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Origins of human language pathway in the brain at least 25 million years old

Scientists have discovered an earlier origin to the human language pathway in the brain, pushing back its evolutionary origin by at least 20 million years.

Previously, a precursor of the language pathway was thought by many scientists to have emerged more recently, about 5 million years ago, with a common ancestor of both apes and humans.

For neuroscientists, this is comparable to finding a fossil that illuminates evolutionary history. However, unlike bones, brains did not fossilize. Instead neuroscientists need to infer what the brains of common ancestors may have been like by studying brain scans of living primates and comparing them to humans.

Professor Chris Petkov from the Faculty of Medical Sciences, Newcastle University, UK the study lead said: "It is like finding a new fossil of a long lost ancestor. It is also exciting that there may be an older origin yet to be discovered still."

The international teams of European and US scientists carried out the brain imaging study and analysis of auditory regions and brain pathways in humans, apes and monkeys which is published in *Nature Neuroscience*.

They discovered a segment of this language pathway in the human brain that interconnects the auditory cortex with frontal lobe regions, important for processing speech and language. Although speech and language are unique to humans, the link via the auditory pathway in other primates suggests an evolutionary basis in auditory cognition and vocal communication.

Professor Petkov added: "We predicted but could not know for sure whether the human language pathway may have had an evolutionary basis in the auditory system of nonhuman primates. I admit we were astounded to see a similar pathway hiding in plain sight within the auditory system of nonhuman primates."

Remarkable transformation

The study also illuminates the remarkable transformation of the human language pathway. A key human unique difference was found: the human left side of this brain pathway was stronger and the right side appears to have diverged from the auditory evolutionary prototype to involve non-auditory parts of the brain.

The study relied on brain scans from openly shared resources by the global scientific community. It also generated original new brain scans that are globally shared to inspire further discovery. Also since the authors predict that the auditory precursor to the human language pathway may be even older, the work inspires the neurobiological search for its earliest evolutionary origin - the next brain 'fossil' - to be found in animals more distantly related to humans.

Professor Timothy Griffiths, consultant neurologist at Newcastle University, UK and joint senior author on the study notes: "This discovery has tremendous potential for understanding which aspects of human auditory cognition and language can be studied with animal models in ways not possible with humans and apes. The study has already inspired new research underway including with neurology patients."

The study involved Newcastle University, Faculty of Medical Sciences, UK; Max Planck Institute for Cognitive and Brain Sciences, Germany; Birkbeck UCL Centre for NeuroImaging, UK; University of Texas MD Anderson Cancer Center, USA; University of Iowa, USA.

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Large population study links blood infection with certain bacteria to increased risk of colorectal cancer

Link shown between blood infections with certain anaerobic bacteria and the risk of developing colorectal cancer.

New research due to be presented at this year's European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)* shows a link between blood infections with certain anaerobic bacteria and the risk of developing colorectal cancer. The study is by Dr Ulrik Stenz Justesen, Odense University Hospital, Denmark, and colleagues.

Anaerobic bacteria are bacteria that do not require oxygen for energy production, and live in various environments including the human gut, where they usually do not cause infections directly. Previous studies have reported an association between bacteria from the Bovis group streptococci, Clostridium septicum and colorectal cancer (CRC). Recently associations between different Bacteroides species, Fusobacterium nucleatum and CRC have also been reported. The authors aimed to investigate this further in a large-scale study.

The researchers performed a population-based cohort study including data on blood cultures from 2007 to 2016 covering a population of more than 2 million people in two regions of Denmark (Southern Denmark and Zealand regions).

They combined blood culture data with the national register for colorectal cancer (Danish Colorectal Cancer Group Database) and identified new cases of CRC after blood infection with these bacteria. The risk of incident CRC until 2018 was investigated for Bacteroides spp., Clostridium spp. and Fusobacterium spp. and compared with Bovis group streptococci, Escherichia coli, Staphylococcus aureus and with blood samples that contained no infection (controls). Each case of infection was matched by age and sex with five controls.

The data included 45,760 bacteraemia episodes, of which 492 (1.1%) were diagnosed with CRC after the bacterial infection; 241 (0.5%) within 1 year. The risk of CRC for selected bacteria is shown in in the full abstract (link below). Results for infection with E. coli and S. aureus are not shown but were similar to negative (control) blood cultures. Most anaerobic species were associated with a considerable increased risk of CRC (up to 42 times) compared with negative blood cultures.

Clostridium septicum infection was associated with a 42 times increased risk of CRC within 1 year (0.5% of controls developing CRC versus 20.8% in C. septicum), and a 21-times risk overall (1.1% controls versus 22.6%). Bacteroides ovatus was linked to a 13 times increased risk of CRC within 1 year (0.5% of controls versus 6.7% B. ovatus), and a 6-times increased risk overall (1.1% controls versus 6.7%).

The authors conclude: "In this large scale cohort study, it was found that, in patients with blood infections caused by selected anaerobic bacteria, the risk of developing colorectal cancer was increased by up to 42 times compared with patients with blood infections caused by aerobic bacteria such as E.coli or S.aureus or negative controls. The discovery of blood infections with certain anaerobic bacteria could potentially result in a recommendation of screening for colorectal cancer in selected patients."

To put the findings in context, in Dr Justesen's own clinical microbiology department, there are usually two cases of blood infection causes by these anaerobic bacteria each week. They are usually caused by a breach in the intestinal wall, which can itself be caused by cancer. Dr Justesen says: "At this stage we are not sure if the bacteria are directly causing cases of colorectal cancer, of if the blood infection with these bacteria is itself caused by the cancer. It's an example of the question 'is this the chicken or the egg?'"

He continues: "Our follow up research of this study will focus on the specific bacteria from cancer patients to see if we can identify specific characteristics that could be implicated in cancer development. If this is the case it could be of great importance when it comes to screening and treatment of colorectal cancer."

He adds: "With regards to screening, if we saw these high-risk bacteria in combination with advanced age, then it would definitely be worth screening the patient for colorectal cancer. At the other end, we would not need to screen children, but it is very rare to see either colorectal cancer or blood infections caused by anaerobic bacteria in children. We need to do further analysis to come up with specific recommendations on screening."

https://wb.md/2zms4ZU

Pay Attention to In-Hospital Glucose to Save Lives in COVID-19

Diabetes and hyperglycemia among people without prior diabetes are strong predictors of mortality among hospitalized patients with COVID-19, new research suggests.

Miriam E. Tucker

The data suggest that although glycemic control may not be at the forefront of most clinicians' minds when it comes to COVID-19, it is important, and paying more attention to it could save lives, say the researchers, led by Bruce Bode, MD, of Atlanta Diabetes Associates, Georgia, and colleagues, including employees of Glytec, an insulin management software company. The results were published online April 17 in the *Journal of Diabetes Science and Technology*.

In the observational study of more than 1000 inpatients with COVID-19 at US hospitals between March 1 and April 6, 2020, those with diabetes and those with hyperglycemia throughout their stay had a fourfold greater inpatient mortality than those without diabetes or hyperglycemia. And for those without evidence of diabetes prior to admission who developed hyperglycemia in hospital, mortality was sevenfold greater.

This is the first published report characterizing glycemic control among patients hospitalized with COVID-19 in the United States.

"The coronavirus outbreak has stretched our hospitals and health systems to a point we've never experienced before, so it's understandable that glycemic management may not have been a major point of focus thus far," said Bode, an advisory board member for Glytec, in a statement.

"This research confirms that diabetes is an important risk factor for dying from COVID-19." "It also suggests that patients with acutely uncontrolled hyperglycemia — with or without a diabetes diagnosis — are dying at a higher rate than clinicians and hospitals may recognize," he added.

Therefore, Bode and colleagues write, "in the absence of evidence to the contrary, clinicians should interpret COVID-19 associated hyperglycemia as a potential indicator of pancreatic islet cell injury and a risk for poor outcome."

"Clinicians should treat hyperglycemia to achieve [blood glucose] targets < 180 mg/dL for most patients. This equates to basal–bolus insulin therapy in most non-ICU patients and continuous insulin infusion in the critically ill as directed by national guidelines," they add.

Dysglycemia Predicts Mortality, Longer Hospital Stay

The study involved 1122 patients with COVID-19 at 88 hospitals in 11 representative US states. A1c data was available for 282 patients. There were 194 patients with diabetes (A1c > 6.5%) and another 257 patients with "uncontrolled hyperglycemia," defined as two or more blood glucose readings above 180 mg/dL during any 24-hour period, either with an A1c < 6.5% ("stress hyperglycemia") or no A1c testing during hospitalization.

Compared to the 671 patients without diabetes or uncontrolled hyperglycemia, the 451 patients with one or the other were more likely to be male (59% vs 53%; $P = .035$) and were older (65 vs 61 years; $P = .005$).

On admission, mean blood glucose levels were 202 mg/dL in the diabetes/uncontrolled hyperglycemia group versus 114 mg/dL in those without either (P < .001). Renal dysfunction (estimated glomerular filtration rate < 60 mL/min) was also more common in the former (40.6% vs 23.5%; P < .001).

At the time of analysis, 552 patients were still hospitalized and 570 patients were "inactive" (had been discharged or died).

Of the inactive group, 77 patients (13.5%) had died; 53 patients were in the diabetes/uncontrolled hyperglycemia group (28.8%) compared to 24 patients (6.2%) with neither diabetes or hyperglycemia (P < .001). Among the 493 patients who survived to discharge, the diabetes/uncontrolled hyperglycemia group also had significantly longer median hospital stays (5.7 days) compared to those without diabetes or hyperglycemia (4.3 days).

Outcomes Worse for Those Without a Previous Diabetes Diagnosis

In a further subset analysis, death rates were considerably higher among those with uncontrolled hyperglycemia, at 41.7%, compared to those admitted with a diabetes diagnosis, at 14.8% (P < .001).

And those with uncontrolled hyperglycemia spent longer in hospital than those with diabetes, whether they died there or were ultimately discharged (both P < .001).

The reason for this is not clear, but hospital staff may overlook high blood glucose readings in patients who don't arrive with a diabetes diagnosis, especially in the current pandemic crisis situation.

Speaking to *Medscape Medical News* about hospital care for patients with COVID-19 and dysglycemia, Irl B. Hirsch, MD, of the University of Washington, Seattle, said: "I see this all the time." Patients "go into the hospital for a different reason and have a random glucose of 300 mg/dL, but in many hospitals they only do routine point-of-care glucose testing if they come in with a diagnosis of diabetes. That's a huge problem." Bode and colleagues agree, and reiterate: "We recommend health systems ensure inpatient hyperglycemia is safely and effectively treated."

Bode is an advisory board member for Glytec, and five coauthors are company employees. Hirsch consults for Abbott Diabetes Care, Roche, and Bigfoot Biomedical, conducts research for Medtronic, and is a diabetes editor on for UpToDate.

J Diabetes Sci Technol. Published online April 17, 2020. Full text

https://bit.ly/3cEIk6G

New research gives further evidence that autoimmunity plays a role in Parkinson's disease

LJI scientists link immune cells to Parkinson's disease onset

LA JOLLA--A new study co-led by scientists at the La Jolla Institute for Immunology (LJI) adds increasing evidence that Parkinson's disease is partly an autoimmune disease. In fact, the researchers report that signs of autoimmunity can appear in Parkinson's disease patients years before their official diagnosis.

The research could make it possible to someday detect Parkinson's disease before the onset of debilitating motor symptoms--and potentially intervene with therapies to slow the disease progression.

The study, published in the April 20, 2020, issue of *Nature Communications*, was co-led by LJI professor Alessandro Sette, Dr. Biol. Sci, and Professor David Sulzer, Ph.D., of the Columbia University Medical Center.

Scientists have long known that clumps of a damaged protein called alpha-synuclein build up in the dopamine-producing brain cells of patients with Parkinson's disease. These clumps eventually lead to cell death, causing motor symptoms and cognitive decline.

"Once these cells are gone, they're gone. So if you are able to diagnose the disease as early as possible, it could make a huge difference," says LJI research assistant professor Cecilia Lindestam Arlehamn, Ph.D., who served as first author of the new study.

A 2017 study led by Sette and Sulzer was the first to show that alpha-synuclein can act as a beacon for certain T cells, causing them to mistakenly attack brain cells and potentially contribute to

the progression of Parkinson's. This was the first direct evidence that autoimmunity could play a role in Parkinson's disease.

The new findings shed light on the timeline of T cell reactivity and disease progression. The researchers looked at blood samples from a large group of Parkinson's disease patients and compared their T cells to a healthy, age-matched control group. They found that the T cells that react to alpha-synuclein are most abundant when patients are first diagnosed with the disease. These T cells tend to disappear as the disease progresses, and few patients still have them ten years after diagnosis.

The researchers also did an in-depth analysis of one Parkinson's disease patient who happened to have blood samples preserved going back long before his diagnosis. This case study showed that the patient had a strong T cell response to alpha-synuclein ten years before he was diagnosed with Parkinson's disease. Again, these T cells faded away in the years following diagnosis.

"This tells us that detection of T cell responses could help in the diagnosis of people at risk or in early stages of disease development, when many of the symptoms have not been detected yet," says Sette. "Importantly, we could dream of a scenario where early interference with T cell responses could prevent the disease from manifesting itself or progressing."

Sulzer added, "One of the most important findings is that the flavor of the T cells changes during the course of the disease, starting with more aggressive cells, moving to less aggressive cells that may inhibit the immune response, and after about 10 years, disappearing altogether. It is almost as if immune responses in Parkinson's disease are like those that occur during seasonal flu, except that the changes take place over ten years instead of a week."

In fact, already therapies exist to treat inflammation from autoreactive T cells, and these TNF therapies are associated with lower incidence of Parkinson's disease. Going forward, the researchers are especially interested in using a tool called a T cell-based assay to monitor patients already at risk for Parkinson's to see if they could benefit from TNF therapies. These patients include people with REM sleep disorders and certain genetic mutations.

The researchers hope to study more Parkinson's patients and follow them over longer time periods to better understand how T cell reactivity changes as the disease progresses.

The study, titled "α-Synuclein-specific T cell reactivity is associated with preclinical and early Parkinson's disease," was supported by the National Institutes of Health's (NIH) National Institute of Neurological Disorders and Stroke (R01NS095435, P50NS108675), the NIH National Institute on Aging (P50AG08702), the Parkinson's Foundation, the Michael J. Fox Foundation, JPB Foundation, William F. Richter Foundations, and the UCSD-LJI Program in Immunology.

Additional study authors included Rekha Dhanwani, John Pham, Rebecca Kuan, April Frazier, Juliana Rezende Dutra, Elizabeth Phillips, Simon Mallal, Mario Roederer, Karen S. Marder, Amy W. Amara, David G. Standaert, Jennifer G. Goldman, Irene Litvan, and Bjoern Peters. DOI: 10.1038/s41467-020-15626-w

https://bit.ly/2KqF5Uo

Woman's Breast Implant Saved Her Life by Deflecting a Bullet, Case Study Shows

First documented case of a silicone breast implant altering a bullet's trajectory and most likely saving a woman's life.

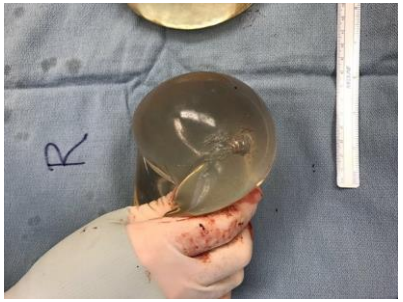
Peter Dockrill

In a remarkable study, researchers report what they say is the first documented case in medical literature of a silicone breast implant altering a bullet's trajectory and most likely saving a woman's life.

This horrific but ultimately non-fatal incident took place in Ontario, Canada, and the events of the evening are the subject of an ongoing investigation, with the shooter remaining unidentified, and the firearm used in the episode never having been recovered.

What is certain, though, is that a 30-year-old woman with breast implants sustained severe chest trauma after being struck by a bullet in public at night, with the projectile hitting her suddenly and without warning.

"The patient reported walking down [the] street and feeling heat and pain in her left chest, looking down and seeing blood," a research team led by plastic surgeon Giancarlo McEvenue explains in a case note. After being transferred to a trauma centre, the woman was in a stable condition, with no additional injuries except for a single entry wound in the upper part of her left breast.



Right breast implant with damage from bullet trajectory. **(McEvenue et al., Plastic Surgery Case Studies, 2020)**

Examination of the wound revealed thermal injury surrounding the bullet hole on the left breast, suggesting close proximity to the discharging firearm, and a hard, bullet-like mass could be felt under the woman's skin on the other side of her body, lodged behind her right breast.

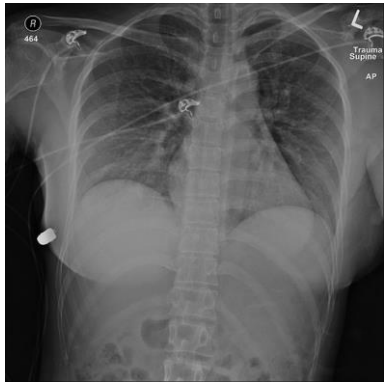
X-rays confirmed this mass was the bullet still inside the patient's body, in the right lateral thoracic wall, while also showing a fractured rib – clues to the bullet's trajectory through the body, the researchers say, entering the left breast and passing through to the right thoracic wall, where it was eventually stopped.

CT scans revealed pulmonary contusion (damage to lung tissue) but no intrathoracic injury, although signs of debris and air indicated both breast implants had been struck by the bullet.

The surgeons removed both damaged implants, and extracted the projectile, which was given to police, and identified as a copper-jacketed 0.40 calibre bullet. After the successful operation, the woman's medical team used CT imaging in conjunction with the clinical evidence to reconstruct how the bullet passed through the patient's body and her breast implants.

According to the researchers, the bullet was on course to pass directly through the chest wall and might have struck the woman's heart, had it not been for a deflection in the projectile's trajectory due to the presence of the left implant.

"Based on trajectory of bullet entry clinically and evaluation radiologically, the only source of bullet deflection of the bullet is the left breast implant," the authors write. "This implant overlies the heart and intrathoracic cavity and therefore likely saved the women's life."



Bullet in right lateral thoracic wall on chest X-ray. **(McEvenue et al., Plastic Surgery Case Studies, 2020)**

The researchers suggest deflection occurred within the implant likely at the point when the bullet pressed against and ultimately ruptured the implant's membrane.

While the hypothetical role of breast implants slowing down bullet velocity has been investigated before, the researchers say their patient's case is the first showing multiple lines of evidence that suggest deflection can also occur. "Our study adds to this knowledge by using high-resolution CT technology to analyse bullet trajectory in an actual patient case," the authors write.

"This trajectory change could only have been due to the bullet hitting the implant in our patient's case, as the bullet did not hit bone on the left side (as evidenced by lack of left-sided fracture and a bullet that retained enough energy to cause right-sided fractures)."

Although reported cases like this might be rare, the team found at least two other cases in medical literature where ruptured breast implants are thought to have played a role in saving patients' lives after they were stuck by bullets.

"The unfortunate story has a happy ending in that the patient only suffered minor injuries and made a complete recovery," McEvenue says. The findings are reported in *Plastic Surgery Case Studies*.

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Human pregnancy is weird -- new research adds to the mystery

Research provides insight into the evolution of the progesterone receptor gene -- and raises more questions

BUFFALO, N.Y. -- From an evolutionary perspective, human pregnancy is quite strange, says University at Buffalo biologist Vincent Lynch. "For example, we don't know why human women go into labor," Lynch says. "Human pregnancy tends to last longer than pregnancy in other mammals if you adjust for factors like body size. The actual process of labor tends to last longer than in other animals. And human pregnancy and labor are also much more dangerous."

With these oddities in mind, Lynch and colleague Mirna Marinic set out to investigate the evolution of a gene that helps women stay pregnant: the progesterone receptor gene.

But the results of the study only add to the mystery, says Lynch, PhD, an assistant professor of biological sciences in the UB College of Arts and Sciences.

Unexpected findings about a gene that's critical to pregnancy

Past research has shown that the progesterone receptor gene underwent rapid evolution in humans, and some scientists have suggested that these swift changes occurred because they improved the function of the gene. This is called positive selection.

But Lynch and Marinic's study -- published online on April 17 in the journal *PLOS Genetics* -- draws a different conclusion.

Their research finds that while the progesterone receptor gene evolved rapidly in humans, there's no evidence to support the idea that this happened because those changes were advantageous. In fact, the evolutionary force of selection was so weak that the gene accumulated many harmful mutations as it evolved in humans, Lynch says.

The results come from an analysis of the DNA of 115 mammalian species. These included a variety of primates, ranging from modern humans and extinct Neanderthals to monkeys, lemurs and lorises, along with non-primate mammalian species such as elephants, pandas, leopards, hippos, aardvarks, manatees and walruses.

The findings were a surprise, Lynch says.

"We expected something very different. It opens up this mystery that we didn't anticipate," he says. "I thought that the progesterone receptor gene would have evolved to respond better to progesterone, to be better at suppressing inflammation or contractions to keep us pregnant for longer. It looks like it's the reverse: In human pregnancy, there's just an incredible amount of progesterone around, and yet the gene is less good at doing its job. I wonder if this might predispose us to things like preterm birth, which is not that common in other animals."

"Pregnancy is such an everyday event -- none of us would be here without it -- and yet, so many aspects of this process remain puzzling," says Marinic, PhD, a postdoctoral researcher in the University of Chicago Department of Organismal Biology and Anatomy. "This study focused on an essential ingredient, progesterone signaling via progesterone receptors, and our results add another step toward deeper understanding of specificities of human pregnancy."

The progesterone receptor gene is crucial to pregnancy because it provides cells with instructions for how to create tiny structures called progesterone receptors.

During human pregnancy, these receptors detect the presence of progesterone, an anti-inflammatory hormone that pregnant women and the placenta produce at various points in time. When progesterone is present, the receptors jump into action, triggering processes that help keep women pregnant in part by preventing the

uterus from contracting, reducing uterine inflammation, and suppressing the maternal immune response to the fetus, Lynch says.

Evolution changed the function of progesterone receptors in humans

In addition to exploring the evolutionary history of the progesterone receptor gene, Lynch and Marinic conducted experiments to test whether mutations in the human version of the gene altered its function. The answer is yes.

As the scientists wrote in their paper, "We resurrected ancestral forms of the progesterone receptor and tested their ability to regulate a target gene. We found that the human progesterone receptor forms have changed in function, suggesting the actions regulated by progesterone may also be different in humans. Our results suggest caution in attempting to apply findings from animal models to progesterone biology of humans."

The research was funded by the March of Dimes and the Burroughs Wellcome Fund Preterm Birth Initiative.

https://nyti.ms/2xSd7OO

Asthma Is Absent Among Top Covid-19 Risk Factors, Early Data Shows

Despite warnings that asthmatics were at higher risk for severe illness from the coronavirus, asthma is showing up in only about five percent of New York State's fatal Covid cases.

By Danny Hakim

For people with asthma, the outbreak of a pandemic that can lead to respiratory failure has not been a welcome event. Many health organizations have cautioned that asthmatics are most likely at higher risk for severe illness if they get the coronavirus. There's been a run on inhalers, and coronavirus patients like the actor Idris Elba have openly worried about their asthma.

But this month, when New York State, the epicenter of the outbreak in the United States, began releasing data on the top 10 chronic health problems suffered by people who died from coronavirus, asthma was notably absent from the list. State officials said only about five percent of Covid-19 deaths in New York were of people who were known to also have asthma, a relatively modest amount.

The research at this early stage is minimal and not always consistent, as one would expect. A recent commentary published in Lancet by a group of European researchers called it "striking" that asthma appeared "to be underrepresented in the comorbidities reported for patients with Covid-19" — comorbidity being the term for a secondary health problem. A small study of 24 critically ill patients in Washington State noted that three had asthma.

"We're not seeing a lot of patients with asthma," said Dr. Bushra Mina, a pulmonary and critical care physician at Lenox Hill Hospital in New York City, which has treated more than 800 Covid cases. The more common risk factors, he added, are "morbid obesity, diabetes and chronic heart disease."

The top Covid-19 comorbidities listed by New York, in order, are hypertension, diabetes, high cholesterol, coronary artery disease, dementia and atrial fibrillation, a heart condition. Chronic obstructive pulmonary disease, another respiratory ailment, but one with an older demographic than asthma, ranks seventh. Renal disease, cancer and congestive heart failure round out the list.

Nearly eight percent of the U.S. population — close to 25 million people — has asthma, according to the Centers for Disease Control and Prevention. It is a lung disease that causes the airways to constrict and can make breathing hard work as the body fights for enough oxygen. Symptoms include wheezing and coughing.

One thing doctors agree on is that people with asthma should be taking long acting medications like steroids that keep their symptoms in check, because having your asthma under control is better than battling asthma and a virus simultaneously.

Health experts have generally seen little to no evidence that asthma increases the risk of developing Covid-19, but the question has been whether it causes worse outcomes for those who do have it.

“If you have mild or moderate disease, you’re probably not going to behave much differently than someone who doesn’t have asthma, particularly if you’re a younger person,” said Dr. David Hill, a board member of the American Lung Association. But he added that those with more severe cases “may get more severity of the disease.”

Dr. Linda Rogers, a specialist in pulmonary medicine at the Mt. Sinai Health system, which is on the front line of Covid treatment, said one would assume that patients with underlying lung diseases would be “at risk of worse outcomes.” But she said that “asthma is underrepresented” in patients that are sick enough to seek treatment.

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Her practice focuses on people with more serious cases of asthma, but she has been able to successfully manage many of her asthma patients through telemedicine. “These are patients who, just based on their asthma alone, are on steroids all the time. I’m just surprised some of them haven’t done worse.”

Still, the data analysis on the effects of asthma is in its infancy, and health experts cited an existing body of research that shows the flu and milder coronaviruses exacerbate asthma as worrisome indicators for those with Covid-19. Dr. Rogers said that she did not want to exclude asthma “as a potential problem as it is well known that viral infections are the No. 1 cause of asthma flares in both children and adults under normal conditions.”

Dr. J. Allen Meadows, president of the American College of Allergy, Asthma and Immunology, said much the same: “Since common coronaviruses in the United States, and influenza, trigger asthma flares in well controlled patients, we might expect Covid-19 to be similar.”

One doctor who has studied viruses extensively is Young J. Juhn, a clinical epidemiologist, and professor of pediatrics and medicine at the Mayo Clinic, whose laboratory research has examined the impact of asthma on the risk of infectious and inflammatory diseases.

Dr. Juhn said the data would have to be studied and weighted in more detail, but added that, in his view, asthma put people at greater risk of poor outcomes, and potentially even more susceptible to infection, though there was limited data on the latter point. He noted that asthma disproportionately affects lower-income people who have less access to Covid testing and care.

“It may be still fair to say that the emerging data support the current guidelines considering asthma as a high-risk condition,” he cautioned, adding that “we need more definite data.”

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Penn Engineering's new scavenger technology allows robots to 'eat' metal for energy

Rather than from the chemicals in a battery, the researchers' metal-air scavenger vehicle gets energy from breaking chemical bonds in the metal surfaces it travels over

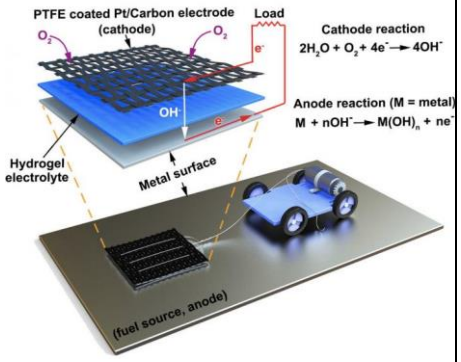
When electronics need their own power sources, there are two basic options: batteries and harvesters. Batteries store energy internally, but are therefore heavy and have a limited supply. Harvesters, such as solar panels, collect energy from their environments. This gets around some of the downsides of batteries but introduces new ones, in that they can only operate in certain conditions and can't turn that energy into useful power very quickly.

New research from the University of Pennsylvania's School of Engineering and Applied Science is bridging the gap between these

two fundamental technologies for the first time in the form of a "metal-air scavenger" that gets the best of both worlds.

This metal-air scavenger works like a battery, in that it provides power by repeatedly breaking and forming a series of chemical bonds. But it also works like a harvester, in that power is supplied by energy in its environment: specifically, the chemical bonds in metal and air surrounding the metal-air scavenger.

The result is a power source that has 10 times more power density than the best energy harvesters and 13 times more energy density than lithium-ion batteries.



Like a traditional battery, the researchers' MAS starts with a cathode that's wired to the device it's powering. Underneath the cathode is a slab of hydrogel, a spongy network of polymer chains that conducts electrons between the metal surface and the cathode via the water molecules it carries. With the hydrogel acting as an electrolyte, any metal surface it touches functions as the anode of a battery, allowing electrons to flow to the cathode and power the connected device. **Credit: Pikul Research Group, Penn Engineering**

In the long term, this type of energy source could be the basis for a new paradigm in robotics, where machines keep themselves powered by seeking out and "eating" metal, breaking down its chemical bonds for energy like humans do with food.

In the near term, this technology is already powering a pair of spin-off companies.

The winners of Penn's annual Y-Prize Competition are planning to use metal-air scavengers to power low-cost lights for off-grid homes in the developing world and long-lasting sensors for shipping containers that could alert to theft, damage or even human trafficking.

The researchers, James Pikul, assistant professor in the Department of Mechanical Engineering and Applied Mechanics, along with Min Wang and Unnati Joshi, members of his lab, published a study demonstrating their scavenger's capabilities in the journal *ACS Energy Letters*.

The motivation for developing their metal-air scavenger, or MAS, stemmed from the fact that the technologies that make up robots' brains and the technologies that power them are fundamentally mismatched when it comes to miniaturization.

As the size of individual transistors shrink, chips provide more computing power in smaller and lighter packages. But batteries don't benefit the same way when getting smaller; the density of chemical bonds in a material are fixed, so smaller batteries necessarily mean fewer bonds to break.

"This inverted relationship between computing performance and energy storage makes it very difficult for small-scale devices and robots to operate for long periods of time," Pikul says. "There are robots the size of insects, but they can only operate for a minute before their battery runs out of energy."

Worse still, adding a bigger battery won't allow a robot to last longer; the added mass takes more energy to move, negating the extra energy provided by the bigger battery. The only way to break this frustrating inverted relationship is to forage for chemical bonds, rather than to pack them along.

"Harvesters, like those that collect solar, thermal or vibrational energy, are getting better," Pikul says. "They're often used to power sensors and electronics that are off the grid and where you might not have anyone around to swap out batteries. The problem is that they have low power density, meaning they can't take energy out of the environment as fast as a battery can deliver it."

"Our MAS has a power density that's ten times better than the best harvesters, to the point that we can compete against batteries," he

says, "It's using battery chemistry, but doesn't have the associated weight, because it's taking those chemicals from the environment."

Like a traditional battery, the researchers' MAS starts with a cathode that's wired to the device it's powering. Underneath the cathode is a slab of hydrogel, a spongy network of polymer chains that conducts electrons between the metal surface and the cathode via the water molecules it carries.

With the hydrogel acting as an electrolyte, any metal surface it touches functions as the anode of a battery, allowing electrons to flow to the cathode and power the connected device.

For the purposes of their study, the researchers connected a small motorized vehicle to the MAS. Dragging the hydrogel behind it, the MAS vehicle oxidized metallic surfaces it traveled over, leaving a microscopic layer of rust in its wake.

To demonstrate the efficiency of this approach, the researchers had their MAS vehicle drive in circles on an aluminum surface. The vehicle was outfitted with a small reservoir that continuously wicked water into the hydrogel to prevent it from drying out.

"Energy density is the ratio of available energy to the weight that has to be carried," Pikul says.

"Even factoring in the weight of the extra water, the MAS had 13 times the energy density of a lithium ion battery because the vehicle only has to carry the hydrogel and cathode, and not the metal or oxygen which provide the energy."

The researchers also tested the MAS vehicles on zinc and stainless steel. Different metals give the MAS different energy densities, depending on their potential for oxidation.

This oxidation reaction takes place only within 100 microns of the surface, so while the MAS may use up all the readily available bonds with repeated trips, there's little risk of it doing significant structural damage to the metal it's scavenging.

With so many possible uses, the researchers' MAS system was a natural fit for Penn's annual Y-Prize, a business plan competition that challenges teams to build companies around nascent technologies developed at Penn Engineering.

This year's first-place team, Metal Light, earned $10,000 for their proposal to use MAS technology in low-cost lighting for off-grid homes in the developing world. M-Squared, which earned $4,000 in second place, intends to use MAS-powered sensors in shipping containers.

"In the near term, we see our MAS powering internet-of-things technologies, like what Metal Light and M-Squared propose," Pikul says. "But what was really compelling to us, and the motivation behind this work, is how it changes the way we think about designing robots."

Much of Pikul's other research involves improving technology by taking cues from the natural world. For example, his lab's high-strength, low-density "metallic wood" was inspired by the cellular structure of trees, and his work on a robotic lionfish involved giving it a liquid battery circulatory system that also pneumatically actuated its fins.

The researchers see their MAS as drawing on an even more fundamental biological concept: food.

"As we get robots that are more intelligent and more capable, we no longer have to restrict ourselves to plugging them into a wall. They can now find energy sources for themselves, just like humans do," Pikul says.

"One day, a robot that needs to recharge its batteries will just need to find some aluminum to 'eat' with a MAS, which would give it enough power to for it work until its next meal."

This work was supported by the Office of Naval Research, grant N00014-19-1-2353. It was carried out in part at the Singh Center for Nanotechnology, which is supported by the NSF National Nanotechnology Coordinated Infrastructure Program under grant NNCI-1542153.

https://bit.ly/3eJAACd

Are Cosmic Rays a Key to Forecasting Volcanic Eruptions?

A combination of relativistic particles and artificial intelligence may provide a new way to forecast when a volcano could erupt.

By Mara Johnson-Groh 21 April 2020

Forecasting volcanic eruptions is notoriously challenging, but a team of Japanese scientists may have found a new method using relativistic particles from space.

A new pilot study, conducted on a highly active Japanese volcano, used a type of high-energy particle called a muon to map the interior structure of the volcano. When analyzed with machine learning algorithms, these maps could help diagnose when a volcano is about to blow. Thus far, the feasibility of the method has been examined on only one volcano, but it could eventually be more widely applied as the technique is further refined.

By placing specialized detectors that record muons passing through a volcano, scientists can use the particles to create more finely defined maps of the interior of a volcano than possible with previous techniques. Eruption forecasting typically relies on volcanic gas emissions, surface changes, or seismography—which measures trembles in the ground that are often a precursor to eruptions. The new method instead took a visual approach and built on the imaging technique known as muography. First developed in the 1970s to map secret chambers in Egyptian pyramids, muography uses cosmic rays—high-energy particles originating on the Sun and across the galaxy—to map giant objects, similar to an oversized X-ray machine.

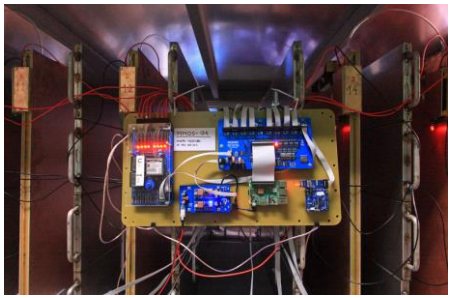
Cosmic rays continually rain down into Earth's atmosphere from outer space. When they run into atmospheric particles, they decay into smaller components, including an elementary particle called a muon. Muons' relatively high mass allows them to penetrate deeply into materials, even solid rock. By placing specialized detectors that record muons passing through a volcano, scientists can use the particles to create more finely defined maps of the interior of the volcano than possible with previous techniques.

For over a decade, scientists have been using muography to peer inside volcanoes around the world. The new work by the Japanese team, recently published in *Scientific Reports*, was the first effort to use muographic images to forecast eruptions.

Deep Learning

In medical imaging, scientists have applied a type of artificial intelligence called deep learning to X-ray images. Deep learning has been highly successful in identifying changes between images, tracking features such as cancer tumor growth. Since X-ray radiography and muography are conceptually similar, the scientists adapted a deep learning algorithm to analyze the volcano images. Although the specific type of deep learning they used—convolutional neural networks—has been previously used in the geosciences, it hadn't been applied to muographic images.

The scientists applied the technique to the Sakurajima volcano, one of the most active in the world. (It has erupted 7,000 times in the past decade.) This stratovolcano, located in southern Kyushu, Japan, has been monitored by the Sakurajima Muography Observatory for 6 years, providing a wealth of historical data. Deep learning suffers from the need of an extensive library of images in which to train the algorithm, but the long timeline of data collection provided a sufficient set of images for calibration.



One of the instruments—a muographic observation system—measures muons traveling through Sakurajima. **Credit: University of Tokyo**

"For around 500 eruption events, daily muographic images were learned and interpreted by a machine for the 7 days [leading up to the eruption] to judge whether the eruption would occur or not on the following day," said Hiroyuki Tanaka, a coauthor on the new study and a researcher at the Earthquake Research Institute and the International Muography Research Organization (MUOGRAPHIX) at the University of Tokyo.

The researchers' results showed a correlation between the images and eruptions, which suggests that this technique could be used to forecast future eruptions. The method might also allow predictions more than a few days out, but that will require additional refinement of the technique.

Although this pilot study was conducted on only one volcano (Sakurajima), it has the potential to be extended to other volcanoes in the future. Although this pilot study was conducted on only one volcano, it has the potential to be extended to other volcanoes in the future, though there are potential roadblocks. Deep learning works only for large data sets, which don't yet exist for many volcanoes. And acquiring sufficient data requires a large number of eruptions, a limiting factor for volcanoes that aren't as active as Sakurajima. But some scientists are hopeful that key features that can signal imminent eruptions can be identified from Sakurajima and applied to other, less active volcanoes. Procedures used in the new research could also be combined with existing methods to more fully study volcanic activity.

"Forecasting of a volcanic eruption rarely relies upon a single parameter, and therefore, the combined use of monitoring tools and forecasting methods is likely to give the 'best' outcome," said Rebecca O. Salvage, a geophysicist and volcanologist at the University of Calgary. "Since Sakurajima has been well monitored for a long time, it would be interesting to see how muography compares to other, more traditional, monitoring techniques, such as seismicity, deformation, and gas emission, in terms of its ability to successfully forecast an eruption."

—Mara Johnson-Groh (marakjg@gmail.com), Science Writer

Citation: *Johnson-Groh, M. (2020), Are cosmic rays a key to forecasting volcanic eruptions?, Eos, 101, https://doi.org/10.1029/2020EO142927. Published on 21 April 2020.*

https://bit.ly/3bCKJP7

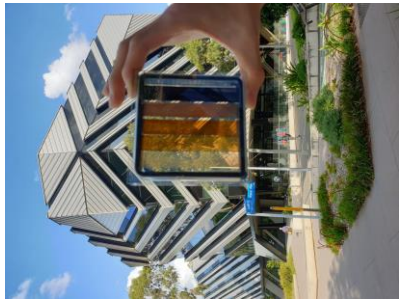
Windows will soon generate electricity, following solar cell breakthrough

Two square metres of solar window will do the same job as a standard rooftop solar panel, Australian researchers say.

Semi-transparent solar cells that can be incorporated into window glass are a "game-changer" that could transform architecture, urban planning and electricity generation, Australian scientists say in a paper in *Nano Energy*.

The researchers - led by Professor Jacek Jasieniak from the ARC Centre of Excellence in Exciton Science (Exciton Science) and Monash University - have succeeded in producing next-gen perovskite solar cells that generate electricity while allowing light to pass through. They are now investigating how the new technology could be built into commercial products with Viridian Glass, Australia's largest glass manufacturer.

This technology will transform windows into active power generators, potentially revolutionising building design. Two square metres of solar window, the researchers say, will generate about as much electricity as a standard rooftop solar panel.



A semi-transparent perovskite solar cell with contrasting levels of light transparency. **Credit: Dr Jae Choul Yu**

The research was also supported by the Australian Renewable Energy Agency (ARENA).

The idea of semi-transparent solar cells is not new, but previous designs have failed because they were very expensive, unstable or inefficient.

Professor Jasieniak and colleagues from Monash's Materials Science and Engineering Department and Australia's national science agency, CSIRO, used a different approach.

They used an organic semiconductor that can be made into a polymer and used it to replace a commonly used solar cell component (known as Spiro-OMeTAD), which shows very low stability because it develops an unhelpful watery coating. The substitute produced astonishing results.

"Rooftop solar has a conversion efficiency of between 15 and 20%," Jacek said.

"The semi-transparent cells have a conversion efficiency of 17%, while still transmitting more than 10% of the incoming light, so they are right in the zone. It's long been a dream to have windows that generate electricity, and now that looks possible."

Co-author and CSIRO research scientist, Dr Anthony Chesman, said the team is now working on scaling up the manufacturing process.

"We'll be looking to develop a large-scale glass manufacturing process that can be easily transferred to industry so manufacturers can readily uptake the technology," he said.

Solar windows will be a boon for building owners and residents, and will bring new challenges and opportunities for architects, builders, engineers and planners.

"There is a trade-off," explained Professor Jasieniak, "The solar cells can be made more, or less, transparent. The more transparent they are, the less electricity they generate, so that becomes something for architects to consider."

He added that solar windows tinted to the same degree as current glazed commercial windows would generate about 140 watts of electricity per square metre.

The first application is likely to be in multistorey buildings.

Large windows deployed in high-rise buildings are expensive to make. The additional cost of incorporating the semi-transparent solar cells into them will be marginal.

"But even with the extra spend, the building then gets its electricity free!" Professor Jasieniak said.

"These solar cells mean a big change to the way we think about buildings and the way they function. Up until now every building has been designed on the assumption that windows are fundamentally passive. Now they will actively produce electricity.

"Planners and designers might have to even reconsider how they position buildings on sites, to optimise how the walls catch the sun."

Lead author Dr Jae Choul Yu, also from Exciton Science and Monash, added that more efficiency gains would flow from further research.

"Our next project is a tandem device," he said. "We will use perovskite solar cells as the bottom layer and organic solar cells as the top one."

As to when the first commercial semi-transparent solar cells will be on the market, "that will depend on how successful scaling of the technology will be, but we are aiming to get there within 10 years," said Professor Jasieniak.

Jatin Khanna, Operations Manager for Viridian Glass, added: "The development of such solar windows presents an opportunity that could translate into the new glass innovations and technologies going forward."

The paper is scheduled for the May edition of Nano Energy. It is available in early-release online at https://www.sciencedirect.com/science/article/abs/pii/S2211285520301920

https://bit.ly/3cKLGVR

Research reveals a new malaria vaccine candidate

Researchers have discovered a promising new strategy for combating malaria, a mosquito-borne parasite that claims nearly a half-million lives each year.

PROVIDENCE, R.I. - For a study reported in the journal *Nature*, researchers screened blood samples from children who had natural immune resistance to severe malaria infection. The study identified an antibody to a particular malaria protein, called PfGARP, that appears to protect resistant children from severe disease. Lab tests showed that antibodies to PfGARP seem to activate a malarial self-destruct mechanism, causing parasite cells living inside human red blood cells to undergo a form of programmed cell death.

The team is hopeful that vaccinating individuals with PfGARP to generate anti-PfGARP antibodies, or directly infusing anti-PfGARP antibodies, would protect them against severe malaria. The team developed preliminary versions of those vaccines, and testing in nonhuman primates has shown promise, the researchers report.

"We demonstrated in two independent studies in nonhuman primates that vaccination with PfGARP protects against a lethal malaria parasite," said study senior author Dr. Jonathan Kurtis, a professor at the Warren Alpert Medical School of Brown University and laboratory director of the Center for International Health Research at Rhode Island Hospital."What's exciting is that this is a vaccination strategy that attacks malaria in a way that it has never been attacked before -- one in which the parasite becomes complicit in its own demise. We are hopeful that this vaccine, perhaps combined with other malarial antigens, will translate into a strategy that can help prevent severe malaria in people."

Testing of a human vaccine is likely years away, the researchers say, and there's no way to be certain it will work. But the team is hopeful that the approach taken in this study, which looks for the factors that contribute to naturally occurring disease resistance, will prove effective where other approaches have not.

Searching for antibodies

The results described in this new paper were nearly 20 years in the making, beginning with epidemiological research led by Michal Fried and Patrick Duffy of the National Institutes of Health. Starting around 2001, they began recruiting cohorts of children in Tanzania. The kids were enrolled at birth and followed for years to see who among them developed an acquired immune response to malaria.

"There was a ton of hard epidemiological work that went into simply identifying which kids were resistant and which weren't," Kurtis said. "Only after we knew their resistance levels could we use this information to identify the parasite targets that were recognized by antibodies made only by the resistant kids but not by the susceptible kids."

For this latest research, the team selected 12 resistant and 14 susceptible children from the Tanzanian cohort. The researchers looked at blood samples taken from the children around age two, when naturally acquired immunity seems to develop. Using a sophisticated method to introduce malaria proteins to each blood sample one by one, the researchers could look for any antibodies to a particular protein that were present in the resistant samples and not in the susceptible samples. That work identified PfGARP as a potential factor in conferring resistance.

Having identified PfGARP, the researchers then examined whether antibody responses to PfGARP were associated with resistance in a larger sample of 246 children. They found that children without anti-PfGARP antibodies were at 2.5 times higher risk of severe malaria compared to those who had the antibody.

"Kill switch"

The next step was trying to understand how anti-PfGARP antibodies affect the parasite. A series of laboratory experiments showed that the PfGARP protein is produced by malarial trophozoite cells, which live and feed off of nutrients inside red blood cells. The protein is then transported to the outer membrane of the red blood cell, where it makes the parasite cell vulnerable to the antibody.

"It's a kill switch," Kurtis said. "When the antibody binds to the protein, it sends a signal that tells the trophozoite to shrivel up and die. When we introduce the antibody to samples in petri dishes, we end up with 98% or 99% dead parasites."

The activity of the protein begs the question of why an organism would evolve such a self-destruct mechanism. Kurtis thinks it might have evolved as a means of sensing when the parasite's host is in distress.

"It's not necessarily in a parasite's best interest to kill its host," Kurtis said. "Keeping the host infected but alive means more chances for the parasite to reproduce. So what this might be is a means of sensing a host in distress and then reducing parasite load accordingly." The anti-PfGARP antibody hijacks that evolved system and turns it against the parasite.

Having shown that PfGARP antibodies kill the parasite, the researchers developed two types of PfGARP vaccines. Both of those were shown to be protective in nonhuman primates exposed to a human form of malaria.

A new strategy

Previous efforts to develop vaccines against malaria have met with limited success. But the researchers involved in this latest work say there's reason to believe this new strategy may succeed where others have failed. That's because it attacks the parasite at a different point in the infection cycle from other vaccines.

When an infected mosquito bites someone, it injects thread-like cells called sporozoites, which travel through the bloodstream to the liver. There, the parasite morphs into a different type of cell called merozoites that exit the liver in large quantities to infect red blood cells. Once they've invaded red blood cells, the parasites morph again into trophozoites, which feed off of the nutrients inside the cell before they burst out to start the cycle again.

An existing vaccine that targets the first stage -- aiming to prevent infection of the liver -- has had limited success. That's partly, Kurtis says, because the time window to intervene is so small.

"It takes five minutes for the parasite to go from the mosquito to the liver," he said. "Because it's so quick, the amount of antibody needed to stop it is huge. And if just one sporozoite gets in, you've got malaria."

This new vaccine targets the trophozoite stage, which lasts up to a day, Kurtis says. The researchers are hopeful that the longer window for intervention will reduce the amount of antibody needed to kill the parasite, and thereby make for a more effective vaccine.

"This gives us 24 hours as opposed to 5 minutes to intervene," Kurtis said. "During that time, the parasite expresses PfGARP -- a kill switch. We have designed a vaccine that activates it."

The researchers plan to continue testing different versions of the vaccine in animal models and ultimately to begin human trials in the coming years.

"This was an incredible team effort involving infectious disease experts, pathologists, epidemiologists, geneticists and molecular biologists," Kurtis said. "It really took all of these people to make this possible, and we're hopeful that the end result will be a vaccine that can save lives."

This work was supported by from the U.S. National Institutes of Health (R01-AI076353, R01-AI127699, R01-AI110699, R01-AI52059, R01AI092120, R01-AI145941, R01-AI102907, COBRE CCRD P20GM103421), a Lifespan Hospital System Research Pilot Award and the Bill & Melinda Gates Foundation (1364).

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Archivists uncover earliest evidence of a person being killed by a meteorite

Tales of people being killed by meteorite impacts date back to biblical times. But few deaths, if any, have been documented.

By Sid Perkins

Now, Turkish researchers have uncovered the earliest evidence that a meteorite killed one man and paralyzed another when it slammed into a hilltop in what is now Iraq in August 1888.

Documents chronicling the event were found in Turkish state archives, the team reports online today in *Meteoritics & Planetary Science*. According to one of three letters written by local authorities in the region shortly after the event, the killer meteorite was one of several that fell during a 10-minute interval. Reports of a fireball seen in a city nearby suggest the object approached the area from the southeast before it blew up high in the atmosphere (artist's representation of a meteorite strike pictured above).

In addition to the human casualties, some crops and fields were significantly damaged, the letters report. One of the letters was also supposedly accompanied by a sample of the meteorite, but the researchers have yet to find that object in Turkish archives or museums, they note.

Further searches of the millions of documents recently digitized may yield more information about the event.

***Correction, 23 April, 10:20 a.m.:** This item has been updated to reflect the fact that few or no meteorite deaths have been documented in the past decade.

doi:10.1126/science.abc4056

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Which foods do you eat together? How you combine them may raise dementia risk

Study finds 'food networks' centered on processed meats, starches may raise risk

Minneapolis - It's no secret that a healthy diet may benefit the brain. However, it may not only be what foods you eat, but what foods you eat together that may be associated with your risk of dementia, according to a new study published in the April 22, 2020, online issue of *Neurology*®, the medical journal of the American Academy of Neurology. The study looked at "food networks" and found that people whose diets consisted mostly of highly processed meats, starchy foods like potatoes, and snacks like cookies and cakes, were more likely to have dementia years later than people who ate a wider variety of healthy foods.

"There is a complex inter-connectedness of foods in a person's diet, and it is important to understand how these different connections, or food networks, may affect the brain because diet could be a promising way to prevent dementia," said study author Cécilia Samieri, PhD, of the University of Bordeaux in France. "A number of studies have shown that eating a healthier diet, for example a diet rich in green leafy vegetables, berries, nuts, whole grains and fish, may lower a person's risk of dementia. Many of those studies focused on quantity and frequency of foods. Our study went one step further to look at food networks and found important differences in the ways in which food items were co-consumed in people who went on to develop dementia and those who did not."

The study involved 209 people with an average age of 78 who had dementia and 418 people, matched for age, sex and educational level, who did not have dementia.

Participants had completed a food questionnaire five years previously describing what types of food they ate over the year, and how frequently, from less than once a month to more than four times a day. They also had medical checkups every two to three years. Researchers used the data from the food questionnaire to compare what foods were often eaten together by the patients with and without dementia.

Researchers found while there were few differences in the amount of individual foods that people ate, overall food groups or networks differed substantially between people who had dementia and those who did not have dementia.

"Processed meats were a "hub" in the food networks of people with dementia," said Samieri. "People who developed dementia were more likely to combine highly processed meats such as sausages, cured meats and patés with starchy foods like potatoes, alcohol, and snacks like cookies and cakes. This may suggest that frequency with which processed meat is combined with other unhealthy foods, rather than average quantity, may be important for dementia risk. For example, people with dementia were more likely, when they ate processed meat, to accompany it with potatoes and people without dementia were more likely to accompany meat with more diverse foods, including fruit and vegetables and seafood."

Overall, people who did not have dementia were more likely to have a lot of diversity in their diet, demonstrated by many small food networks that usually included healthier foods, such as fruit and vegetables, seafood, poultry or meats.

"We found that more diversity in diet, and greater inclusion of a variety of healthy foods, is related to less dementia," said Samieri. "In fact, we found differences in food networks that could be seen years before people with dementia were diagnosed. Our findings suggest that studying diet by looking at food networks may help untangle the complexity of diet and biology in health and disease."

One limitation of the study was that participants completed a food questionnaire that relied on their ability to accurately recall diet rather than having researchers monitor their diets. Another limitation was that diets were only recorded once, years before the onset of dementia, so any changes in diet over time were unknown.

This research was funded by the Alzheimer's Association. The overall study was funded by the INSERM Research Center at the University of Bordeaux, Sanofi-Aventis, and the French Foundation for Medical Research, as well as other French organizations including the French National Research Agency and the Plan Alzheimer Foundation.

https://bit.ly/2VVwsXf

Human-caused warming will cause more slow-moving hurricanes, warn climatologists

Hurricanes moving slowly over an area can cause more damage than faster-moving storms

Hurricanes moving slowly over an area can cause more damage than faster-moving storms, and rising global temperatures will likely cause more hurricanes to slow down, said Princeton atmospheric scientist Gan Zhang.

Hurricanes moving slowly over an area can cause more damage than faster-moving storms, because the longer a storm lingers, the more time it has to pound an area with storm winds and drop huge volumes of rain, leading to flooding. The extraordinary damage caused by storms like Dorian (2019), Florence (2018) and Harvey (2017) prompted Princeton's Gan Zhang to wonder whether global climate change will make these slow-moving storms more common. Zhang, a postdoctoral research associate in atmospheric and oceanic sciences, decided to tackle the question by using a large ensemble of climate simulations. He worked with an international team of researchers from the Geophysical Fluid Dynamics Laboratory on Princeton University's Forrestal campus and the Meteorological Research Institute in Tsukuba, Japan. The results of this work appear in the April 22 issue of Science Advances.

Zhang and his colleagues selected six potential warming patterns for the global climate, then ran 15 different possible initial conditions on each of the six patterns, resulting in an ensemble of 90 possible futures. In all 90 simulations, they told the computers to assume that global carbon dioxide levels have quadrupled and the planet's average temperature has risen by about 4 degrees Celsius --

a level of warming that experts predict could be reached before the turn of the century, if no action is taken to curb fossil fuel use.

"Our simulations suggest that future anthropogenic warming could lead to a significant slowing of hurricane motion, particularly in some populated mid-latitude regions," Zhang said. His team found about the storms' forward motion would slow by about 2 miles per hour -- about 10 to 20% of the current typical speeds -- at latitudes near Japan and New York City. "This is the first study we are aware of that combines physical interpretation and robust modeling evidence to show that future anthropogenic warming could lead to a significant slowing of hurricane motion," he said.

"Since the occurrence of Hurricane Harvey, there has been a huge interest in the possibility that anthropogenic climate change has been contributing to a slow down in the movement of hurricanes," said Suzana Camargo, the Marie Tharp Lamont Research Professor at Columbia University's Lamont-Doherty Earth Observatory, who was not involved in this research. "In a new paper, Gan Zhang and collaborators examined the occurrence of a slowdown of tropical cyclones in climate model simulations. They showed that in this model, there is a robust slowdown of tropical cyclone motion, but this occurs mainly in the mid-latitudes, not in the tropics."

Why would the storms slow down? The researchers found that 4 degrees of warming would cause the westerlies -- strong currents blowing through the midlatitudes -- to push toward the poles. That shift is also accompanied by weaker mid-latitude weather perturbations. These changes could slow down storms near populated areas in Asia (where these storms are called typhoons or cyclones, not hurricanes) and on the U.S. eastern seaboard.

Usually when people talk about hurricane speeds, they're referring to the winds whipping around the eye of the storm. Those wind speeds are what determine a storm's strength -- a Category 5 hurricane, for example, has sustained winds of more than 157 miles per hour. By contrast, Zhang and his colleagues are looking at the "translational motion," sometimes called the "forward speed" of a storm, the speed at which a hurricane moves along its path. (The term comes from geometry, where a figure is "translated" when it slides from one part of a graph to another.) No matter how fast its winds are, a storm is considered "slow-moving" if its translational speed is low. Hurricane Dorian, which battered Grand Bahama Island from Sept. 1 to 3, 2019, was a Category 5 hurricane with wind gusts reaching 220 miles per hour, but it had a translational speed of just 1.3 mph, making it one of the slowest hurricanes ever documented.

Are storms already slowing down?

Some researchers have suggested that tropical storm translation speeds have slowed over land regions in the United States since 1900. Zhang and his colleagues used their climate models to see if human-caused warming was responsible for the observed slowdown, but they couldn't find a compelling link, at least based on trends since 1950 in their simulations. In addition, they noted that observed slowing translational speeds reported in recent studies could arise primarily from natural variability rather than human-caused climate changes.

Zhang used the metaphor of dieting to explain the ambiguity of hurricane observations. "If I go to the gym and eat fewer sweets," he said, "I would expect to lose weight. But if I'm only using a bathroom scale to weigh myself, I'm not going to get convincing data very soon, for many reasons including that my bathroom scale isn't the most accurate," he continued. "Assume after two weeks, I see some weak trend," he said. "I still can't tell whether it's due to exercise, diet or just randomness."

Similarly, the observed slowdown trend in hurricanes or tropical storms over the past century could be due to small-scale local changes or could just be random, he said.

"In the debate between 'Everything is caused by climate change' and 'Nothing is caused by climate change' -- what we are doing here is trying to offer that maybe not everything can be immediately attributed to climate change, but the opposite is not right, either," Zhang said. "We do offer some evidence that there could be a slowdown of translational motion in response to a future warming on the order of 4 degrees Celsius. Our findings are backed by physics, as captured by our climate models, so that's a new perspective that offers more confidence than we had before."

"Tropical Cyclone Motion in a Changing Climate," by Gan Zhang, Hiroyuki Murakami, Thomas Knutson, Ryo Mizuta and Kohei Yoshida, was published in the April 22 issue of Science Advances (DOI: 10.1126/sciadv.aaz7610). The research was supported by Princeton University's Cooperative Institute for Modeling the Earth System through the Predictability and Explaining Extremes Initiative.

https://bit.ly/3avSzcc

Researchers discover a key to the survival of dormant breast cancer cells

A common anti-diabetes drug being tested in many clinical trials as an anti-cancer agent activated fat metabolism that promoted the survival of dormant breast cancer cells, suggesting that the drug has context-dependent effects on cancer cells.

Lebanon, NH - Most breast cancers utilize the female hormone estrogen to grow, so drug-induced estrogen deprivation is used as a treatment in many patients. However, cancer will recur in one-third of these patients. A research team at Dartmouth's and Dartmouth-Hitchcock's Norris Cotton Cancer Center, led by Todd W. Miller, PhD, is trying to understand why dormant breast cancer cells survive despite being starved of estrogen. The team discovered that an anti-diabetes drug, metformin, which is being tested in many clinical trials as an anti-cancer agent, actually activated fat metabolism that protected dormant breast cancer cells during estrogen deprivation. The findings suggest that the drug has context-dependent effects on cancer cells. The results, entitled "AMPK activation by metformin promotes survival of dormant ER+ breast cancer cells," are newly published online in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

Metformin activates AMPK, which is a metabolic sensor that signals cells to make energy. Miller's team found that breast cancer cells survived estrogen deprivation through activation of AMPK. "A major output of AMPK is activation of fat breakdown to produce energy, which we observed in dormant cancer cells," says Miller. "Drugs that block fat breakdown are used to treat patients with angina (chest pain). Treatment of mice with anti-angina drugs decreased dormant cancer cell numbers."

Knowledge that metformin has context-dependent effects on cancer cells will inform a better understanding of ongoing and prior clinical trials testing metformin, and help shape the design of trials moving forward. "Our study indicates that the development of drugs targeting fat metabolism is warranted for breast cancer. Most excitingly, anti-angina drugs that block fat metabolism may be quickly repurposed as potential treatments for cancer and tested in clinical trials," says Miller.

Next steps include clinical trials testing drugs that block fat metabolism in breast cancer. "We're also designing preclinical studies to further dissect the roles of fat metabolism in breast and other cancers, with the goal of identifying more refined therapeutic targets that will selectively kill cancer cells and not harm healthy cells," notes Miller.

Todd W. Miller, PhD, is Co-Director of the Cancer Biology & Therapeutics Research Program and Scientific Director of the Comprehensive Breast Program at Dartmouth's and Dartmouth-Hitchcock's Norris Cotton Cancer Center, and Associate Professor of Molecular and Systems Biology at the Geisel School of Medicine at Dartmouth. His research interests include identification of cancer signaling pathways and the development of targeted therapies for breast and other cancers. geiselmed.dartmouth.edu/miller. @DartmouthLab.

https://bit.ly/3eN802V

USGS releases first-ever comprehensive geologic map of the moon

New authoritative map helps explain the 4.5-billion-year-old history of our nearest neighbor in space.

Flagstaff, Ariz. - Have you ever wondered what kind of rocks make up those bright and dark splotches on the moon?

Well, the USGS has just released a new authoritative map to help explain the 4.5-billion-year-old history of our nearest neighbor in space.

For the first time, the entire lunar surface has been completely mapped and uniformly classified by scientists from the USGS, in collaboration with NASA and the Lunar Planetary Institute.

The lunar map, called the "Unified Geologic Map of the Moon," will serve as the definitive blueprint of the moon's surface geology for future human missions and will be invaluable for the international scientific community, educators and the public-at-large.

The digital map is available online now and shows the moon's geology in incredible detail (1:5,000,000 scale).

"People have always been fascinated by the moon and when we might return," said current USGS Director and former NASA astronaut Jim Reilly.

"So, it's wonderful to see USGS create a resource that can help NASA with their planning for future missions."

To create the new digital map, scientists used information from six Apollo-era regional maps along with updated information from recent satellite missions to the moon.

The existing historical maps were redrawn to align them with the modern data sets, thus preserving previous observations and interpretations.

Along with merging new and old data, USGS researchers also developed a unified description of the stratigraphy, or rock layers, of the moon.

This resolved issues from previous maps where rock names, descriptions and ages were sometimes inconsistent.

"This map is a culmination of a decades-long project," said Corey Fortezzo, USGS geologist and lead author.

"It provides vital information for new scientific studies by connecting the exploration of specific sites on the moon with the rest of the lunar surface."

Elevation data for the moon's equatorial region came from stereo observations collected by the Terrain Camera on the recent SELENE (Selenological and Engineering Explorer) mission led by JAXA, the Japan Aerospace Exploration Agency.

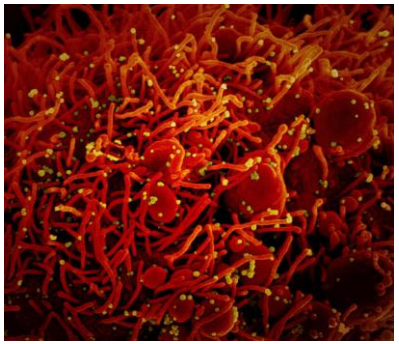
Topography for the north and south poles was supplemented with NASA's Lunar Orbiter Laser Altimeter data.

For more details about the map, read the abstract or download it directly at the Unified Geologic Map of the Moon website.

https://bit.ly/3bEoZCH

Study Reveals New Clues about Biology of COVID-19

A new study published in the journal Cell pinpoints the likely cell types SARS-CoV-2, a new coronavirus virus behind the COVID-19 disease, infects; it also shows that one of the human body's main defenses against viral infections may actually help SARS-CoV-2 infect those very cells.



Colorized scanning electron micrograph of an apoptotic cell (red) infected with SARS-COV-2 virus particles (yellow), isolated from a patient sample. **Image credit: NIAID.**

"We started to look at cells from tissues such as the lining of the nasal cavity, the lungs, and gut, based on reported symptoms and where the SARS-CoV-2 virus has been detected," said study lead author Dr. Jose Ordovas-Montanes, of Boston Children's Hospital.

"We wanted to provide the best information possible across our entire spectrum of research models."

Like the closely related SARS-CoV-1 virus that caused the SARS pandemic, SARS-CoV-2 uses a receptor called ACE2 to gain entry into human cells, aided by an enzyme called TMPRSS2.

That led Dr. Ordovas-Montanes and colleagues to ask a simple question: which cells in respiratory and intestinal tissue express both ACE2 and TMPRSS2?

To address this question, the researchers turned to single-cell RNA sequencing, which identifies which of roughly 20,000 genes are 'on' in individual cells. They found that only a tiny percentage of human respiratory and intestinal cells, often well below 10%, make both ACE2 and TMPRSS2.

Those cells fall in three types: goblet cells in the nose that secrete mucus; lung cells known as type II pneumocytes that help maintain the alveoli (the sacs where oxygen is taken in); and one type of so-called enterocytes that line the small intestine and are involved in nutrient absorption. Sampling from non-human primates showed a similar pattern of susceptible cells.

"Many existing respiratory cell lines may not contain the full mix of cell types, and may miss the types that are relevant," Dr. Ordovas-Montanes said. "Once you understand which cells are infected, you can start to ask, 'How do these cells work?' 'Is there anything within these cells that is critical for the virus' life cycle?'"

"With more refined cellular models, we can perform better screens to find what existing drugs target that biology, providing a stepping stone to go into mice or non-human primates."

But it was the study's second finding that most intrigues the authors. They discovered that the ACE2 gene is stimulated by interferon — one of the body's main defenses when it detects a virus.

Interferon actually turned the ACE2 gene on at higher levels, potentially giving the virus new portals to get in.

"ACE2 is also critical in protecting people during various types of lung injury," Dr. Ordovas-Montanes said.

"When ACE2 comes up, that's usually a productive response. But since the virus uses ACE2 as a target, we speculate that it might be exploiting that normal protective response."

Interferons, in fact, are being tested as a treatment for COVID-19. Would they help, or would they do more harm than good? That's not yet clear. "It might be that in some patients, because of the timing or the dose, interferon can contain the virus, while in others, interferon promotes more infection," Dr. Ordovas-Montanes said.

"We want to better understand where the balance lies, and how we can maintain a productive antiviral response without producing more target cells for the virus to infect."

The findings may also raise new lines of inquiry around ACE inhibitors. These drugs are commonly used to treat hypertension,

which has been linked to more severe COVID-19 disease. Are ACE inhibitors affecting people's risk?

"ACE and ACE2 work in the same pathway, but they actually have different biochemical properties," Dr. Ordovas-Montanes said. "It's complex biology, but it will be important to understand the impact of ACE inhibitors on people's physiological response to the virus."

It's also too soon to try to relate the study findings to the cytokine storm, a runaway inflammatory response that has been reported in very sick COVID-19 patients.

"It might be that we're seeing a cytokine storm because of a failure of interferon to restrict the virus to begin with, so the lungs start calling for more help. That's exactly what we're trying to understand right now."

Carly G.K. Ziegler et al. 2020. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell, in press; doi: 10.1016/j.cell.2020.04.035

https://bit.ly/2x8qvoq

What Life Is Like After Being Taken Off a Ventilator

A near-death experience in the ICU could have lasting effects on the brain—from PTSD to cognitive impairment on par with mild dementia.

Sarah Zhang

Even after Kyle Mullicane came home from the ICU, he would have nightmares about being back in the hospital, struggling to breathe. He had been on a ventilator, but his body fought so hard against the breathing tube in his throat that his arms and legs had to be restrained. Immobilized, he tried to chew through the plastic. In his post-ICU dreams, he would succeed at doing so, only to suffocate as the broken pieces fell into his lungs.

It has been eight months since Mullicane, 35, survived multiple organ failure from a bad reaction to heart medications. Physically, he feels well enough to have hiked a national park in January. But mentally, he's still recovering. "My memory is shot," he says. Loud noises startle him. And while the nightmares have gotten better, he remembers vivid hallucinations from the ICU, when doctors and nurses appeared to him as witches with shimmering faces. Even at home, normal life doesn't quite feel normal. "I don't feel safe anymore," he says, "like there's a low hum of menace."

In hospitals across America, thousands of the sickest COVID-19 patients are now needing intensive care. The marvels of 21st-century medicine will help keep them alive in the best-case scenarios. But surviving can be just the start of a long recovery, and even after this pandemic fades, some survivors might have to face lingering aftereffects. For reasons still not entirely understood, some patients may develop what's known as "post-intensive-care syndrome," which can include a constellation of physical, cognitive, and psychological symptoms. About 1 in 10 of all patients who have been in the ICU have PTSD. About 30 percent experience depression. Thirty percent have symptoms of anxiety. And another 40 percent report cognitive impairment on par with moderate brain injury.

"It isn't intuitive that being in the ICU for a lung condition would have an obvious consequence for your brain," says James Jackson, the director of long-term outcomes at Vanderbilt University's ICU Recovery Center. But the combination of a near-death experience, sedation, and a phenomenon called "ICU delirium"—likely exacerbated by sedative drugs—can have lasting effects.

Sedation is necessary for many patients in the ICU, especially ones with COVID-19, as part of being on a ventilator. This requires threading a plastic breathing tube down the throat and past the vocal cords into the upper chest, which conscious patients will instinctively fight. "Put it this way: If you have a tube down your throat and it doesn't bother you, there's something wrong," says John Kress, a pulmonary and critical-care doctor at the University of Chicago. In addition, many COVID-19 patients have what looks

like a form of respiratory failure called ARDS, in which the lungs fare best with short, quick puffs of air from the ventilator. This feels deeply unnatural. “As humans, we like to take big breaths,” says Daniela Lamas, a pulmonary and critical-care doctor at Brigham and Women’s Hospital in Boston. All of this is so uncomfortable that doctors use powerful drugs such as propofol and fentanyl to sedate patients on ventilators. Even then, some need to have their arms and legs restrained to prevent them from ripping the breathing tube out.

When Jeri Sharp, 62, was sedated and restrained while hospitalized for ARDS from H1N1, or swine flu, in 2016, she also had frightening delusions. The proportion of intensive-care patients who experience such ICU delirium is anywhere from 20 to 87 percent, depending on the study, though it appears to be more common in patients with ventilators than in those without. Sharp remembers at one point being strapped to a bed and her legs being spread apart. “I thought I was being molested,” she says. The memory has some basis in reality: She really was restrained in bed, and a nurse was probably placing a catheter. But in her delirium, it took on a sinister cast. Other patients have reported experiencing being taken to the MRI machine as being put into an oven or misinterpreting overhead conversations as plans to kill them—then lying awake for hours trying to escape.

These delusions are experienced at the time as real, and like genuine traumatic memories, they can rewire the emotional circuits of the brain. They “can lead to PTSD just like something a person literally and really experiences can lead to PTSD,” says Shawniqua Williams Roberson, a neurologist at Vanderbilt. The drugs used in sedation alter chemicals in the brain too. These factors, Williams Roberson says, in addition to the interrupted sleep, inflammation, lack of oxygen, and toxins from kidney or liver failure that are part of critical illness, may all play a role in psychological and cognitive changes after the ICU.

Back in her moment of delirium, Sharp remembers, she was comforted by a voice she recognized—her mother saying, “Jeri, it’s okay. It’s okay.” When she woke up, Sharp learned that her mother really had been by her side for several days. COVID-19 patients in the ICU, in contrast, are no longer allowed visitors, because of the risk of infection. They are alone, and the only people they do see are strangers covered head to toe in protective gear.

The coronavirus may compound other factors in post-intensive-care syndrome too. “In the ICU, our goal is generally to keep people the least sedated as possible,” Lamas says. Research suggests that lighter sedation is linked to better outcomes. But COVID-19 patients actually need to be sedated for a long time because of the extensive damage in their lungs. They also require deeper sedation when they are turned onto their stomach, which can be uncomfortable but seems to help open up parts of the lungs to improve oxygen levels. And doctors and nurses are simply less able to check on patients when each interaction becomes an infection risk. At her hospital, Lamas says, the monitors for ventilators have been moved into the hallway so that they can be adjusted from the outside. “Which is handy,” she says. “But it also separates us from the patients quite physically and visibly. A resident said to me walking by, ‘It’s like a video game.’ And that’s true, but also a very eerie feeling of these deeply sedated humans whose faces a lot of the team has never seen.”

Patients who are able to come off the ventilator can be so weak that they cannot walk or shower on their own. They’re usually put into physical therapy right away. But it is the psychological and cognitive recovery, several patients told me, that they were never warned about when they were discharged. They fell into a gap in the health-care system. “The providers typically working in the ICU,

they're critical-care intensivists," Jackson says. "The person who saved your life in the ICU, you can't see them in a follow-up clinic." Sharp told me that she once went back to the hospital to share her experience with some of the doctors and nurses who took care of her; she remembers how their eyes widened in disbelief as she spoke. They had no idea that she had been going through all that.

Today, more than three years later, Sharp says she still has trouble reading a book or adding a tip. She gets overwhelmed easily. When she started driving again, she found simply going to the grocery store to be too much. "It was too many choices to make. I got one aisle and I just started crying," she said. "To this day, I still have trouble going to the grocery store." She didn't understand why she was feeling this way until she found Facebook support groups for other ARDS survivors, who experienced some of the same symptoms.

Jan Hunter, 70, told me that she had to put the pieces together herself by reading her own medical records. Beginning in late 2016, Hunter spent two and a half months in the ICU after complications from routine surgery. Once home, she continued to struggle with basic tasks and she became depressed. "I felt bad I wasn't more grateful to be a miracle survivor," she said. Not until later, when she started looking at her medical records, did she realize she was not alone. When she found the word *delirium* in her records, she learned that the hallucinations she had in the ICU were not unusual. Eventually, she learned that what she was still experiencing had a name: post-intensive-care syndrome.

Although she lives in Virginia, Hunter ended up joining a support group out of Vanderbilt in Tennessee. The group has members across the country, and they've been meeting every Tuesday on Zoom—long before all support groups had to go virtual in the coronavirus era.

Mullicane, who is part of the same support group, says he has been thinking about COVID-19 patients who have to be in the ICU alone. When the disease began spreading in the United States, he began pleading with his friends and family who compared it to the flu. "I'll tell you what isn't 'just the flu'—it's being on a ventilator," he says. "I would not wish the experience on my worst enemy." The ICU saved his life, of course, but he knows from personal experience that it changed his life too.

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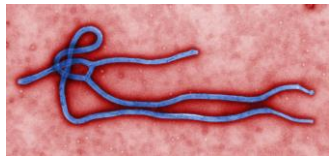
There seems to be no pattern to where humans pick up new viruses

No groups of species appear to be especially likely to transfer viruses to humans.

John Timmer



A virus that normally infects animals makes the jump to humans, whose immune systems have never seen it before.

A colorized transmission electron micrograph (TEM) of an Ebola virus virion. **CDC**

It suddenly sweeps across the globe, leaving death and chaos in its wake. We're living with that reality now and have gone through it previously with HIV, SARS, MERS, Ebola, Hanta, and various flu viruses that have threatened humanity in just the past few decades.

While there are many organizations that try to stay on top of threats of emerging diseases, it would be helpful if we could identify major sources of potential threats. If, for example, we knew that certain species were more prone to carrying viruses that could make the jump to humans, we could potentially survey the viruses found in those species, identify major threats, and potentially even develop therapies or vaccines in advance.

But a study published recently in PNAS suggests there's no real pattern to where humans are picking up new viruses. Instead,

groups with lots of species tend to have lots of viral species, and those make the jump to humans largely in proportion to the number of species.

Zoonotic risk

A disease that can be transmitted from animals to people is technically called "zoonotic." While there are a variety of diseases that incorporate time in another species as part of their lifestyle—malaria is a classic example—the risk we're concerned about is a virus that normally circulates within a non-human species but evolves the ability to spread within humans and leaves its original host behind.

These sorts of events are relatively common. Flu viruses seem to hop among us and our agricultural species with some regularity. Other viruses, like members of the hantavirus family, seem to frequently make the jump to humans without ever establishing the ability to spread from human to human.

It's the latter feature of being able to jump from human to human that creates the risk of a global pandemic. Two earlier coronaviruses, SARS-CoV-1 and MERS, didn't spread among humans as effectively as SARS-CoV-2, allowing containment methods to halt their spread before a pandemic could develop.

Are there any species that might be especially good launch pads for a pandemic? A couple of hypotheses suggest this could be the case. One hypothesis is that evolutionary distance matters. A virus that normally circulates in a species that's related to humans is more likely to have components that can interact more effectively with the proteins that are present in human cells. If this were the case, we'd probably expect to see more zoonotic jumps taking place from viruses that infect our fellow primates.

An alternate idea has come out of the fact that this doesn't seem to be consistently true. Bats, for example, have "gifted" humans with such distantly related viruses as SARS-CoV-1 and Ebola, and they're not especially closely related to us. As a result, researchers have hypothesized that there might be what have been called "special reservoirs," or species that, for ecological or lifestyle reasons, have ended up with viruses that can adapt more readily to human hosts. These special reservoirs could simply be more likely to live in close proximity to humans, raising the risk of transmission.

Two Glasgow researchers, Nardus Mollentze and Daniel Streicker, decided to conduct a test of these two hypotheses by figuring out whether there were any groups of species that were more likely to spread viruses to humans.

Building trees

To do so, Mollentze and Streicker built a comprehensive database of every virus that has been reported to make the jump to humans, as well as the host from which it jumped. In all, there were 415 different viruses that had a host assigned and could be used for the analysis (that's out of 673 known virus species). These were spread across 30 families (the designation two levels above species) and had made their way out of 11 different orders of host species (an order is the level above family).

On their own, the results would seem to point to the special reservoir model, as hoofed ungulates (like our agricultural animals) and rodents collectively accounted for half the viruses that had transitioned to human hosts. But things got more complex when the authors tried to analyze the properties of a virus that made it more likely to make this transition. The best combination of properties, which could explain about half the probability of a zoonotic jump, was dominated by things like transmission through insects and a relatively simple replication cycle inside cells.

And while the host's order on the evolutionary tree appeared to matter at first, it mattered much less once the authors adjusted for a critical factor: how many individual species make up that order. For example, rodent and ungulate species may transmit more viruses to

us, but there are a *lot* of species in these groups. If you adjust the rate by species number, the effect largely goes away. If you also control for the fact that we've identified far more virus species in mammals than in birds, then the effect becomes little more than statistical noise. The probability that a group of species will transmit a virus to humans becomes a function of how many species are in that group.

This is inconsistent with the special-reservoir hypothesis. But things don't look great for the evolutionary explanation, either. While the zoonotic risk dropped as you got further from primates, this accounted for less than 1 percent of the overall risk.

In fact, if you simply estimated the number of zoonotic jumps based on the species number, groups that seemed threatening start to look fairly mundane. Rodents, for example, would be expected to have given 42 viruses to humans; we're aware of 41 instances where that took place. Bats would be expected to have transferred 28 viruses to us but have only sent 22 of them. The one exception is, again, the ungulates, which seem to send viruses our way at rates above what we'd expect.

Now what?

The hope was that, by identifying the rules of zoonotic transfers, we could identify groups of species that have an elevated risk of causing problems and thus could be subjected to more careful monitoring. This analysis suggests that these groups might not exist. It doesn't rule out the possibility that there are groups of species below the order level that are hotspots for zoonotic transfers. But at this point, the number of viruses transferred per group is likely to be small and might not stand out from statistical noise.

That said, some species/virus combinations are notable. For example, while bats are notable for having been the source of SARS-CoV-1 and Ebola, they're actually most likely to transfer a new species of rabies virus to humans. Other primates are a major source of adenovirus and Dengue species, while rodents tend to transfer hantaviruses and arenaviruses.

While this isn't especially good news for targeted surveillance efforts, that might not be bad news overall. Having obvious targets might mean we over-focus on those, leaving us vulnerable to risks we hadn't anticipated.

PNAS, 2020. DOI: 10.1073/pnas.1919176117 (About DOIs).

https://bit.ly/2YcHv1f

Boosting the immune system's appetite for cancer

Immunotherapy combo that encourages immune cells to consume tumors could lead to long-term remission for glioblastoma

DALLAS - A combination of immunotherapy agents that encourages some immune cells to eat cancer cells and alert others to attack tumors put mice with a deadly type of brain cancer called glioblastoma into long-term remission, a new study led by UT Southwestern scientists suggests. The finding, published online March 20, 2020, in *Nature Communications*, could lead to new therapies that may significantly extend survival for human glioblastoma patients, which stands at an average of 15 months after diagnosis even with current state-of-the-art therapies.

The immune system has two branches: innate immunity, an evolutionarily older system that continually scans the body and removes foreign invaders such as bacteria or viruses often by "eating" them in a process called phagocytosis; and adaptive immunity, which provides a more targeted and stronger response based on memory acquired from previous exposure to a pathogen. These branches overlap somewhat: For example, the innate immune system trains the adaptive one on where to focus its efforts using the potential pathogens it encounters.

In recent years, researchers have had considerable success in harnessing the immune system to fight some cancers, developing several drugs that have vastly extended survival. However, explains

study leader Wen Jiang, M.D., Ph.D., assistant professor of radiation oncology at UT Southwestern Medical Center, these efforts have mostly focused on adaptive immunity.

Some pharmaceuticals in development aim to boost the innate immune system's action against cancer by blocking CD47, a protein that many cancer cells display on their surfaces that functions as a "don't eat me" signal. Glioblastoma (GBM) - the most common primary central nervous system malignancy in adults and a cancer that Jiang frequently treats in clinic - often displays substantially elevated amounts of CD47 on its tumor cell surfaces, with higher amounts generally suggesting worse outcomes for patients. But these drugs have had mixed results in clinical trials, Jiang says; although they've shown promise for blood cancers, such as leukemias, their performance for solid tumors has been disappointing.

Seeking to boost survival for GBM patients, Jiang and his colleagues searched for ways to encourage innate immune cells to eat GBM cells, which not only destroys these cells directly but also helps train the adaptive immune system to continue the attack.

The researchers first tested how well CD47 monoclonal antibodies - proteins that stick to and mask CD47 - work on GBM cells grown with innate immune cells called phagocytes in petri dishes. Although this agent did boost the phagocytes' consumption of the cancer cells, "the activity wasn't too striking," Jiang says. "It was nothing to brag about."

Next, he and his colleagues tested increasing the cancer cells' "eat me" signal by administering a drug called temozolomide (TMZ), a decade-old pharmaceutical that's a mainstay for most GBM treatment protocols. The drug activates stress responses in cancer cells that make the immune system more likely to eliminate them. Although this drug also increased phagocyte consumption of the cancer cells, these results were also lackluster, says Jiang, also a member of UT Southwestern's Harold C. Simmons Comprehensive Cancer Center.

Jiang and his colleagues then reasoned that because these two pharmaceuticals operate using completely different mechanisms, they might get more of a response combined. Sure enough, when they administered both agents together, they appeared to work in synergy, prompting phagocytes to eat many more GBM cells than either drug alone. Further experiments showed that once phagocytes had eaten their cancerous prey, they used components from these tumor cells to prime the immune system's T cells - the primary adaptive immune cells that fight cancers - to kill more GBM cells.

When the researchers tested this combination therapy in a mouse model of GBM, it successfully shrank tumors and extended life. However, in time, the tumor cells developed a different way to evade the immune system by boosting their production of a protein called PD-L1, which shields them from T cell attack. Thwarting this move, the researchers added an antibody against this protein called anti-PD-1. Together, this three-part regimen - anti-CD47 antibodies, TMZ, and anti-PD-1 antibodies - dramatically extended survival. About 55 percent of these animals did not die over the course of the study, a scenario akin to long-term remission in patients, Jiang says. He and his colleagues hope to test this approach in humans soon in a clinical trial, he adds.

"If a new therapy extends survival by even one to two months, it's considered a blockbuster drug," Jiang says. "Here, we're talking potentially about a significant proportion of patients who could be cured. Bridging the innate and adaptive immune systems could prove to be a major advance for GBM."

Other UTSW researchers who contributed to this study include Yifan Wang, Zhaogang Yang, Mingming Yang, and Weiye Deng.

This research was supported by grants from the National Institute of Neurological Disorders and Stroke Grant R01 NS104315, the Cancer Prevention and Research Institute

of Texas RR180017, the American Brain Tumor Association DG1900021, the National Cancer Institute K08 CA241070, and the Preston A. Wells, Jr. Endowment at the University of Florida.

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Coronaviruses and bats have been evolving together for millions of years

There's a deep evolutionary history between bats and coronaviruses

Bats do a lot of good for the world—they pollinate plants, they eat disease-carrying insects, and they help disperse seeds that help with the regeneration of tropical forest trees. Bats and a range of other mammal groups are also natural carriers of coronaviruses. To better understand this very diverse family of viruses, which includes the specific coronavirus behind COVID-19, scientists compared the different kinds of coronaviruses living in 36 bat species from the western Indian Ocean and nearby areas of Africa. They found that different groups of bats at the genus and in some cases family level had their own unique strains of coronavirus, revealing that bats and coronaviruses have been evolving together for millions of years.

"We found that there's a deep evolutionary history between bats and coronaviruses," says Steve Goodman, MacArthur Field Biologist at Chicago's Field Museum and an author of a paper just released in *Scientific Reports* detailing the discovery. "Developing a better understanding of how coronaviruses evolved can help us build public health programs in the future." The study was led by Université de La Réunion scientists Léa Joffrin and Camille Lebarbenchon, who conducted the genetic analyses in the laboratory of "Processus infectieux en milieu insulaire tropical (PIMIT)" on Réunion Island, focusing on emerging infectious diseases on islands in the western Indian Ocean.

A lot of people use "coronavirus" as a synonym for "COVID-19," the kind of coronavirus causing the current pandemic. However, there are a vast number of types of different coronaviruses, potentially as many as bat species, and most of them are unknown to be transferred to humans and pose no known threat. The coronaviruses carried by the bats studied in this paper are different from the one behind COVID-19, but by learning about coronaviruses in bats in general, we can better understand the virus affecting us today.

All animals have viruses that live inside them, and bats, as well as a range of other mammal groups, happen to be natural carriers of coronaviruses. These coronaviruses don't appear to be harmful to the bats, but there's potential for them to be dangerous to other animals if the viruses have opportunities to jump between species. This study examines the genetic relationships between different strains of coronaviruses and the animals they live in, which sets the stage for a better understanding of the transfer of viruses from animals to humans.

Goodman, who has been based on Madagascar for several decades, and his colleagues took swab and some cases blood samples from more than a thousand bats representing 36 species found on islands in the western Indian Ocean and coastal areas of the African nation of Mozambique. Eight percent of the bats they sampled were carrying a coronavirus.

"This is a very rough estimate of the proportion of infected bats. There is increasing evidence for seasonal variation in the circulation of these viruses in bats, suggesting that this number may significantly vary according to the time of the year," says Camille Lebarbenchon, Disease Ecologist at the Université de La Réunion.

The researchers ran genetic analyses of the coronaviruses present in these bats. By comparing the coronaviruses isolated and sequenced in the context of this study with ones from other animals including dolphins, alpacas, and humans, they were able to build a giant

coronavirus family tree. This family tree shows how the different kinds of coronavirus are related to each other.

"We found that for the most part, each of the different genera of families of bats for which coronavirus sequences were available had their own strains," says Goodman. "Moreover, based on the evolutionary history of the different bat groups, it is clear that there is a deep coexistence between bats (at the level of genus and family) and their associated coronaviruses." For example, fruit bats of the family Pteropodidae from different continents and islands formed a cluster in their tree and were genetically different than the coronavirus strains of other groups of bats found in the same geographical zones.

The team found that in rare cases, bats of different families, genera, and species that live in the same caves and have closely spaced day roost sites shared the same strain of coronavirus. But in this study, the transmission between species is the exception, not the rule. "It is quite reassuring that the transmission of coronavirus in the region between two bat species seems to be very rare given the high diversity of bat coronaviruses. Next, we need to understand environmental, biological, and molecular factors leading to these rare shifts" says Léa Joffrin, a disease ecologist who worked on bat coronavirus during her Ph.D. at the Université de La Réunion.

Learning how different strains of coronavirus evolved could be key for preventing future coronavirus outbreaks. "Before you can actually figure out programs for public health and try to deal with the possible shift of certain diseases to humans, or from humans to animals, you have to know what's out there. This is kind of the blueprint," says Goodman.

Co-author Patrick Mavingui, microbial ecologist and head of the PIMIT Laboratory adds, "The development of serological methods targeting coronavirus strains circulating in the Indian Ocean will help show whether there have already been discrete passages in human populations, and their interaction with the hosts will allow a better understanding of the emergence risk."

The study also highlights the importance of museum collections, says Goodman. The researchers used, in part, bat specimens housed in the Field Museum, to confirm the identities of the animals employed in this study. These voucher specimens helped them confidently say which bats and from which geographical regions hosted the different strains of coronaviruses. The research also drew from genetic databases like GenBank. "This information is important for public health, and the point of departure is closely linked to museum specimens," says Goodman. "We're able to use museum material to study the evolution of a group of viruses and its potential applications across wildlife in the world."

Goodman also notes that despite the fact that bats carry coronaviruses, we shouldn't respond by harming or culling of bats in the name of public health. "There's abundant evidence that bats are important for ecosystem functioning, whether it be for the pollination of flowers, dispersal of fruits, or the consumption of insects, particularly insects that are responsible for transmission of different diseases to humans," he says. "The good they do for us outweighs any potential negatives."

More information: *Scientific Reports (2020).* *DOI: 10.1038/s41598-020-63799-7*
Journal information: *Scientific Reports*

https://wb.md/2W4LTg6

The Great Invader: How COVID-19 Attacks Every Organ

We have underestimated and misunderstood COVID-19 since it first appeared.

Neha Pathak. MD

And as we learn more, it's clear that COVID-19 can be more than just a respiratory disease. It's joined the ranks of other "great imitators" — diseases that can look like almost any condition.

It can be a gastrointestinal disease causing only diarrhea and abdominal pain. It can cause symptoms that may be confused with a cold or the flu. It can cause pinkeye, a runny nose, loss of taste and smell, muscle aches, fatigue, diarrhea, loss of appetite, nausea and vomiting, whole-body rashes, and areas of swelling and redness in just a few spots.

In a more severe disease, doctors have also reported people having heart rhythm problems, heart failure, kidney damage, confusion, headaches, seizures, Guillain-Barre syndrome, and fainting spells, along with new sugar control problems.

It's not just a fever and coughing, leading to shortness of breath, like everyone thought at first. This makes it incredibly difficult to diagnose and even harder to treat."This is a disease progression we have never seen for any infection that I can think of, and I've been doing this for a couple of decades," says Joseph Vinetz, MD, an infectious disease specialist at Yale School of Medicine.

How It Invades

When viral particles land in our eyes, nose, or mouth, "spike proteins" on the virus connect with a specific receptor, known as ACE2, on the surface of our cells, allowing entry. ACE2 receptors make a great target because they are found in organs throughout our bodies. Once the virus enters, it turns the cell into a factory, making millions and millions of copies of itself — which can then be breathed or coughed out to infect others.

In order to evade early detection, the coronavirus uses multiple tools to prevent the infected cells from calling out for help. The virus snips off distress signal proteins that cells make when they are under attack. It also destroys antiviral commands inside the infected cell. This gives the virus much more time to make copies of itself and infect surrounding areas before it is identified as an invader. This is part of the reason why the virus spreads before immune responses, like fever, begin.

Direct Attack

Many with mild or no symptoms are able to fend off the virus before it gets worse. These people may have symptoms only in the upper airway, at the site where they were first infected. But when someone's body can't destroy the virus at its entry point, viral particles march deeper into the body. The virus seems to take a few paths from there, either setting up camp in the lungs, fighting its way into the digestive tract, or doing some combination of both.

"There's clearly a respiratory syndrome, and that's why people end up in the hospital. Some people get a gastrointestinal illness with diarrhea, maybe some abdominal pain, which may or may not be associated with a respiratory illness," says Vinetz.

Once the virus is deeply embedded in the body, it begins to cause more severe disease. This is where direct attack on other organs that have ACE2 receptors can occur, including heart muscle, kidneys, blood vessels, the liver, and potentially the central nervous system. This may be one reason for the vast array of symptoms COVID-19 can cause.

"It's highly unlikely that any other organs can be affected through direct invasion without severe disease," Vinetz adds.

The brain and nerves may also fall prey to direct attack. Kenneth Tyler, MD, chair of the Department of Neurology at the University of Colorado School of Medicine, cautions that direct central nervous system (CNS) attack is still being worked out at this time. There are many routes a virus could take to invade the CNS.

One somewhat disputed view is that the loss of smell could indicate that the nerve responsible for smell is infected and can carry the virus into the CNS, including the brain. "This can be shown to occur in experimental models with non-human coronaviruses and is a potential route of invasion for some other viruses. However, there is no evidence to date establishing that this actually occurs

with SARS-CoV-2," the official name of the virus that causes COVID-19.

Early findings, including those from autopsy and biopsy reports, show that viral particles can be found not only in the nasal passages and throat, but also in tears, stool, the kidneys, liver, pancreas, and heart. One case report found evidence of viral particles in the fluid around the brain in a patient with meningitis.

Collateral Damage That Kills

Severe damage to the lungs may be one trigger that activates and overstimulates the immune system through a barrage of signaling chemicals, known as cytokines.

The flood of these chemicals can set off what is referred to as a "cytokine storm." This is a complex interplay of chemicals that can cause blood pressure to drop, attract more killer immune and inflammatory cells, and lead to even more injury within the lungs, heart, kidneys, and brain. Some researchers say cytokine storms may be the cause of sudden decompensation, leading to critical illness in COVID-19 patients.

A new finding suggests there may be another deadly culprit. Many doctors are discovering that abnormal clotting, known as thrombosis, may also play a major role in lethal COVID-19. Doctors are seeing clots everywhere: large-vessel clots, including deep vein thrombosis (DVT) in the legs and pulmonary emboli (PE) in the lungs; clots in arteries, causing strokes; and small clots in tiny blood vessels in organs throughout the body. Early autopsy results are also showing widely scattered clots in multiple organs.

Adam Cuker, MD, a hematologist at the Hospital of the University of Pennsylvania who specializes in clotting disorders, says these clots are happening at high rates even when patients are on blood thinners for clot prevention. In one study from the Netherlands, 31% of patients hospitalized with COVID-19 got clots while on blood thinners.

Cuker says that "new studies validate what we have all been seeing with our eyes, which is that 'boy, it seems that these patients are clotting a lot.' …And it could be that the rate of thrombotic events are even higher than we truly recognize." Though the reason for the clotting is still not clear, it seems to be playing a much larger role in death than previously understood.

Beyond the collateral damage from cytokine storms and clotting, other things like low blood pressure that comes from a severe illness, low oxygen levels, ventilator use, and drug treatments themselves can all harm organs throughout the body, including the heart, kidneys, liver, brain, and other organs.

Double-Edged Sword

Even though researchers are learning more each day about the virus and how and where it attacks the body, treatment geared toward these targets also pose significant problems. Many drugs come with a risk of destroying the delicate balance that allows the body to help fight the disease or to manage inflammation.

The ACE2 receptor that the virus uses to enter cells is a key player in lowering inflammation and reducing blood pressure. Targeting or blocking this receptor as a treatment strategy to prevent viral entry into cells may actually worsen blood pressure, increase the risk of heart failure and kidney injury, and increase inflammation that may worsen lung injury.

Drugs that target the immune response to lower the risk of a cytokine storm may also tamp down the immune response, making it hard to kill off the virus over the long run.

Using medicines to prevent clotting may end up causing severe bleeding. Cuker points out that "we don't have a good read on bleeding…we have limited evidence about the clotting risk…we have zero evidence on bleeding risk in these patients, and it's a real

priority to understand this risk, especially because one of our strategies to treat the clotting is stepping up intensity the of anti-coagulation."

Timing is likely to be key in treatment strategies. For example, patients may need a drug to boost the immune system early on in the disease, and then one to tamp it down if the disease progresses and cytokine markers begin to rise.

Just the Tip of the Iceberg

Cuker says that what we know about clotting and almost everything else when it comes to COVID-19 "is just the tip of the iceberg."

Sanober Amin, MD, PhD, a dermatologist in Texas, agrees. She's been tracking the wide variety of skin findings that dermatologists across the world have been noting on social media.

She recently posted images on social media that show the wide variety of skin findings she has been seeing and hearing about. Her post received a massive response. Amin says that "dermatologists from around the world, from Turkey to France to Canada to the U.S., are sharing information about rashes that they've observed in people with COVID-19."

Some rashes seem to be consistent with what's called a viral exanthema, which is a term for a general rash that can happen with almost any virus. But, Amin says, "some skin findings are more consistent with superficial clotting in blood vessels close to the skin."

This is what some have started to call "COVID toes," also called pernio. Dermatologists are seeing more cases of these small clots in toes and fingers, especially in children.

It's hard to know which skin conditions are related to COVID-19 because a lot of people without "typical" symptoms are not being tested, Amin says. Researchers will still need to work out which symptoms may be caused by the virus and which may just be unrelated early findings.

Unanswered Questions

For now, much of the information we have about the symptoms of COVID-19 come from hospitalized patients who are very sick by the time they seek care and may not be able to share information about the early signs and symptoms they may have had.

Because of the lag in testing in the U.S., we still don't know the full extent of what mild and moderate versions of the disease look like, or what effects the disease has on people who have many symptoms but aren't quite sick enough to be hospitalized.

One open question is what the long-term effects may be for survivors. What does life look like after being on a ventilator or suddenly needing dialysis? Will we see decreases in heart, lung, and kidney function that is long-lasting and permanent, or will patients eventually recover?

We also don't know how people will clear infections. If the new coronavirus ends up being an acute infection, like other coronaviruses, most recovered people should develop at least a short-term immunity. It's also possible that the virus may persist as a latent infection, like chickenpox, lying dormant in the body, only to re-emerge periodically as shingles does, or become a chronic infection, like hepatitis B, living within the body for a sustained period of time, causing long-term damage.

"It's definitely going to be an acute infection...there's no way it's going to be latent or chronic, no way...I think so…we'll see," Vinetz says.

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https://bit.ly/2xRV4bE

Paleontologists reveal 'the most dangerous place in the history of planet Earth'

100 million years ago, ferocious predators, including flying reptiles and crocodile-like hunters, made the Sahara the most dangerous place on Earth.

Predator paradise - The giant predatory dinosaur Carcharodontosaurus eyes a group of Elosuchus - crocodile-like hunters - near a carcass. **Artwork by Davide Bonadonna**

This is according to an international team of scientists, who have published the biggest review in almost 100 years of fossil vertebrates from an area of Cretaceous rock formations in south-eastern Morocco, known as the Kem Kem Group.

The review, published in the journal *ZooKeys*, "provides a window into Africa's Age of Dinosaurs" according to lead author Dr Nizar Ibrahim, an Assistant Professor of Biology at the University of Detroit Mercy and Visiting Researcher from the University of Portsmouth.

About 100 million years ago, the area was home to a vast river system, filled with many different species of aquatic and terrestrial animals. Fossils from the Kem Kem Group include three of the largest predatory dinosaurs ever known, including the sabre-toothed Carcharodontosaurus (over 8m in length with enormous jaws and long, serrated teeth up to eight inches long) and Deltadromeus (around 8m in length, a member of the raptor family with long, unusually slender hind limbs for its size), as well as several predatory flying reptiles (pterosaurs) and crocodile-like hunters. Dr Ibrahim said: "This was arguably the most dangerous place in the history of planet Earth, a place where a human time-traveller would not last very long."

Many of the predators were relying on an abundant supply of fish, according to co-author Professor David Martill from the University of Portsmouth. He said: "This place was filled with absolutely enormous fish, including giant coelacanths and lungfish. The coelacanth, for example, is probably four or even five times large than today's coelacanth. There is an enormous freshwater saw shark called Onchopristis with the most fearsome of rostral teeth, they are like barbed daggers, but beautifully shiny."

Researchers from the Universities of Detroit, Chicago, Montana, Portsmouth (UK), Leicester (UK, David Unwin), Casablanca (Morocco), and McGill (Canada), as well as the Paris Museum of Natural History, have produced the first detailed and fully illustrated account of the fossil-rich escarpment, previously known as the "Kem Kem beds". The researchers now define this sedimentary package as the Kem Kem Group, which consists of two distinct formations, the Gara Sbaa Formation and the Douira Formation.

To assemble the huge datasets and fossil images, which were originally included in his PhD thesis, Dr Ibrahim visited Kem Kem collections on several continents.

Shedding light on Africa's ancient past is important says Professor Martill, "This is the most comprehensive piece of work on fossil vertebrates from the Sahara in almost a century, since the famous German palaeontologist Ernst Freiherr Stromer von Reichenbach published his last major work in 1936."

https://bit.ly/3bEStjR

New COVID-19 vaccine shows promise in monkeys. Next step: humans.

The vaccine has entered early clinical trials in human volunteers.

By Nicoletta Lanese - Staff Writer

An experimental COVID-19 vaccine protected monkeys from catching the viral infection, according to an unreviewed report. The new vaccine has now entered clinical trials in China to test the drug in humans. Although the animal study, posted April 19 to the preprint database bioRxiv, has not been subject to formal review, scientists took to Twitter to share their first impressions.

"So, this is the first 'serious' preclinical data I have seen for an actual vaccine candidate," Florian Krammer, a professor in the Department of Microbiology at the Icahn School of Medicine at Mount Sinai, tweeted on April 22. Before being tested in healthy humans, vaccines undergo so-called preclinical tests in animals. The experimental vaccine, developed by the Beijing-based company Sinovac Biotech, showed promising results in rhesus macaques before entering human trials, Krammer noted.

"I'm a fan," he added in another tweet.

Now in clinical trials, various doses of the vaccine will be given to 144 individuals to determine whether it's safe, meaning it does not cause dangerous side effects, according to ClinicalTrials.gov. The vaccine would then move into efficacy trials with more than 1,000 additional people to determine whether it triggers an adequate immune response, Meng Weining, Sinovac's senior director for overseas regulatory affairs, told Science magazine.

The Sinovac vaccine contains an inactivated version of SARS-CoV-2, the virus that causes COVID-19. By introducing an inactive virus into the body, the vaccine should prompt the immune system to build antibodies that target the pathogen without triggering an actual COVID-19 infection. When given to mice, rats and rhesus macaques, the vaccine sparked the production of such antibodies, according to the bioRxiv report.

"This is old-fashioned technology," which would make the product easy to manufacture, Krammer wrote on Twitter. "What I like most is that many vaccine producers, also in lower–middle-income countries, could make such a vaccine," he added in an interview with Science magazine.

To test whether the vaccine-generated antibodies would neutralize SARS-CoV-2, the research team collected samples from the mice and rats and exposed those antibodies to 10 different SARS-CoV-2 strains in test tubes. The distinct strains of SARS-CoV-2 were originally sampled from patients in China, Italy, Spain, Switzerland and the United Kingdom, and represent, "to some extent, the circulating populations" of SARS-CoV-2, according to the report.

The vaccine-generated antibodies were able to neutralize the various strains, suggesting that the vaccine could "exhibit potent neutralization activities against SARS-CoV-2 strains circulating worldwide," the research team wrote. The finding that the antibodies could neutralize different strains "provides strong evidence that the virus is not mutating in a way that would make it resistant to a #COVID19 vaccine. Good to know," Mark Slifka, a professor of molecular microbiology and immunology at Oregon Health & Science University, tweeted in response to Krammer's thread.

After their test tube experiments, the research team tested how well the vaccine worked in rhesus macaques, a type of monkey that develops "COVID-19-like symptoms" when infected with SARS-CoV-2. Twelve monkeys received either a placebo treatment, a medium dose of the vaccine or a high dose of the vaccine; all the injections were delivered in three doses over two weeks.

Eight days after giving the final dose, the researchers introduced the SARS-CoV-2 virus into the monkey's lungs through a long tube. While the virus replicated widely in the placebo group and triggered symptoms of pneumonia, all the vaccinated monkeys "were largely protected against SARS-CoV-2 infection," the authors wrote.

Those in the high dose group fared the best: One week after being exposed to the virus, the high dose group showed no detectable SARS-CoV-2 in their lungs or throats. Some virus could still be detected in the medium dose group after a week, but the infection still appeared well-controlled. Given that vaccinated monkeys did not develop adverse side effects, the results "give us a lot of confidence" that the vaccine will work in humans, Meng told Science magazine.

Despite this apparent success, Douglas Reed, an associate professor of immunology at the University of Pittsburgh who was not involved in the research, told Science magazine that the number of monkeys included in the study "was too small to yield statistically significant results." Reed also expressed concern about how the Sinovac team grew the coronavirus for use in the vaccinated monkeys, stating that the procedure could have altered the virus to be unlike the version that infects humans.

Barring more data, though, the small study does "[lessen] the concern" about certain side effects that could be elicited by a COVID-19 vaccine, Reed added.

The Sinovac team found that the vaccinated monkeys did not show adverse side effects, such as fever, weight loss or a phenomenon called "antibody dependent enhancement (ADE)," wherein the body reacts *worse* to a virus after vaccination, rather than developing protection. Previous vaccines tested against other coronaviruses in animals and the human coronavirus SARS triggered ADE in early animal studies, so there's some concern that a SARS-CoV-2 vaccine might do the same, Live Science previously reported.

Even if the promising results in monkeys carry over to humans, "whether there is long-lasting protection remains a key question," Lucy Walker, a professor of immune regulation at University College London, who was not involved in the research, wrote on Twitter. In other words, if the vaccine protects humans against COVID-19 infection, we don't know how long that protection would last.

"But encouraging data [from the bioRxiv study]: no ADE, no obvious surprises," Walker added. "Many vaccines are in development, increasing chances of success."

https://wb.md/2VDpTcX

COVID-19 Linked to Large Vessel Stroke in Young Adults

Physicians in New York City, which still leads the nation in reported COVID-19 cases, are reporting significantly more acute, large vessel strokes in young adults infected with COVID-19.

Damian McNamara

In a rapid communication to be published online April 29 in the *New England Journal of Medicine*, investigators led by Thomas Oxley, MD, PhD, department of neurosurgery, Mount Sinai Health System, report five cases of large vessel stroke over a 2-week period in COVID-19 patients under age 50 years. This represents a sevenfold increase in what would normally be expected.

The five cases had either no, or mild, COVID-19 symptoms.

"It's been surprising to learn that the virus appears to cause disease through a process of blood clotting," Oxley told *Medscape Medical News*.

The message for neurologists and other physicians is "we're learning that this can disproportionally affect large vessels more than small vessels in terms of presentation of stroke," he said.

Inflammation in the blood vessel walls may be driving thrombosis formation, Oxley added. This report joins other research pointing to this emerging phenomenon.

Recently, investigators in the Netherlands found a "remarkably high" 31% rate of thrombotic complications among 184 critical care patients with COVID-19 pneumonia.

Oxley and colleagues also suggest that since the onset of the pandemic, fewer patients may be calling emergency services when they experience signs of a stroke. The physicians note that two of the five cases in the report delayed calling an ambulance.

"I understand why people do not want to leave the household. I think people are more willing to ignore other [non-COVID-19] symptoms in this environment," he said.

As previously reported by *Medscape Medical News*, physicians in hospitals across the United States and elsewhere have reported a significant drop in stroke patients since the COVID-19 pandemic took hold, suggesting patients may indeed be foregoing emergency care.

The observations from Oxley and colleagues call for greater awareness of the association between COVID-19 and large vessel strokes in this age group, they add. One patient in the case series died, one remains hospitalized, two are undergoing rehabilitation, and one was discharged home as of April 24.

Oxley and colleagues dedicate their report to "our inspiring colleague Gary Sclar, MD, a stroke physician who succumbed to COVID-19 while caring for his patients."

Oxley has disclosed no relevant financial relationships.

N Engl J Med. Scheduled for publication online April 29, 2020.

https://nyti.ms/2Y5rslz

Amid the Coronavirus Crisis, Heart and Stroke Patients Go Missing

Emergency physicians are seeing declines in the number of patients arriving with cardiac problems. Some say they were afraid to go to the hospital.

By Gina Kolata

Bishnu Virachan was a bicycle deliveryman for a grocery store in Queens. With New York City locked down, he was busier than ever. But in early April, as he was watching television, he felt “a pain in my heart.” It frightened him, but he did not go to the emergency room. Mr. Virachan, 43, was even more afraid of that. “What can I do? What can I do?” he asked. “Everywhere, the coronavirus.”

After a few days, pain overrode fear and he went to Mount Sinai Hospital in Manhattan. Doctors discovered a nearly complete blockage of his left main coronary artery.

A surgeon opened the artery, but Mr. Virachan was left with a weakened heart. Had he waited much longer, doctors said, he would have died.

Fear of the coronavirus is leading people with life-threatening emergencies, like a heart attack or stroke, to stay home when ordinarily they would have rushed to the emergency room, preliminary research suggests. Without prompt treatment, some patients, like Mr. Virachan, have suffered permanent damage or have died.

Emergency rooms have about half the normal number of patients, and heart and stroke units are nearly empty, according to doctors at many urban medical centers. Some medical experts fear more people are dying from untreated emergencies than from the coronavirus.

A recent paper by cardiologists at nine large medical centers estimated a 38 percent reduction since March 1 in the number patients with serious heart attacks coming in to have urgently needed procedures to open their arteries.

On a recent day at the Cleveland Clinic, there were only seven patients in the 24-bed coronary care unit. Usually the unit is full.

“Where are the patients?” asked Dr. Steven Nissen, a cardiologist there. “That can’t be normal.”

One of the few was a man who lives in Cleveland. According to Dr. Nissen, the man felt chest pain while doing push-ups, but feared going to the hospital because there might be coronavirus patients there. He stayed home for a week, growing weaker — out of breath with the slightest exertion, his legs swelling. Finally, on April 16, he went to the Cleveland Clinic.

What should have been an easily treated heart attack had progressed to a life-threatening disaster. He survived after a dicey operation and spent nearly a week in intensive care, including several days on a ventilator, Dr. Nissen said.

The inpatient stroke unit at Stanford University Medical Center in California usually has 12 to 15 patients, said its director, Dr. Gregory Albers. On one recent day in April, there were none at all, something that had never happened. “It’s frightening,” Dr. Albers said. Yet few Covid-19 patients have been admitted to the hospital, and people needing emergency treatment have little to fear. “We prepared for an onslaught, but it has not arrived,” Dr. Albers said.

According to Dr. Samin Sharma, who heads the cardiac catheterization lab at Mount Sinai Hospital in New York, the number of heart attack patients fell from seven in February to three in March. So far in April there have been only two.

It’s not just the United States. Dr. Valentin Fuster, editor of the Journal of American College of Cardiology, said he is getting so many papers from around the world on the steep decline in heart attack patients in hospitals that he simply cannot publish them all.

A hospital in Jaipur, India, for example, that Dr. Sharma owns, treated 45 heart attack patients in January, he said. In February, there were 32, and in March, 12. In April, so far the number is just six.

Researchers in Austria estimated that in March 110 citizens died from untreated heart attacks, compared with 86 who died of Covid-19. They based their calculations on a precipitous decline in patients going to hospitals, the expected number of heart attacks in Austria, and the mortality rates of untreated heart attacks.

“I am very very worried that we are creating a problem that will have long-term consequences for the health of the community,” said Dr. Richard A. Chazal, medical director of the Heart and Vascular Institute at Lee Health in Fort Myers, Fla., and a past president of the American College of Cardiology.

Could it be that there actually are fewer medical emergencies now? Dr. Fuster speculated that perhaps people are healthier because they are eating better, exercising more and under less stress now that so many are working from home. And, of course, the air is cleaner in urban areas.

Other experts doubt that better health habits could have such dramatic and immediate effects. Far from eating better, Dr. Nissen said, many patients tell him they are overeating comfort food. There is no evidence that people are exercising more, and people are hardly under less stress. “They are scared to death,” Dr. Nissen said. And, he said, even if some people changed their habits, studies have failed to find any immediate effects of short-term lifestyle changes on heart attack rates.

At the moment, it is nearly impossible to know who is not showing up in emergency rooms, and why, said Dr. Harlan Krumholz, a cardiologist at Yale University. “You can’t find the dog that doesn’t

bark," he said. But you can get a sense from the patients who do show up, even belatedly.

Kaplana Jain, 60, of Cresskill, N.J, was watching CNN late at night on April 18. She got up to go to the bathroom and collapsed on the floor. Her blood sugar was elevated, and her family called 911.

When the paramedics arrived, Ms. Jain told them she did not want to go to the hospital. "I was scared because of the coronavirus going on," she said.

The next day, unable to walk, she called Dr. Sharma, a family friend. He urged her to go to the hospital, but still fearful, she insisted on going to his office the next day. When she arrived, Dr. Sharma did an EKG that confirmed she was having a heart attack. He rushed her to the hospital and opened a blocked artery.

"She is one of the lucky people with this kind of heart attack who didn't develop cardiac arrest or go into shock," he said. Had she not gone to the hospital, she likely would have died at home.

Back at the Cleveland Clinic, a man arrived with stroke symptoms on April 15. According to Dr. Thomas Waters, an emergency room physician, the man had waited two days to come in because he was afraid of the coronavirus. There was nothing doctors could do to prevent permanent brain damage.

"What's done is done," Dr. Waters said. "Now we are at a point where we have nothing to offer but rehab."

https://bit.ly/3ePOeUy

New York clinical trial quietly tests heartburn remedy against coronavirus

The fast-growing list of possible treatments for the novel coronavirus includes an unlikely candidate: famotidine, the active compound in the over-the-counter heartburn drug Pepcid.

By Brendan Borrell

On 7 April, the first COVID-19 patients at Northwell Health in the New York City area began receiving famotidine intravenously, at nine times the heartburn dose. Unlike other drugs the 23-hospital system is testing, including Regeneron's sarilumab and Gilead Science's remdesivir, Northwell kept the famotidine study under wraps to secure a research stockpile before other hospitals, or even the federal government, started buying it. "If we talked about this to the wrong people or too soon, the drug supply would be gone," says Kevin Tracey, a former neurosurgeon in charge of the hospital system's research.

As of Saturday, 187 COVID-19 patients in critical status, including many on ventilators, have been enrolled in the trial, which aims for a total of 1174 people. Reports from China and molecular modeling results suggest that the drug, which seems to bind to a key enzyme in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), could make a difference. But the hype surrounding hydroxychloroquine and chloroquine—the unproven antimalarial drugs touted by President Donald Trump and some physicians and scientists—has made Tracey wary of sparking premature enthusiasm. He is tight-lipped about famotidine's prospects, at least until interim results from the first 391 patients are in. "If it does work, we'll know in a few weeks," he says.

A globe-trotting infectious disease doctor named Michael Callahan was the first to call attention to the drug in the United States. Callahan, who is based at Massachusetts General Hospital in Boston and has extensive connections in the biodefense world, has spent time in disease hot zones around the world, including the 2003 outbreak of another coronavirus disease, SARS, in Hong Kong. In mid-January, he was in Nanjing, China, working on an avian flu project. As the COVID-19 epidemic began exploding in Wuhan, he followed his Chinese colleagues to the increasingly desperate city.

The virus was killing as many one out of five patients over 80 years of age. Patients of all ages with hypertension and chronic

obstructive pulmonary disease were faring poorly. Callahan and his Chinese colleagues got curious about why many of the survivors tended to be poor. “Why are these elderly peasants not dying?” he asks.

In reviewing 6212 COVID-19 patient records, the doctors noticed that many survivors had been suffering from chronic heartburn and were on famotidine rather than more-expensive omeprazole (Prilosec), the medicine of choice both in the United States and among wealthier Chinese. Hospitalized COVID-19 patients on famotidine appeared to be dying at a rate of about 14% compared with 27% for those not on the drug, although the analysis was crude and the result was not statistically significant.

But that was enough for Callahan to pursue the issue back home. After returning from Wuhan, he briefed Robert Kadlec, assistant secretary for Preparedness and Response at the Department of Health and Human Services, then checked in with Robert Malone, chief medical officer of Florida-based Alchem Laboratories, a contract manufacturing organization. Malone is part of a classified project called DOMANE that uses computer simulations, artificial intelligence, and other methods to rapidly identify U.S. Food and Drug Administration-approved drugs and other safe compounds that can be repurposed against threats such as new viruses.

Malone had his eyes on a viral enzyme called the papainlike protease, which helps the pathogen replicate. To see if famotidine binds to the protein, he would ordinarily need the enzyme’s 3D structure, but that would not be available for months. So Malone recruited computational chemist Joshua Pottel, president of Montreal-based Molecular Forecaster, to predict it from two crystal structures of the protease from the 2003 SARS coronavirus, combined with the new coronavirus’s RNA sequence.

It was hardly plug-and-play. Among other things, they compared the gene sequences of the new and old proteases to rule out crucial differences in structure. Pottel then tested how 2600 different compounds interact with the new protease. The modeling yielded several dozen promising hits that pharmaceutical chemists and other experts narrowed to three. Famotidine was one. (The compound has not popped up in in vitro screens of existing drug libraries for antiviral activity, however.)

With both the tantalizing Chinese data and the modeling pointing towards famotidine, a low-cost, generally safe drug, Callahan contacted Tracey about running a double-blind randomized study. COVID-19 patients with decreased kidney function would be excluded because high doses of famotidine can cause heart problems in them.

After getting Food and Drug Administration approval, Northwell used its own funds to launch the effort. Just getting half of the needed famotidine in sterile vials took weeks, because the injectable version is not widely used. On 14 April, the U.S. Biomedical Advanced Research and Development Authority (BARDA), which operates under Kadlec, gave Alchem a $20.7 million contract for the trial, most of which paid Northwell’s costs.

The study’s draft protocol was aimed only at evaluating famotidine’s efficacy, but Trump’s “game-changer” antimalarial drug was rapidly becoming the standard of care for hospitalized COVID-19 patients. That meant investigators would only be able to recruit enough subjects for a trial that tested a combination of famotidine and hydroxychloroquine. Those patients would be compared with a hydroxychloroquine-only arm and a historic control arm made up of hundreds of patients treated earlier in the outbreak. “Is it good science? No,” Tracey says. “It’s the real world.”

Anecdotal evidence has encouraged the Northwell researchers. After speaking to Tracey, David Tuveson, director of the Cold Spring Harbor Laboratory Cancer Center, recommended famotidine

to his 44-year-old sister, an engineer with New York City hospitals. She had tested positive for COVID-19 and developed a fever. Her lips became dark blue from hypoxia. She took her first megadose of oral famotidine on 28 March. The next morning, her fever broke and her oxygen saturation returned to a normal range. Five sick coworkers, including three with confirmed COVID-19, also showed dramatic improvements upon taking over-the-counter versions of the drug, according a spreadsheet of case histories Tuveson shared with *Science*. Many COVID-19 patients recover with simple symptom-relieving medications, but Tuveson credits the heartburn drug. “I would say that was a penicillin effect,” he says.

After an email chain about Tuveson’s experience spread widely among doctors, Timothy Wang, head of gastroenterology at Columbia University Medical Center, saw more hints of famotidine’s promise in his own retrospective review of records from 1620 hospitalized COVID-19 patients. Last week, he shared the results with Tracey and Callahan, and he added them as a co-authors on a paper now under review at *Annals of Internal Medicine*. All three researchers emphasize, though, that the real test is the trial now underway. “We still don’t know if it will work or not,” Tracey says.

Callahan has kept busy since his return from China. Kadlec deployed him on medical evacuation missions of Americans on two heavily infected cruise ships. Now back to doing patient rounds in Boston, he says the famotidine lead underscores the importance of science diplomacy in the face of an infectious disease that knows no borders. When it comes to experience with COVID-19, he says, “No amount of smart people at the [National Institutes of Health] or Harvard or Stanford can outclass an average doctor in Wuhan."