to get back a confirmatory PCR test.

Much like we do for the flu, the confirmatory test is a nasopharyngeal swab that is run for COVID/coronavirus PCR. Unfortunately the sensitivity of that test is not great. Some studies

have quoted 75%-80%, so even a negative PCR does not necessarily rule out the disease, especially if you have a high clinical suspicion. A clinical suspicion is based on the typical symptoms. Many patients, although not all, will have symptoms of lower respiratory tract infection.

Dr Gary Ferenchick: So the right clinical scenario with the right hematologic/biochemical findings dramatically raises the chance that the patient has COVID?

Dr Hannah Ferenchick: Yes, and one thing that we have all been astonished by is how terrible some of these x-rays can look. There are a lot of typical findings on x-ray. Some describe them as looking like pulmonary edema, but the patient has no history of heart failure. Peripheral consolidation and ground-glass opacities are classically described. If you saw one of these x-rays from a patient with bacterial pneumonia, you would expect that patient to be very ill-appearing. Sometimes we get x-rays on patients who are sitting there, maybe mildly symptomatic on room air, and we are astonished by how terrible their x-rays look.

Unfortunately, imaging studies are something we haven't been able to rely on too much for diagnosis. Part of that is to maintain hospital safety, because to take a patient to CT scan, you have to consider the turnaround time for cleaning the CT scanner and the exposure of additional staff to a possibly infected patient. Some of those logistical considerations have limited the availability of radiography.

Gary S. Ferenchick, MD, MS, is a family physician and professor in the Department of Medicine at Michigan State University in East Lansing, Michigan. His daughter, Hannah R.B. Ferenchick, MD, is an assistant professor in the Department of Emergency Medicine, Division of Pulmonary & Critical Care and Sleep Medicine, at Wayne State University, Detroit, Michigan, and a medical intensivist and emergency medicine physician at Detroit Medical Center.

https://wb.md/2z8lPsl

How to Sanitize N95 Masks for Reuse: NIH Study

Vaporized hydrogen peroxide or UV light appears to eliminate the SARS-CoV-2 virus from the material

Marcia Frellick

Exposing contaminated N95 respirators to vaporized hydrogen peroxide (VHP) or ultraviolet (UV) light appears to eliminate the SARS-CoV-2 virus from the material and preserve the integrity of the masks' fit for up to three uses, a National Institutes of Health (NIH) study shows. Dry heat (70° C) was also found to eliminate the virus on masks but was effective for two uses instead of three.

Robert Fischer, PhD, with the National Institute of Allergy and Infectious Diseases in Hamilton, Montana, and colleagues posted the findings on a preprint server on April 15. The paper has not yet been peer reviewed.

Four Methods Tested

Fischer and colleagues compared four methods for decontaminating the masks, which are designed for one-time use: UV radiation (260 – 285 nm); 70° C dry heat; 70% ethanol spray; and VHP. For each method, the researchers compared the rate at which SARS-CoV-2 is inactivated on N95 filter fabric to that on stainless steel.

All four methods eliminated detectable SARS-CoV-2 virus from the fabric test samples, though the time needed for decontamination varied. VHP was the quickest, requiring 10 minutes. Dry heat and UV light each required approximately 60 minutes. Ethanol required an intermediate amount of time.

To test durability over three uses, the researchers treated intact, clean masks with the same decontamination method and assessed function via quantitative fit testing. Volunteers from the Rocky Mountain laboratory wore the masks for 2 hours to test fit and seal. The researchers found that masks that had been decontaminated

with ethanol spray did not function effectively after decontamination, and they did not recommend use of that method.

By contrast, masks decontaminated with UV and VHP could be used up to three times and function properly. Masks decontaminated with dry heat could be used two times before function declined.

"Our results indicate that N95 respirators can be decontaminated and re-used in times of shortage for up to three times for UV and HPV, and up to two times for dry heat," the authors write. "However, utmost care should be given to ensure the proper functioning of the N95 respirator after each decontamination using readily available qualitative fit testing tools and to ensure that treatments are carried out for sufficient time to achieve desired risk-reduction."

Reassurance for Clinicians

The results will reassure clinicians, many of whom are already using these decontamination methods, Ravina Kullar, PharmD, MPH, an infectious disease expert with the Infectious Diseases Society of America, told *Medscape Medical News*.

Kullar, who is also an adjunct faculty member at the David Geffen School of Medicine of the University of California, Los Angeles, said the most widely used methods have been UV light and VPH.

UV light has been used for years to decontaminate rooms, she said. She also said that so far, supplies of hydrogen peroxide are adequate.

A shortcoming of the study, Kullar said, is that it tested the masks for only 2 hours, whereas in clinical practice, they are being worn for much longer periods.

After the study is peer reviewed, the Centers for Disease Control and Prevention (CDC) may update its recommendations, she said.

So far, she noted, the CDC has not approved any method for decontaminating masks, "but it has said that it does not object to using these sterilizers, disinfectants, devices, and air purifiers for effectively killing this virus."

Safe, multiple use of the masks is critical in the COVID-19 crisis, she said. "We have to look at other mechanisms to keep these N95 respirators in use when there's such a shortage," she said.

Integrity of the fit was an important factor in the study. "All healthcare workers have to go through a fitting to have that mask fitted appropriately. That's why these N95s are only approved for healthcare professionals, not the lay public," she said.

The study was supported by the National Institutes of Health; the Defense Advanced Research Projects Agency; the University of California, Los Angeles; the US National Science Foundation; and the US Department of Defense.

https://bit.ly/2VhOOma

Here's a look at the coronavirus's complicated journey through the body

Patients with severe symptoms are developing damage in various organs, from the kidneys to the heart.

By Yasemin Saplakoglu - Staff Writer

From the very first cases of the novel coronavirus reported in China, doctors knew the virus targeted the lungs. But now, doctors are seeing patients with severe symptoms who are developing other damage around the body — from the kidneys to the heart.

"While the lungs are kind of taking the brunt of it, because our immunity is so low to coronavirus, it's actually able to move around and circulate throughout our whole body," said Dr. Eric Cioe-Peña, an emergency room physician and the director of global health at Northwell Health in New York who is also co-directing a coronavirus treatment hospital at the South Beach psychiatric facility on Staten Island.

The coronavirus enters the body through the respiratory tract — through the mouth or nose and into the lungs — so to infect a

person it needs to bind to an enzyme found on the surface of respiratory cells, Cioe-Peña said.

But once the coronavirus is actually in the body, it can get into the bloodstream, and from the bloodstream, SARS-CoV-2 can travel to, and invade, other organs. "Once it's in the human body, it doesn't have a problem getting into different types of cells," Cioe-Peña told Live Science. That is "unfortunate because it causes all these other organ problems."

In treating severe COVID-19 patients in the emergency room, Cioe-Peña has seen patients develop viral myocarditis, or infection of the heart muscle. When one of his patients with COVID-19 undergoes sudden cardiac death, or a sudden death caused by heart problems, it's typically from infections around the heart, he added.

Heart problems have been reported in COVID-19 patients before. More than 1 in 5 patients developed heart damage as a result of COVID-19 in Wuhan, China, one small study published March 27 in the journal JAMA Cardiology suggested.

SARS-CoV-2 can infiltrate both the heart and the lungs, because they each contain cells covered with the surface proteins known as angiotensin-converting enzyme 2 (ACE2), which serves as the gateway for the virus to enter cells, Live Science previously reported.

Other organs also contain this enzyme. The gastrointestinal (GI) tract, for example, has many of these gateways — and its thought that the virus might be getting into other organs in a similar way.

Some patients who don't have respiratory symptoms instead experience GI-tract symptoms, which means that the virus has infiltrated their small intestines and sometimes large intestines, Cioe-Peña said.

"And then we see elevated liver enzymes a lot," sometimes in mild cases, suggesting that SARS-CoV-2 is invading liver cells, he said. When liver cells die, they spill their enzymes into the bloodstream, he added. But the liver is "incredibly good at regenerating, so there's probably no long-term damage," to the liver from the virus, he said.

Sometimes patients also develop kidney failure, he said.

While some organ damage is a result of the virus directly invading cells, the immune system causes much of the rest, Cioe-Peña said. Cytokine storms — in which an army of immune cells are released into the bloodstream and then attack healthy tissues throughout the body — cause severe lung injury and can also cause multi-organ system failure, Cioe-Peña said. It's "an overwhelming response that essentially kind of shuts down our body."

It's not clear why some people have such an elevated immune response compared with others, but some people could be genetically prone to it, Dr. Erin Michos, the associate director of preventive cardiology at Johns Hopkins School of Medicine previously told Live Science.

Such cytokine storms can even affect the brain, and some COVID-19 patients may have cytokine storms in the brain, according to a previous Live Science report. What's more, loss of smell and taste have recently been added to the list of possible symptoms of COVID-19, which could suggest that the coronavirus might be able to invade the nervous system and the part of the brain responsible for the sense of smell, Live Science previously reported.

Because there's currently no cure or specific treatment for the coronavirus, treatment at the hospital involves supportive care for the affected organs.

It's not all bad news. "In very, very severe cases, there's likely some permanent damage," Cioe-Peña said. But "we've seen evidence of people that have complete recoveries." The liver and kidneys in particular can shut down and then come right back on and go back to normal.

Even with multifocal pneumonia, or pneumonia that affects more than one part of the lungs, "we see a lot of people's chest X-rays and lung scans return to normal," he added. So for most people, "the organs are going to recover, as long as you survive the infection." That's even true in patients with damage to the heart—an organ that's not as competent at regenerating as others. Patients who have myocarditis have a very high rate of mortality, Cioe-Peña said. But "most people with heart damage from myocarditis fully recover, assuming they survive."

None of this is particularly surprising. In many viruses, "we see a lot of organ involvement," Cioe-Peña said. Any new virus that hops to humans, "can kind of go rampant in the body," because our immune system hasn't seen anything similar, he added. Once individuals develop some immunity to it, the multi-organ involvement will be less common, he said.

It's still unknown how much immunity people who have recovered from the virus will have. But even if they don't gain full immunity, surviving the infection once will likely mean someone has a less severe infection with less multi-organ involvement the second time around, he said.

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Study Links Neutrophil Infiltration in Lungs to COVID-19 Symptoms

Activity of as neutrophils may contribute to organ damage and mortality in COVID-19

A little known yet powerful function of overactive white blood cells known as neutrophils — the ability to form neutrophil extracellular traps (NETs) — may contribute to organ damage and mortality in COVID-19, according to a study from the NETwork Consortium.

Patients with severe COVID-19 infection develop Acute Respiratory Distress Syndrome (ARDS), pulmonary inflammation, thick mucus secretions in the airways, extensive lung damage, and blood clots.

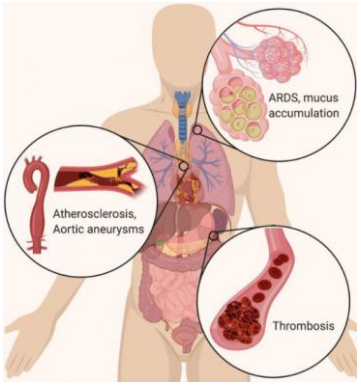
This late stage of the disease is difficult to manage. In the worst cases, patients require invasive mechanical ventilation, and still, a large number of patients die. This new study suggests that the severity of COVID-19 may result from neutrophils.

Part of the body's immune system, neutrophils detect bacteria and can expel their DNA to attack the bacteria with a gauzy web of DNA laced with toxic enzymes, called a NET.

These NETs can ensnare and digest the unwanted pathogen but in cases of ARDS, they damage the lungs and other organs.

"Given the clear similarities between the clinical presentation of severe COVID-19 and other known diseases driven by NETs, such as ARDS, we propose that excess NETs may play a major role in the disease," said Feinstein Institutes Professor Betsy Barnes, lead and co-corresponding author of the study.

"As samples from patients become available, it will be important to determine whether the presence of NETs associates with disease severity and/or particular clinical characteristics of COVID-19."



In the lungs, NETs drive the accumulation of mucus in cystic fibrosis patients' airways. NETs also drive acute respiratory distress syndrome (ARDS) after a variety of inducers, including influenza. In the vascular system, NETs drive atherosclerosis and aortic aneurysms, as well as thrombosis (particularly microthrombosis), with devastating effects on organ function. **Image credit: Cold Spring Harbor Laboratory.**

"NETs were identified in 2004, but many scientists have never heard of them. Most of the researchers in the NETwork have worked on NETs in other diseases, and when we started hearing about the symptoms of the COVID-19 patients, it sounded

familiar," said Cold Spring Harbor Laboratory cancer biologist Dr. Mikala Egeblad, senior and co-corresponding author of the study.

"We see in these patients severe lung damage known as ARDS, another serious problem caused by excess NETs and seen in cases of severe influenza," said co-author Dr. Jonathan Spicer, a thoracic surgeon in the Research Institute of the McGill University Health Centre and McGill University.

"In addition, their airways are often clogged with thick mucus and unlike most severe lung infections, these patients tend to form small clots throughout their body at much higher rates than normal."

"NETs have also been found in the blood of patients with sepsis or cancer, where they can facilitate the formation of such blood clots."

The NETwork Consortium is now pursuing studies into whether NETs are a common feature in COVID-19 cases.

If the findings show that excess NETs cause the severe symptoms of COVID-19, then a new avenue of treatments may be deployed to help COVID-19 patients. Current treatments used in other NET and neutrophil-driven diseases — like cystic fibrosis, gout, and rheumatoid arthritis — might dampen the activity of NETs in COVID-19 patients, reducing the need for invasive mechanical ventilation. The team's paper was published in the *Journal of Experimental Medicine*.

Betsy J. Barnes et al. 2020. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med 217 (6): e20200652; doi: 10.1084/jem.20200652

https://nyti.ms/3eCGuF9

C.D.C. Labs Were Contaminated, Delaying Coronavirus Testing, Officials Say

Fallout from the agency's failed rollout of national coronavirus kits two months ago continues to haunt U.S. efforts to combat the spread of the highly infectious virus.

By Sheila Kaplan

Sloppy laboratory practices at the Centers for Disease Control and Prevention caused contamination that rendered the nation's first coronavirus tests ineffective, federal officials confirmed on Saturday.

Two of the three C.D.C. laboratories in Atlanta that created the coronavirus test kits violated their own manufacturing standards, resulting in the agency sending tests that did not work to nearly all of the 100 state and local public health labs, according to the Food and Drug Administration.

Early on, the F.D.A., which oversees laboratory tests, sent Dr. Timothy Stenzel, chief of in vitro diagnostics and radiological health, to the C.D.C. labs to assess the problem, several officials said. He found an astonishing lack of expertise in commercial manufacturing and learned that nobody was in charge of the entire process, they said.

Problems ranged from researchers entering and exiting the coronavirus laboratories without changing their coats, to test ingredients being assembled in the same room where researchers were working on positive coronavirus samples, officials said. Those practices made the tests sent to public health labs unusable because they were contaminated with the coronavirus, and produced some inconclusive results.

In a statement on Saturday, a spokeswoman for the F.D.A., Stephanie Caccomo, said, "C.D.C. did not manufacture its test consistent with its own protocol."

The F.D.A. confirmed its conclusions late this week after several media outlets requested public disclosure of its inquiry, which assuredly is part of a larger federal investigation into the C.D.C. lab irregularities by the Department of Health and Human Services.

Forced to suspend the launch of a nationwide detection program for the coronavirus for a month, the C.D.C. lost credibility as the nation's leading public health agency and the country lost ground in

ways that continue to haunt grieving families, the sick and the worried well from one state to the next.

To this day, the C.D.C.'s singular failure symbolizes how unprepared the federal government was in the early days to combat a fast-spreading outbreak of a new virus and it also highlights the glaring inability at the onset to establish a systematic testing policy that would have revealed the still unknown rates of infection in many regions of the country.

The blunders are posing new problems as some states with few cases agitate to reopen and others remain in virtual lockdown with cases and deaths still climbing.

While President Trump and other members of his administration assert almost daily that the U.S. testing capacity is greater than anywhere else in the world, many public health officials and epidemiologists have lamented the lack of consistent, reliable testing across the country that would reflect the true prevalence of the infection and perhaps enable a return to some semblance of normal life.

Dr. Robert R. Redfield, the director of the C.D.C., and other health experts have long suggested that contamination in the labs might have been the culprit. But even as several officials at the F.D.A. late this week cited contamination as the cause, a spokesman for the C.D.C., Benjamin Haynes, asserted that it was still just a possibility and that the agency was still awaiting the formal findings of H.H.S.

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In a statement, however, he acknowledged that the agency's quality control measures were insufficient during the coronavirus test development. Since then, he said, "C.D.C. implemented enhanced quality control to address the issue and will be assessing the issue moving forward."

Initially, the C.D.C. was responsible for creating a coronavirus test that state and local public health agencies could use to diagnose Covid-19 in people, and then isolate them to prevent the spread of the disease.

"It was just tragic," said Scott Becker, executive director of the Association of Public Health Laboratories. "All that time when we were sitting there waiting, I really felt like, here we were at one of the most critical junctures in public health history, and the biggest tool in our toolbox was missing."

Mr. Becker said that public health laboratories started receiving the C.D.C. kits on Feb. 7, and by the next day members were already calling him to report that the test was not working accurately. He alerted both the C.D.C. and the F.D.A., which regulates medical devices, including laboratory tests.

"This is consistent with what we said was plausible when we found the problem at the beginning," Mr. Becker said. "When we found the problem, it seemed to our community that it was a contamination issue that would cause a problem to this extent."

The F.D.A. concluded that C.D.C. manufacturing issues were to blame and pushed the agency to shift production to an outside firm. That company, I.D.T., accelerated production of the C.D.C. test and says no more issues were reported.

Meanwhile, the F.D.A. also came under fire for not initially allowing commercial labs like Quest and LabCorp and others to begin ramping up production of their own tests.

More than two months later, nearly 700,000 Americans have become infected and close to 40,000 have died. Testing is still rationed in some states and uneven in others, and it can take days before doctors and patients receive results.

Many infectious disease and public health experts say testing is nowhere near widespread enough to reopen the country or return to some semblance of normal.

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The origin of the faeces

How to tell dog poo from human poo.

By Ian Connellan

Coprolites from Xiaosungang archaeological site, Anhui Province, China.
Jada Ko, courtesy of the Anhui Provincial Institute of Cultural Relics and Archaeology.

The archaeological record is littered – aha – with poo, a potential goldmine for insights into ancient health and diet, parasite evolution, and the ecology and evolution of the microbiome.

The issue for researchers has always been determining which species' faeces it is that they're looking at.

Now, a study published in the journal *PeerJ* and led by Maxime Borry and Christina Warinner, of the Max Planck Institute for the Science of Human History, Germany, has unveiled "coproID" – a reliable method of inferring sources of paleofaeces.

The specific origin of paleofaeces – often thousands of years old – can be difficult to determine for many reasons.

For instance, telling human and dog poo apart is particularly difficult: faecal deposits are similar in size and shape, occur at the same archaeological sites, and have similar compositions.

Further compounding the problem, dogs were a food source for many ancient societies, and given our canine friends' tendency to scavenge on human faeces, simple genetic analysis becomes problematic because it can return DNA from both species.

Enter coproID (coprolite identification). The method combines analysis of ancient host DNA with machine-learning software that's been "trained" on the microbiomes within modern faeces.

Applying coproID to both newly sequenced and previously published datasets, the German-US research team was able to reliably predict the sources of ancient faeces. A combination of host DNA and the distinct colonies of microbes living inside humans and dogs allow their faeces to be accurately distinguished.

"One unexpected finding of our study is the realisation that the archaeological record is full of dog poop," says Warinner, the study's senior author.

She also expects coproID to have broader applications, especially in the fields of forensics, ecology and microbiome sciences.

The ability to accurately identify the source of ancient poo enables the direct investigation of changes in the structure and function of the human gut microbiome throughout time. Researchers hope this will provide insights into food intolerances and a host of other issues in human health.

"Identifying human coprolites should be the first step for ancient human microbiome analysis," says Borry. "With additional data about the gut metagenomes of non-Westernised rural dogs, we'll be better able to classify even more ancient dog faeces as in fact being canine, as opposed to 'uncertain'."

As the catalogue of human and dog microbiome data grows, coproID will continue to improve its classifications and better aid researchers that encounter paleofaeces in a range of geographic and historical contexts.