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Three longtime antibiotics could offer alternative to addictive opioid pain relievers

Three decades-old antibiotics administered together can block a type of pain triggered by nerve damage in an animal model

Dallas - Three decades-old antibiotics administered together can block a type of pain triggered by nerve damage in an animal model, UT Southwestern researchers report. The finding, published online today in *PNAS*, could offer an alternative to opioid-based painkillers, addictive prescription medications that are responsible for an epidemic of abuse in the U.S.

Over 100 million Americans are affected by chronic pain, and a quarter of these experience pain on a daily basis, a burden that costs an estimated $600 billion in lost wages and medical expenses each year. For many of these patients - those with cancer, diabetes, or trauma, for example - their pain is neuropathic, meaning it's caused by damage to pain-sensing nerves.

To treat chronic pain, prescriptions for opioid painkillers have increased exponentially since the late 1990s, leading to a rise in abuse and overdoses. Despite the desperate need for safer pain medications, development of a new prescription drug typically takes over a decade and more than $2 billion according to a study by the Tufts Center for the Study of Drug Development, explains study leader Enas S. Kandil, M.D., associate professor of anesthesiology and pain management at UTSW.

Seeking an alternative to opioids, Kandil and her UT Southwestern colleagues - including Hesham A. Sadek, M.D., Ph.D., professor of internal medicine, molecular biology, and biophysics; Mark Henkemeyer, Ph.D., professor of neuroscience; Mahmoud S. Ahmed, Ph.D., instructor of internal medicine; and Ping Wang, Ph.D., a postdoctoral researcher - explored the potential of drugs already approved by the Food and Drug Administration (FDA).

The team focused on EphB1, a protein found on the surface of nerve cells, which Henkemeyer and his colleagues discovered during his postdoctoral training nearly three decades ago. Research has shown that this protein is key for producing neuropathic pain. Mice genetically altered to remove all EphB1 don't feel neuropathic pain, he explains. Even mice with half the usual amount of this protein are resistant to neuropathic pain, suggesting EphB1's promise as a target for pain-relieving drugs. Unfortunately, no known drugs inactivate EphB1.

Exploring this angle further, Ahmed used computer modeling to scan a library of FDA-approved drugs, testing if their molecular structures had the right shape and chemistry to bind to EphB1. Their search turned up three tetracyclines, members of a family of antibiotics used since the 1970s. These drugs - *demeclocycline*, *chlortetracycline*, and *minocycline* - have a long history of safe use and minimal side effects, Ahmed says.

To investigate whether these drugs could bind to and inactivate EphB1, the team combined the protein and these drugs in petri dishes and measured EphB1's activity. Sure enough, each of these drugs inhibited the protein at relatively low doses. Using X-ray crystallography, Wang imaged the structure of EphB1 with chlortetracycline, showing that the drug fits neatly into a pocket in the protein's catalytic domain, a key portion necessary for EphB1 to function.

In three different mouse models of neuropathic pain, injections of these three drugs *in combination* significantly blunted reactions to painful stimuli such as heat or pressure, with the triplet achieving a greater effect at lower doses than each drug individually. When the researchers examined the brains and spinal cords of these animals, they confirmed that EphB1 on the cells of these tissues had been inactivated, the probable cause for their pain resistance. A combination of these drugs might be able to blunt pain in humans

too, the next stage for this research, says Kandil.

"Unless we find alternatives to opioids for chronic pain, we will continue to see a spiral in the opioid epidemic," she says. "This study shows what can happen if you bring together scientists and physicians with different experience from different backgrounds. We're opening the window to something new."

Sadek holds the J. Fred Schoellkopf, Jr. Chair in Cardiology. Henkemeyer holds the Dick and Martha Brooks Professorship in Nerve Growth Research.

Other researchers who contributed to this study include Ngoc Uyen Nhi Nguyen, Yuji Nakada, Ivan Menendez-Montes, and Robert Bachoo, all of UTSW; Yuji Nakada of the University of Alabama at Birmingham, and Muhammad Ismail of The British University in Egypt.

This study was funded by the Hamon Center for Regenerative Science and Medicine at UT Southwestern Medical Center.

http://bit.ly/3soHyCN

Yale scientists repair injured spinal cord using patients' own stem cells

Injection of bone marrow derived stem cells in patients with spinal cord injuries led to improvement in motor functions

Intravenous injection of bone marrow derived stem cells (MSCs) in patients with spinal cord injuries led to significant improvement in motor functions, researchers from Yale University and Japan report Feb. 18 in the *Journal of Clinical Neurology and Neurosurgery*.

For more than half of the patients, substantial improvements in key functions -- such as ability to walk, or to use their hands -- were observed within weeks of stem cell injection, the researchers report. No substantial side effects were reported.

The patients had sustained, non-penetrating spinal cord injuries, in many cases from falls or minor trauma, several weeks prior to implantation of the stem cells. Their symptoms involved loss of motor function and coordination, sensory loss, as well as bowel and bladder dysfunction. The stem cells were prepared from the patients' own bone marrow, via a culture protocol that took a few weeks in a specialized cell processing center. The cells were injected intravenously in this series, with each patient serving as their own control. Results were not blinded and there were no placebo controls.

Yale scientists Jeffery D. Kocsis, professor of neurology and neuroscience, and Stephen G. Waxman, professor of neurology, neuroscience and pharmacology, were senior authors of the study, which was carried out with investigators at Sapporo Medical University in Japan. Key investigators of the Sapporo team, Osamu Honmou and Masanori Sasaki, both hold adjunct professor positions in neurology at Yale.

Kocsis and Waxman stress that additional studies will be needed to confirm the results of this preliminary, unblinded trial. They also stress that this could take years. Despite the challenges, they remain optimistic.

"Similar results with stem cells in patients with stroke increases our confidence that this approach may be clinically useful," noted Kocsis. "This clinical study is the culmination of extensive preclinical laboratory work using MSCs between Yale and Sapporo colleagues over many years."

"The idea that we may be able to restore function after injury to the brain and spinal cord using the patient's own stem cells has intrigued us for years," Waxman said. "Now we have a hint, in humans, that it may be possible."

http://wb.md/3pQjAhW

Why I've Changed My Approach to Mammography in Older Women

Optimal approach to patients with a history of breast cancer has much in common with the approach already taken with older women who have never had breast cancer

Kenneth W. Lin, MD, MPH

Hi, everyone. I'm Dr Kenny Lin. I am a family physician at Georgetown University Medical Center, and I blog at Common

Sense Family Doctor.

In my practice, when a female patient without a history of breast cancer reaches the age of 75, I make a point to discuss discontinuing screening mammograms. The US Preventive Services Task Force found insufficient evidence to assess the balance of benefits or harms of screening for breast cancer in this age group because they were not included in clinical trials, but a large observational study published last year found no significant mortality benefit from continuing mammography after age 75. By stopping screening, women avoid the inconvenience of radiology visits and possible COVID-19 exposures, anxiety associated with false-positive results, and overdiagnosis and overtreatment of small tumors that would have never otherwise bothered them during their lifetimes.

Until recently, though, I approached older women with a personal history of breast cancer quite differently. Guidelines recommend that breast cancer survivors receive surveillance with annual mammography and clinical breast exams and don't say anything about stopping them. Although primary care clinicians are not universally comfortable with caring for cancer survivors, studies show that we are as capable as oncologists of providing follow-up care for women who have completed breast cancer treatment. I had assumed that this group was at much higher risk of developing new breast cancer, enough to justify continuing mammograms even in women whose life expectancy was limited by other chronic conditions. I was apparently far from alone in making this assumption; a 2017 study found that 57% of surveyed breast cancer survivors with an estimated life expectancy of less than 5 years reported having a mammogram in the past year.

It turns out, though, that the optimal approach to these patients has a lot in common with the approach I already take with older women who have never had breast cancer. In a consensus guideline recently published in *JAMA Oncology*, an expert panel reviewed the evidence on the 10-year risks of recurrent breast cancer based on cancer type and therapy or therapies received. For most scenarios, their risk is only slightly higher than that of a 75-year-old woman at average risk without a personal history of breast cancer. Consequently, the guideline recommends stopping surveillance mammography in all women at age 85 or who have a life expectancy of less than 5 years, regardless of the type of breast cancer they had.

For breast cancer survivors between age 75 and 84 years with an estimated life expectancy of 5 years or more, the recommendations are stratified by previous cancer risk, based on hormone receptor and *ERBB2* positivity, triple-negative cancers, and cancer stage at the time of diagnosis. Women with a history of lower-risk cancers can continue mammograms every 1-2 years and consider stopping when life expectancy is less than 10 years. Women with a history of higher-risk cancers can continue mammograms annually through age 79, or through age 84 if life expectancy is at least 5 years.

The guideline also includes some helpful talking points to share with patients who may be reluctant to change follow-up routines that they have adhered to for many years after cancer treatment: Provide reassurance that their risk for new breast cancers is low; discontinuing mammography does not mean "giving up"; and continuing clinical breast exams may be as effective as mammograms in finding cancer recurrences while reducing false positives. Although the guideline did not recommend a specific tool to estimate life expectancy, the ePrognosis website includes calculators that have been validated with community-dwelling and institutionalized older adults.

The bottom line is that family physicians should carefully consider the individual patient's likelihood of benefit before ordering a mammogram for screening or surveillance in anyone who is age 75

or older. Also, estimating life expectancy will not only help guide discussions about breast cancer screening but also screening and surveillance for colorectal cancer, taking a statin for cardiovascular prevention, and advance care plans.

This has been Dr Kenny Lin for Medscape Family Medicine. Thank you for reading.

Kenny Lin, MD, MPH, teaches family medicine, preventive medicine, and health policy at Georgetown University School of Medicine. He is deputy editor of the journal American Family Physician.

http://bit.ly/37KYdbP

Catching COVID from surfaces is very unlikely. So perhaps we can ease up on the disinfecting

What is the extent of the role of surface contact in the transmission of the virus?

Hassan Vally*

A lot has happened over the past year, so you can be forgiven for not having a clear memory of what some of the major concerns were at the beginning of the pandemic. However, if you think back to the beginning of the pandemic, one of the major concerns was the role that surfaces played in the transmission of the virus.

As an epidemiologist, I remember spending countless hours responding to media requests answering questions along the lines of whether we should be washing the outside of food cans or disinfecting our mail.

I also remember seeing teams of people walking the streets at all hours wiping down poles and cleaning public benches.

But what does the evidence *actually* say about surface transmission more than 12 months into this pandemic?

Before addressing this, we need to define the question we're asking. The key question isn't whether surface transmission is possible, or whether it can occur in the real world — it almost certainly can.

The real question is: what is the extent of the role of surface contact in the transmission of the virus? That is, what is the likelihood of catching COVID via a surface, as opposed to other methods of transmission?

The evidence is minimal

There's little evidence that surface transmission is a common way in which the coronavirus is spread. The main way it's spread is by the air, either by larger droplets via close contact, or by smaller droplets called aerosols. As a side note, the relative role these two routes play in transmission is probably a much more interesting and important question to clarify from a public health perspective.

One of the best commentaries on COVID surface transmission was published in the journal Lancet Infectious Diseases in July 2020 by Emanuel Goldman, a professor of microbiology from the United States. As he described, one of the drivers for the exaggerated perception of the risk of surface transmission was the publication of a number of studies showing SARS-CoV-2 viral particles could be detected for long periods of time on various surfaces.

You probably saw these studies because they received enormous publicity worldwide and I remember doing numerous interviews in which I had to explain what these findings actually meant.

As I explained at the time, these studies could not be generalised to the real world, and in some instances the media releases accompanying them tended towards overstating the significance of these findings.

The key issue is that as a general principal the time required for a population of microoganisms to die is directly proportional to the size of that population. This means the greater the amount of virus deposited on a surface, the longer you will find viable viral particles on that surface.

So in terms of designing experiments that are relevant to public health, one of the more important variables in these studies is the *amount* of virus deposited on a surface — and the extent to which

this approximates what would happen in the real world.

If you understand this, it becomes apparent that a number of these virus survival studies stacked the odds of detecting viable virus by depositing large amounts of virus on surfaces far in excess of what would be reasonably expected to be found in the real world. What's more, some of these studies customised conditions that would extend the life of viral particles, such as adjusting humidity and excluding natural light.

Although there was nothing wrong with the science here, it was the real world relevance and the interpretation that was amiss at times. It's notable that other studies which more closely replicated real world scenarios found less impressive survival times for three other human coronaviruses (including SARS).

It's important to note we're relying on indirect evidence in assessing the role of surface transmission for the coronavirus. That is, you can't actually do an ethical scientific experiment that confirms the role surface transmission plays because you'd have to deliberately infect people. Despite being such a seemingly straightforward question, it's surprisingly difficult to determine the relative importance of the various transmission pathways for this virus.

What we have to do instead is look at all of the evidence we do have and see what it's telling us, including case studies describing transmission events. And if we do this, there isn't a lot out there to support surface transmission being of major importance in the spread of COVID.

We could save a lot of time and money

We need to put the risks of exposure to SARS-CoV-2 via the various modes of transmission into perspective, so we focus our limited energy and resources on the right things.

This isn't to say surface transmission isn't possible and that it doesn't pose a risk in certain situations, or that we should disregard it completely. But, we should acknowledge the threat surface transmission poses is relatively small.

We can therefore mitigate this relatively small risk by continuing to focus on hand hygiene and ensuring cleaning protocols are more in keeping with the risk of surface transmission.

In doing this, we can potentially save millions of dollars being spent on obsessive cleaning practices. These are probably providing little or no benefit and being done solely because they're easy to do and provide the reassurance of doing something, thereby relieving some of our anxieties.

Associate Professor, La Trobe University

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http://bit.ly/3dJ7oxo

Martian moons have a common ancestor

What is the explanation for the current orbits of Phobos and Deimos?

by Barbara Vonarburg

Mars's two moons, Phobos and Deimos, have puzzled researchers since their discovery in 1877. They are very small: Phobos's diameter of 22 kilometers is 160 times smaller than that of our moon, and Deimos is even smaller, with a diameter of only 12 kilometers. "Our moon is essentially spherical, while the moons of Mars are very irregularly shaped—like potatoes," says Amirhossein Bagheri, a doctoral student at the Institute of Geophysics at ETH Zurich, adding: "Phobos and Deimos look more like asteroids than natural moons."

This led people to suspect that they might in fact be asteroids that were captured in Mars's gravity field. "But that's where the problems started," Bagheri says. Captured objects would be expected to follow an eccentric orbit around the planet, and that

orbit would be at a random inclination. In contradiction to this hypothesis, the orbits of the Martian moons are almost circular and move in the equatorial plane of Mars. So, what is the explanation for the current orbits of Phobos and Deimos? To solve this dynamic problem, the researchers relied on computer simulations.

Artist's impression of the collision between a Martian primordial moon and an asteroid, which could have led to the formation of Phobos and Deimos.
Credit: Mark Garlick / markgarlick.com

Calculating the past

"The idea was to trace the orbits and their changes back into the past," says Amir Khan, a Senior Scientist at the Physics Institute of the University of Zurich and the Institute of Geophysics at ETH Zurich. As it turned out, the orbits of Phobos and Deimos appeared to have crossed in the past. "This means that the moons were very likely in the same place and therefore have the same origin," Khan says. The researchers concluded that a larger celestial body was orbiting Mars back then. This original moon was probably hit by another body and disintegrated as a result. "Phobos and Deimos are the remainders of this lost moon," says Bagheri, who is lead author of the study now published in the journal *Nature Astronomy*.

While easy to follow, these conclusions required extensive preliminary work. First, the researchers had to refine the existing theory describing the interaction between the moons and Mars. "All the celestial bodies exert tidal forces on each other," Khan explains. These forces lead to a form of energy conversion known as dissipation, the scale of which depends on the bodies' size, their interior composition and not least the distances between them.

Insights into the interior of Mars and its moons

Mars is currently being explored by NASA's InSight mission, with ETH Zurich's involvement: the electronics for the mission's seismometer, which is recording marsquakes and possibly meteorite impacts, were built at ETH. "These recordings let us look inside the Red Planet," Khan says, "and this data is used to constrain the Mars model in our calculations and the dissipation occurring inside the red planet."

Images and measurements by other Mars probes have suggested that Phobos and Deimos are made of very porous material. At less than 2 grams per cubic centimeter, their density is much lower than the average density of Earth, which is 5.5 grams per cubic centimeter. "There are a lot of cavities inside Phobos, which might contain water ice," Khan suspects, "and that's where the tides are causing a lot of energy to dissipate."

Using these findings and their refined theory on the tidal effects, the researchers ran hundreds of computer simulations to track the orbits of the moons backward in time until they reached the intersection—the moment Phobos and Deimos were born. Depending on the simulation, this point in time lies between 1 and 2.7 billion years in the past. "The exact time depends on the physical properties of Phobos and Deimos, that is, how porous they are" Bagheri says. A Japanese probe scheduled for launch in 2025 will explore Phobos and return samples to Earth. The researchers expect that these samples will provide the needed details about the interior of the Martian moons that will enable more precise calculations of their origin.

The end of Phobos

Another thing their calculations show is that the common ancestor of Phobos and Deimos was further away from Mars than Phobos is today. While the smaller Deimos has remained in the vicinity of where it came into being, tidal forces are causing the larger Phobos to approach Mars—and this process is ongoing, as the researchers explain. Their computer simulations also show the future

development of the moons' orbits. It seems Deimos will move away from Mars very slowly, just as our moon is slowly receding from Earth. Phobos, however, will crash into Mars in less than 40 million years or be torn apart by the gravitational forces as it nears Mars.

More information: *Amirhossein Bagheri et al. Dynamical evidence for Phobos and Deimos as remnants of a disrupted common progenitor, Nature Astronomy (2021). DOI: 10.1038/s41550-021-01306-2*

http://wb.md/3aMi0JV

Fired for Good Judgment a Sign of Physicians' Lost Respect

What happened to Hasan Gokal, MD, should stick painfully in the craws of all physicians.

Melissa Walton-Shirley, MD

It should serve as a call to action because Gokal is sitting at home today without a job and under threat of further legal action while we continue about our day.

Gokal's "crime" is that he vaccinated 10 strangers and acquaintances with soon-to-expire doses of the Moderna COVID-19 vaccine. He drove to the homes of some in the dark of night and injected others on his Sugar Land, Texas, lawn. He spent hours in a frantic search for willing recipients to beat the expiration clock. With minutes to spare, he gave the last dose to his at-risk wife, who has symptomatic pulmonary sarcoidosis, but whose age meant she did not fall into a vaccine priority tier.

According to the *New York Times* Gokal's wife was hesitant, afraid he might get into trouble. But why would she be hesitant ? He wasn't doing anything immoral. Perhaps she knew how far physicians have fallen and how bitterly they both could suffer.

In Barren County, Kentucky, where I live, a state of emergency was declared by our judge executive because of inclement weather. This directive allows our emergency management to "waive procedures and formalities otherwise required by the law." It's too bad that the same courtesy was not afforded to Gokal in Texas. It's a shame that ice and snow didn't drive his actions. Perhaps that would have protected him against the harsh criticism. Rather, it was his oath to patients and dedication to his fellow humans that motivated him, and for that, he was made to suffer.

Gokal was right to think that pouring the last 10 vaccine doses down the toilet would be an egregious act. But he was wrong in thinking his decision to find takers for the vaccine would be viewed as expedient. Instead, he was accused of graft and even nepotism. And there is the rub. That he was fired and charged with the theft of $137 worth of vaccines says everything about how physicians are treated in the year 2021. Gokal's lawyer says the charge carried a maximum penalty of 1 year in prison and a fine of nearly $4000.

Thank God, a sage judge threw out the case and "rebuked" the office of District Attorney Kim Ogg. That hasn't stopped her from threatening to bring the case to a grand jury. That threat invites anyone faced with the same scenario to flush the extra vaccine doses into the septic system. It encourages us to choose the toilet handle to avoid a mug shot.

And we can't ignore the racial slant to this story. The *Times* reported that Gokal asked the officials, "Are you suggesting that there were too many Indian names in this group?"

"Exactly" was the answer. Let that sink in.

None of this would have happened 20 years ago. Back then, no one would have questioned the wisdom a physician gains from all our years of training and residency. In an age when anyone who conducts an office visit is now called "doctor," respect for the letters "MD" has been leveled. We physicians have lost our autonomy and been cowed into submission.

But whatever his profession, Hasan Gokal was fired for being a good human. Today, the sun rose on 10 individuals who now enjoy better protection against a deadly pandemic. They include a bed-

bound nonagenarian. A woman in her 80s with dementia. A mother with a child who uses a ventilator. All now have antibodies against SARS-CoV2 because of the tireless actions of Gokal.

Yet Gokal's future is uncertain. Will we help him or will we leave him to the wolves? In an email exchange with his lawyer's office, I learned that Gokal has received offers of employment but is unable to entertain them because the actions by the Harris County District Attorney triggered an automatic review by the Texas Medical Board. A GoFundMe page was launched, but an appreciative Gokal stated publicly that he'd rather the money go to a needy charity.

In the last paragraph of the *Times* article Gokal asks, "How can I take it back?" referencing stories about "the Pakistani doctor in Houston who stole all those vaccines."

Let's help him take back his story. In helping him, perhaps we can take back a little control. We could start with letters of support that could be mailed to his lawyer, Paul Doyle, Esq., of Houston, or tweet, respectfully of course, to the district attorney @Kimoggforda. We can also let the Harris County Public Health Department in Houston know what we think of their actions.

On Martin Luther King Day, Kim Ogg, the district attorney who charged Gokal, tweeted MLK's famous quote: "Injustice anywhere is a threat to justice everywhere."

Let that motivate us to action.

Melissa Walton-Shirley, MD, is a native Kentuckian who retired from full-time invasive cardiology. She enjoys locums work in Montana and is a champion of physician rights and patient safety. In addition to opinion writing, she enjoys spending time with her husband, daughters and parents, and sidelines as a backing vocalist for local rock bands.

http://bit.ly/2NALmlF

Remains of oldest American dog bolster idea that first humans arrived along the coast

Dogs accompanied the first humans who set foot on these continents—and both traveled there along the Pacific coast

By Andrew Curry

When researchers began to excavate a tunnellike cave on the west coast of Alaska in 1998, they were hoping to discover the remains of ancient bears. Instead, they unearthed something even more intriguing: a tiny chip of bone belonging to the first known dog in the Americas. The find supports the idea that dogs accompanied the first humans who set foot on these continents—and that both traveled there along the Pacific coast.

DNA analysis of this fingernail-size fragment of bone showed it once belonged to the oldest known dog in the Americas. **Douglas Levere/University at Buffalo**

"This is a fantastic study," says archaeologist Loren Davis of Oregon State University, Corvallis, who was not involved in the research. "If the coastal migration theory is correct, we should expect to see exactly the kind of evidence reported in this study."

Researchers once thought humans initially entered the Americas about 12,000 years ago. That's when thick glaciers that covered much of North America began to melt. This opened a corridor, which allowed people to trek from Siberia across now-submerged land in the Bering Sea, and then into North America on the hunt for mammoth and other big game.

But over the past decade, archaeologists have shown people might have begun to move into North America much earlier. To get around the glaciers, they would have island hopped by boat and walked along shorelines exposed by low sea levels. They traveled from Siberia through the Alaskan archipelago about 16,000 years ago, eventually making their way down the Pacific coast.

The sliver of dog bone supports this hypothesis. Recovered from among more than 50,000 prehistoric animal and human remains excavated near Wrangel Island, researchers didn't realize it came

from a dog until they analyzed its DNA. “We started out thinking this was just another bear bone,” says team leader Charlotte Lindqvist, a biologist at the University at Buffalo (UB). “When we went deeper, we found out it was from a dog.”

The bone is about 10,200 years old, making its owner the oldest dog known in the Americas, the scientists report today in the *Proceedings of the Royal Society B: Biological Sciences*. (The previous record holders were two 10,000-year-old dogs unearthed in the U.S. Midwest.) And the dog’s DNA holds clues to an even earlier time.

The pup’s genome revealed it was closely related to the first known dogs, which researchers think were domesticated in Siberia about 23,000 years ago. Based on the number of genetic differences between the Alaskan dog and its Siberian ancestors, the team estimates the two populations split 16,700 years ago, plus or minus a few thousand years.

That’s a clue that dogs—and their humans—left Siberia and entered the Americas thousands of years before North America’s glaciers melted. “Here we have the genetic evidence, if not the physical evidence, [showing] dogs were already in the Americas with humans 16,000 years ago,” says Durham University archaeologist Angela Perri, who was not part of the team.

The dates also line up with DNA-based estimates for when modern Native Americans split off from ancestors in Siberia, providing another line of evidence to pin down when the first migrations happened. “Understanding how the dogs moved also shows you how the humans moved,” says Flavio Augusto da Silva Coelho, a graduate student at UB who did the DNA and other analyses.

Perri agrees. The study shows dogs are a useful way to track ancient human migrations, especially when human remains are missing or can’t be sampled because of descendant community concerns, she says. Even without human samples, “dogs can tell us some really interesting things” about our history, she says.

For example, chemical isotopes in the dog bone suggest the pooch ate marine animals. Because dogs aren’t much good at fishing, their masters likely gave them scraps of fish, seal, or whale that they themselves hunted. “It’s a strong indication people are feeding dogs,” Perri says. “Everything in this study points to coastally adapted people and their dogs moving into the Americas.”

http://bit.ly/3aOYGvx

ALS neuron damage reversed with new compound

Scientists identify first compound to repair degenerating brain cells in paralyzing disease

**** New compound targets neurons that initiate voluntary movement***
**** After 60 days of treatment, diseased brain cells look like healthy cells***
**** More research needed before clinical trial can be initiated***

Chicago and Evanston--- Northwestern University scientists have identified the first compound that eliminates the ongoing degeneration of upper motor neurons that become diseased and are a key contributor to ALS (amyotrophic lateral sclerosis), a swift and fatal neurodegenerative disease that paralyzes its victims.

In addition to ALS, upper motor neuron degeneration also results in other motor neuron diseases, such as hereditary spastic paraplegia (HSP) and primary lateral sclerosis (PLS).

In ALS, movement-initiating nerve cells in the brain (upper motor neurons) and muscle-controlling nerve cells in the spinal cord (lower motor neurons) die. The disease results in rapidly progressing paralysis and death.

So far, there has been no drug or treatment for the brain component of ALS, and no drug for HSP and PLS patients.

"Even though the upper motor neurons are responsible for the initiation and modulation of movement, and their degeneration is an early event in ALS, so far there has been no treatment option to improve their health," said senior author Hande Ozdinler, associate

professor of neurology at Northwestern University Feinberg School of Medicine. "We have identified the first compound that improves the health of upper motor neurons that become diseased."

The study will be published in *Clinical and Translational Medicine* on February 23. Ozdinler collaborated on the research with study author Richard B. Silverman, the Patrick G. Ryan/Aon Professor of Chemistry at Northwestern. The study was initiated after Silverman identified a compound, NU-9, developed in his lab for its ability to reduce protein misfolding in critical cell lines. The compound is not toxic and crosses the blood brain barrier.

The NU-9 compound addresses two of the important factors that cause upper motor neurons to become diseased in ALS: protein misfolding and protein clumping inside the cell. Proteins fold in a unique way to function; when they misfold they become toxic to the neuron. Sometimes proteins aggregate inside the cell and cause pathology as in the TDP-43 protein pathology. This happens in about 90% of all ALS patient brains and is one of the most common problems in neurodegeneration.

The research team began to investigate whether NU-9 would be able to help repair upper motor neurons that become diseased due to increased protein misfolding in ALS. The results in mice were positive. Scientists next performed experiments to reveal how and why the diseased upper motor neurons regained their health.

New compound restores neurons to robust health

After administering NU-9, both the mitochondria (the cell's energy producer) and the endoplasmic reticulum (the cell's protein producer) began to regain their health and integrity resulting in improved neuron health. The upper motor neurons were more intact, their cell bodies were larger and the dendrites were not riddled with holes. They stopped degenerating so much that the diseased neurons became similar to healthy control neurons after 60 days of NU-9 treatment.

Commanders-in-chief of movement

"Improving the health of brain neurons is important for ALS and other motor neuron diseases," Ozdinler said.

Upper motor neurons are the brain's commanders-in-chief of movement. They carry the brain's input to spinal cord targets to initiate voluntary movement. The degeneration of these neurons impairs the connection from the brain to the spinal cord and leads to paralysis in patients.

Lower motor neurons have direct connections with the muscle, contracting muscle to execute movement. Thus, the lower motor neuron activity is in part controlled by the upper motor neurons.

Ozdinler and colleagues will now complete more detailed toxicology and pharmacokinetic studies prior to initiating a Phase 1 clinical trial.

Ozdinler and Silverman are members of the Chemistry of Life Processes Institute at Northwestern.

Other Northwestern study authors include Bar?? Genç, Mukesh Gautam, Öge Gözütok, Ina Dervishi, Santana Sanchez, Gashaw Goshu, Nuran Koçak and Edward Xie.

The study has been funded by grant R01 AG061708 from the National Institute on Aging of the National Institutes of Health, NUCATS, Northwestern University, Les Turner ALS Foundation and the ALSA TREAT ALS Award.

http://wb.md/3pXGSCB

Tree Resin Compound Defeats Drug-Resistant Bacteria in Lab Tests

A new compound made from tree resin kills almost 100% of drug-resistant bacteria without harming healthy tissue, laboratory studies suggest.

Laird Harrison

Made into a film, this nanocellulose could be used as a wound dressing or as a protective surface on medical implants.

Researchers have been surprised by its efficacy in the studies so far. "It was like a wonder," Ghada Hassan, a doctoral student in pharmacy at the University of Helsinki in Finland, told *Medscape*

Medical News. She and her colleagues published their findings in *Applied Bio Materials* .

Bacteria are able to evolve resistance to new antibiotics sometimes within only a few years. Infection by methicillin-resistant *Staphylococcus aureus* (MRSA) is a particular problem in pressure ulcers and wounds from prosthetic, plastic, and reconstructive surgery.

In search of a medicine that could retain its efficacy against these difficult-to-treat bacterial strains, Hassan noticed in Finnish pharmacies a traditional treatment for small wounds made from the resin of conifers. References to resin as a wound dressing date back 500 years in Finland, and there are many favorable anecdotal reports, she said.

Trees produce the resin when injured to protect themselves from infection. As the resin has maintained its effectiveness for millions of years, Hassan reasoned that bacteria could not easily evolve resistance to it. However, raw tree resin would be difficult to use in many medical procedures. "For implants you cannot open the patient and pour in some resin there and then close the patient and hope it will be well," she said.

Using dehydroabietic acid derivatives, Hassan and her colleagues modified the resin, creating a film that could be used both in wound dressings and as a coating for implants.

In an early test, they applied MRSA directly to sheets of the modified nanocellulose and found that 99.999% of the bacteria died.

In a second experiment, they created an artificial dermis containing horse plasma on which they cultivated MRSA. They then applied a film made up of the experimental nanocellulose and found that it was highly effective in killing the bacteria.

In a third experiment they placed human erythrocytes directly on sheets of the modified nanocellulose and found that most of the erythrocytes survived, as did skin fibroblasts in similar experiments.

In further experiments, they found that the nanocellulose could kill multiple strains of *S. aureus*, as well as *Escherichia coli*.

The novel compound seems to damage bacteria through multiple mechanisms, making it more difficult for the organisms to evolve resistance, Hassan said.

Early, but Good Potential

The research suggests a lot of potential for the new compound, said Aaron Glatt, MD, a professor of medicine at the Icahn School of Medicine at Mount Sinai in New York City and a spokesperson for the Infectious Diseases Society of America. But it must undergo clinical trials before it can realize that potential, he told *Medscape Medical News*.

"This paper is certainly no indication that it will become the definitive answer," he said. "What looks good in a laboratory, what looks good in a test tube, let's put it to the test in real life."

In addition, even if it passes muster in clinical trials, it will have to show cost-effectiveness, said Barry Kreiswirth, PhD, adjunct faculty member of the department of medicine at New York University in New York City.

"As an example, we know that using copper bed rails and other copper products in a hospital setting reduces infections, but no one is willing to pay the extra cost to copperize a hospital bed," he told *Medscape Medical News* in an email.

That said, the modified nanocellulose is less expensive and less toxic than copper and silver, which are also being tested as a coating for implants, Hassan said. "Cellulose is the most abundant polymer on Earth," she said. And unlike some other material under consideration, its bacteria-killing ingredients don't leach out into the environment, so it may stay effective for a longer time, she said.

Her laboratory is currently closed as a protection against COVID-19, but when it opens she would like to next test the material against pathogenic fungi and viruses.

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Hassan, Kreiswirth, and Glatts reported no relevant financial relationships.

http://bit.ly/3kmFZ5o

New discoveries on the containment of COVID-19 finds travel bans are of limited value

NYU Tandon researchers join collaboration with Politecnico di Torino revealing that after spread, travel bans are of limited value in thwarting the spread of COVID-19

BROOKLYN, New York, Wednesday, February 24, 2021 - Travel bans have been key to efforts by many countries to control the spread of COVID-19. But new research aimed at providing a decision support system to Italian policy makers, recently published in the *Journal of the Royal Society Interface*, suggests that reducing individual activity (i.e., social distancing, closure of non-essential business, etc.) is far superior in controlling the dissemination of Sars-CoV-2, the virus that causes COVID-19.

The research, which has implications for the United States and other countries, found that limiting personal mobility through travel restrictions and similar tactics is effective only **in the first phases of the epidemic**, and reduces in proportion to the spread of infection across a population.

In the study, "Modelling and predicting the effect of social distancing and travel restrictions on COVID-19 spreading" the researchers, led by Alessandro Rizzo, visiting professor in the Office of Innovation at NYU Tandon and professor at the Politecnico di Torino, and Maurizio Porfiri Institute Professor of mechanical and aerospace, biomedical and civil and urban engineering at NYU Tandon and a member of the Center for Urban Science and Progress (CUSP), detail a data modeling framework for isolating the differential efficacy of different COVID-19 intervention policies. Since their method benefits from a low computational load (it can easily run on a personal computer), it can be a valuable decision support system to policy makers, toward the implementation of combined containment actions that can protect citizens' health, while avoiding total closures, with all their economic, social, and psychological consequences.

"While this project was focused specifically on Italy, the results are revelatory for virtually any country relying on travel restrictions to stem the spread of the pandemic. We look forward to using US data to tune the model and give specific answers to combat this delicate phase of the pandemic," said Porfiri.

Added Rizzo, "We are particularly satisfied with this model, as it provides very detailed answers even though it relies only on aggregated sources of data - a further guarantee of people's privacy."

The work includes a realistic representation of demographic data and travel patterns of both commuters and those taking long-distance trips, using only aggregated and publicly available data, without resorting to individual tracking devices. It follows upon a study on the spread of Covid-19 in New Rochelle, New York predicting the diffusion of COVID-19 in medium-sized cities and provinces, published as the cover of *Advanced Modeling and Simulations (Wiley)*,

The investigators, including Francesco Parino of Politecnico di Torino and Lorenzo Zino of the University of Groningen, The Netherlands, also found that selective lockdown policies, for example restriction only on the activity of the elderly, seems not to have a great effect on the overall transmission of the epidemic.

Deploying their algorithmic framework to model scenarios in which restrictions are lifted, discovered that restrictions on social activity must be gradually removed to avoid a second wave, while the timing and swiftness of removal of travel restrictions seem not to have a great effect on the transmission.

In view of the scarce resources and the inherent slowness of

vaccination campaigns, the research group is now engaged in the use of the model to assess the effect of different vaccination policies, toward the definition of vaccination rollouts that will aim at providing an optimal outcome in spite of the limited resources in terms of vaccine doses and operators.

The U.S. National Science Foundation (CMMI-1561134 and CMMI-2027990), Compagnia di San Paolo, MAECI ('Mac2Mic'), the European Research Council (ERC-CoG-771687), and The Netherlands Organisation for Scientific Research (NWO-vidi-14134) provided generous support for this research.

http://bit.ly/3klDOiy

UK Announces "High-Risk, High-Reward" Research Development Agency

The program, known as ARIA, will be independent and scientist-led.

Lisa Winter

In an effort to reinvigorate the UK's research and development endeavors, the government announced Friday (February 19) the creation of an independent, scientist-led funder named the Advanced Research & Invention Agency. The goal is to have the organization up and running by next year.

In the same vein as the US Defense Advanced Research Projects Agency (DARPA), the goal of ARIA is to take on "high-risk, high-reward" projects that are largely unencumbered by the bureaucratic interference and finicky grant procedures of traditional research projects, according to the announcement. The statement cited DARPA's early work on mRNA vaccines and antibody therapy as being vital to the global COVID-19 response.

"ARIA will unleash our most inspirational scientists and inventors, empowering them with the freedom to drive forward their scientific vision and explore game-changing new ideas at a speed like never before," Science and Innovation Minister Amanda Solloway says in the announcement. "This will help to create new inventions, technologies and industries that will truly cement the UK's status as a global science superpower."

The UK has an annual research and development budget of around £14.6 billion. To start, ARIA will receive £800 million total over the next four years. In comparison, the US allocates around $3.5 billion to DARPA each year. This disparity has drawn some skepticism over what can reasonably be expected from ARIA.

"It is totally not clear what ARIA really will do, especially given its modest budget," Jon Crowcroft, a computer scientist at Cambridge University, tells *CNBC*.

Now that the agency has been announced, the highest leadership roles need to be filled in the coming weeks so that its first goals can be set. The UK government will be recruiting scientists at the top of their fields and it will be up to these experts—and not politicians—to guide ARIA's projects forward.

Defining its mission is critical to the success of the agency, according to Anna Goldstein, the executive director of the Energy Transition Initiative at the University of Massachusetts, Amherst. Unless that is set, "ARIA is a solution in search of a problem," she tells *Science*.

http://bit.ly/2NCvRcZ

Scientists describe earliest primate fossils

A new study published Feb. 24 in the journal Royal Society Open Science documents the earliest-known fossil evidence of primates.

A team of 10 researchers from across the U.S. analyzed several fossils of Purgatorius, the oldest genus in a group of the earliest-known primates called plesiadapiforms. These ancient mammals were small-bodied and ate specialized diets of insects and fruits that varied by species. These newly described specimens are central to understanding primate ancestry and paint a picture of how life on land recovered after the Cretaceous-Paleogene extinction event 66 million years ago that wiped out all dinosaurs -- except for birds -- and led to the rise of mammals.

Gregory Wilson Mantilla, a University of Washington professor of biology and curator of vertebrate paleontology at the UW's Burke Museum of Natural History & Culture, co-led the study with Stephen Chester of Brooklyn College and the City University of New York. The team analyzed fossilized teeth found in the Hell Creek area of northeastern Montana

Shortly after the extinction of the dinosaurs, the earliest known archaic primates, such as the newly described species Purgatorius mckeeveri shown in the foreground, quickly set themselves apart from their competition — like the archaic ungulate mammal on the forest floor — by specializing in an omnivorous diet including fruit found up in the trees. **Andrey Atuchin**

The fossils, which are now part of the collections at the University of California Museum of Paleontology, are estimated to be 65.9 million years old, about 105,000 to 139,000 years after the mass extinction event. Based on the age of the fossils, the team estimates that the ancestor of all primates --including plesiadapiforms and today's primates such as lemurs, monkeys and apes -- likely emerged by the Late Cretaceous and lived alongside large dinosaurs.

"It's mind blowing to think of our earliest archaic primate ancestors," said Wilson Mantilla. "They were some of the first mammals to diversify in this new post-mass extinction world, taking advantage of the fruits and insects up in the forest canopy."

The fossils include two species of Purgatorius: Purgatorius janisae and a new species described by the team named Purgatorius mckeeveri. Three of the teeth found have distinct features compared to any previously known Purgatorius species and led to the description of the new species.

Purgatorius mckeeveri is named after Frank McKeever, who was among the first residents of the area where the fossils were discovered, and also the family of John and Cathy McKeever, who have since supported the field work where the oldest specimen of this new species was discovered.

"This was a really cool study to be a part of, particularly because it provides further evidence that the earliest primates originated before the extinction of non-avian dinosaurs," said co-author Brody Hovatter, a UW graduate student in Earth and space sciences. "They became highly abundant within a million years after that extinction."

"This discovery is exciting because it represents the oldest dated occurrence of archaic primates in the fossil record," said Chester. "It adds to our understanding of how the earliest primates separated themselves from their competitors following the demise of the dinosaurs."

Co-author on the study was the late William Clemens who was a professor emeritus at the University of California, Berkeley and former director of the UC Museum of Paleontology. Additional co-authors are Jason Moore and Wade Mans of the University of New Mexico; Courtney Sprain of the University of Florida; William Mitchell of Minnesota IT Services; Roland Mundil of the Berkeley Geochronology Center; and Paul Renne of UC Berkeley and the Berkeley Geochronology Center. The research was funded by the National Science Foundation, the UC Museum of Paleontology, the Myhrvold and Havranek Charitable Family Fund, the UW, the CUNY and the Leakey Foundation.

http://nyti.ms/3skXuWC

Can Zapping Our Brains Really Cure Depression?

New research suggests that stimulating neurons in the brain can address psychological issues with surprising speed and precision.

By Kim Tingley

The brain is an electrical organ. Everything that goes on in there is a result of millivolts zipping from one neuron to another in particular patterns. This raises the tantalizing possibility that, should we ever decode those patterns, we could electrically adjust them to treat neurological dysfunction — from Alzheimer’s to schizophrenia — or even optimize desirable qualities like intelligence and resilience.

Of course, the brain is so complex, and so difficult to access, that this is much easier to imagine than to do. A pair of studies published in January in the journal Nature Medicine, however, demonstrate that electrical stimulation can address obsessive-compulsive urges and symptoms of depression with surprising speed and precision.

Mapping participants' brain activity when they experienced certain sensations allowed researchers to personalize the stimulation and modify moods and habits far more directly than is possible through therapy or medication. The results also showed the degree to which symptoms that we tend to categorize as a single disorder — depression, for example — may involve electrical processes that are unique to each person.

In the first study, a team from the University of California, San Francisco, surgically implanted electrodes in the brain of a woman whose severe depression had proved resistant to other treatments. For 10 days, they delivered pulses through the electrodes to different areas of the brain at various frequencies and had the patient record her level of depression, anxiety and energy on an iPad. The impact of certain pulses was significant and nuanced. "Within a minute, she would say, 'I feel like I'm reading a good book,'" says Katherine W. Scangos, a psychiatrist and the study's lead author. The patient described the effect of another pulse as "less cobwebs and cotton."

The researchers also recorded what type of unmediated brain activity coincided with periods of low mood or energy. The aim was to use those responses to guide the placement of another set of electrodes that would deliver what is known as deep-brain stimulation — a technique that can restore lost function to neurons by zapping them with a consistent, high-frequency electrical pulse. To date, it has been employed most commonly to treat movement disorders, like Parkinson's. It has also shown promise for depression. "But because depression presents differently in different people, it likely involves multiple neural circuits," Scangos says. She and her colleagues wondered if a "more personalized approach" might make the treatment more effective. Based on their mapping of the patient's brain activity, they programmed the electrodes to detect her depressed states and deliver stimulation in response, much the way a pacemaker acts on the heart. That experimental treatment will continue long term as the patient goes about her daily life.

Deep-brain stimulation is too invasive to use except in extreme circumstances. But in the second study, researchers used a noninvasive technique called transcranial alternating current stimulation to deliver electrical pulses through electrodes placed on participants' scalps. The goal was to try to curb obsessive-compulsive behaviors.

Past studies have suggested that the orbital frontal cortex, an area in the brain's reward network, might play a role in reinforcing such behaviors, by regarding them as beneficial. So the researchers attached the electrodes to 64 volunteers and recorded the frequency in hertz at which their orbital frontal cortex fired when they won a monetary reward in a game.

Crucially, it was noted, the frequency varied slightly by individual. Using that personal frequency, the researchers next stimulated the same area in each participant for 30 minutes a day for five days in a row. Doing so, they found, reduced the number of obsessive-compulsive behaviors in the volunteers by an average of nearly 30 percent over the following three months. (None of the volunteers had an obsessive-compulsive disorder diagnosis. All of them, however, reported varying degrees of repetitive tendencies, and those whose symptoms were most intense got the most relief.)

The researchers hypothesize that the stimulation helped the orbital frontal cortex maintain its optimal rhythm, thereby improving its

coordination with other areas in the reward network.

The findings reinforced the idea that personalized brain stimulation requires determining not just the right area to target but also the right rhythm at which to do so. "The neural code — it's frequency-specific," says Robert M.G. Reinhart, one of the study's authors and the director of the Cognitive and Clinical Neuroscience Laboratory at Boston University. "The channel of information-processing in the brain is just like a channel you might tune in to on the radio."

The study also illustrated that traits like compulsivity exist on a spectrum. Currently, a person for whom those traits are bothersome but not disabling might not seek treatment, particularly if it comes with side effects, as medications often do. Brain stimulation, though, could one day remedy all kinds of conditions we now target inexactly with drugs, Reinhart says. "If you want to get futuristic, you can imagine someone giving themselves a zap to get over a trans-Atlantic flight. What people use coffee for today."

Psychiatrists won't be prescribing brain stimulation to the masses anytime soon. But by identifying the neural circuits that give rise to particular symptoms, and by showing that alterations to the timing of their firing can change those symptoms, they offer new ways to think about what psychiatric disorders are. "There's still a lot of stigma around depression that a lot of patients feel," Scangos says. The subject of her study was no exception: "The fact that there was such an immediate response when we stimulated made her feel like, It's not something I'm doing wrong; it's something in my brain that can be addressed."

Giving a collection of symptoms a diagnostic label like "depression" is useful because it helps doctors more efficiently find a successful treatment, currently a lengthy process of trial and error. "The million-dollar question is how to match the best treatment to the patient and how to avoid treatments that won't work," says Helen Mayberg, a neurologist and director of the Nash Family Center for Advanced Circuit Therapeutics at the Icahn School of Medicine at Mount Sinai; she was co-author of a commentary on the two studies. As neuroscientists map the brain activity of more and more patients, they're getting closer to being able to offer a battery of tests that show, Scangos says, "you have this type of depression, you'll respond best to this medication."

Ultimately, if we could address those symptoms directly, we might be able to get rid of diagnostic categories altogether, says Alvaro Pascual-Leone, medical director of the Wolk Center for Memory Health at Hebrew SeniorLife and a professor of neurology at Harvard Medical School. Rather than applying a default label of depression or obsessive-compulsive disorder, Pascual-Leone says, doctors could instead ask, "What is the disabling symptom that this person presents?" And then treat it specifically.

For now, what these studies offer everyone is additional evidence that "our brains are plastic," says Shrey Grover, a graduate student and a co-author of the Boston University study. "And we can rewire the brain in different ways." Those include psychotherapy and pharmacology. Our neural activity also changes as we learn; it changes as we age. This means we can improve how our minds work at any point in our lives, even without advanced technology.

But the brain's plasticity makes it all the more puzzling that certain psychological states can be so hard to dispel. Research into personalized brain stimulation also probes at the larger question of why moods or habits that are mild or circumstantial in some people — carefully rechecking a tax form, say, or feeling deep sadness at the death of a loved one — are chronic and debilitating in others. "There's nothing that gets right at the cause," Reinhart says. "It's like the water in the sink is running, and you can mop up the floor, but no one's turning off the faucet."

http://nyti.ms/2ND9J28

Deaths Fell in Japan Last Year. How?

The decline indicates that methods for fighting the coronavirus have also been effective at curbing other illnesses.

By Ben Dooley and Hikari Hida

TOKYO — Deaths in Japan fell last year for the first time in more than a decade, a jarring contrast to the huge death tolls suffered by many countries in the pandemic and a signal that Japan's coronavirus measures have had positive spillover effects.

The Health Ministry reported this week that deaths in Japan had dropped by more than 9,300 in 2020 to around 1.4 million. The decrease — seven-tenths of 1 percent from the year before — was a surprising turnabout for a nation with the oldest population in the world.

When the coronavirus first began spreading early last year, many feared that Japan's large cohort of older people would make the country especially vulnerable. But case numbers and deaths have stayed much lower than in the United States and Western Europe.

As of Tuesday, Japan had recorded just under 7,600 deaths from the virus, and the seven-day average for new cases stood around 1,200. Daily infection numbers have never exceeded 8,000.

The United States, by contrast, has recorded more than 500,000 deaths and 28 million infections. Deaths from causes other than Covid-19 have reportedly risen, too, perhaps because people have avoided medical facilities.

Life expectancy for Americans fell by a full year in the first six months of 2020, the largest drop since World War II.

The most recent Japanese government data does not break down mortality by category, so it is difficult to say with certainty what caused the decrease in deaths.

But data from earlier in the year suggests that it was spurred in large part by a drastic decline in respiratory illnesses, a likely side effect of the country's almost ubiquitous adoption of mask wearing and social distancing.

While masks were already a common sight in Japan, over the past year, they have become de rigueur as a virus-fighting measure.

The country has also widely adopted other steps to prevent transmission of the virus, including the placement of hand sanitizer at the entrance to virtually every commercial space and workplace, and broad adherence to government recommendations to avoid the "three C's": closed spaces, crowded places and close contact with others.

One other, albeit small, factor is a decrease in traffic accidents as fewer people took to the roads, especially as the government twice declared states of emergency. Deaths from road accidents dropped nearly 12 percent in 2020, to 2,839, according to data maintained by the National Police Agency. It was the lowest number since the agency began tracking the data in 1948.

Japan is not alone in seeing peripheral benefits from coronavirus measures. Deaths in China fell slightly in the first three months of 2020 outside the virus epicenter of Wuhan, according to a study by the University of Oxford and the Chinese Center for Disease Control and Prevention.

While the decrease in deaths in Japan was a welcome development, there were some ominous signs. The country has seen a resurgence in suicides, particularly among women, with just under 4 percent more people taking their own lives in 2020 than in the previous year. Among women, the increase was nearly 15 percent.

Experts traced the phenomenon to stresses related to the pandemic including job losses, the increased isolation of people sheltering in place and the growing domestic burdens shouldered by women.

Japan's population also continued to contract despite the decline in overall deaths. The country, which began shrinking in 2007 because of falling birthrates and its increasing proportion of older people,

lost more than 511,000 people in 2020, a slight acceleration from the previous year.

Births fell once again last year, suggesting that the pandemic is likely to speed up Japan's depopulation. According to government projections, the population, which now stands at 126 million, will fall below 100 million by 2053 and sink to 88 million by 2065.

http://bit.ly/2ZNdeFx

Exposure to superbacteria among visitors to the tropics proved more extensive than thought

Exposure to superbacteria among visitors to the tropics proved much more extensive than previously thought

Before the corona pandemic, tens of millions international travellers annually headed to the tropics, getting exposed to local intestinal bacteria. A total of 20-70% of those returning from the tropics carry - for the most unknowingly - ESBL-producing bacteria resistant to multiple antibiotics. The likelihood of acquiring such superbacteria depends on destination and health behaviour abroad. The risk is greatest in South and Southeast Asia, and a substantial increase is associated with contracting travellers' diarrhoea and taking antibiotics while abroad.

An investigation led by professor of Infectious diseases Anu Kantele at Helsinki University together with MD Esther Kuenzli from Swiss Tropical and Public Health Institute involved a real-time scrutiny of superbacteria acquisition among a group of 20 Europeans over a three-week visit to Laos. The participants' daily stool samples were initially screened on site in Vientiane, Laos, and later, in Europe, the superbacteria strains isolated were analysed in detail by whole-genome sequencing.

The study was recently published in the *Lancet Microbe*. It belongs to a series of Kantele's studies exploring the spread of antimicrobial resistance by international travel.

"Our study revealed that travellers to the tropics are much more predisposed to acquiring superbacteria than previously thought. In conventional studies, stool samples are only collected before and after travel, not while abroad as we did now. Travellers to the tropics are known to be exposed to superbacteria, but the extent of the risk revealed by our real-time sampling was unexpected," Kantele says.

Travellers contracted superbacteria within the first week abroad

In Laos, daily stool samples from the participants were analysed locally in the Lao-Oxford-Mahosot Hospital-Wellcome Trust - Research laboratory. Had samples only been collected before and after travel, the proportion of superbacteria carriers had been approximately 70%. Daily real-time scrutiny already while abroad revealed, however, that all travellers had contracted a superbacter within a week after arrival.

The findings varied day by day. While some participants carried superbacteria for several days, others had a couple of days' breaks after which superbacteria were found again. Part of the travellers acquired several strains.

"It became evident that acquisition of superbacteria is a dynamic process: bacteria come and go, some strains persisting for a lengthy period of time," Kantele says.

Whole-genome sequencing revealed the great variety among strains of superbacteria

After returning home, to explore the isolated superbacteria strains in more detail, the researchers established a collaboration with Jukka Corander, professor of Statistics at the Universities of Helsinki and Oslo, and Alan McNally, professor of Microbial genetics at the University of Birmingham, England. Whole-genome sequencing and analyses proved colonization to be a dynamic process involving constant switches between the various strains. Indeed, all the travellers had been exposed to a much wider range of

superbacteria than generally thought. Applying the traditional approach, about 20 new strains would have been detected after travel, but daily sampling abroad and whole-genome sequencing enabled the researchers to unravel that the participants acquired 83 different strains altogether.

Only in four cases did two travellers share the same strains, indicating that the bacteria were not in general transmitted from one to another.

None of the participants developed a clinical infection caused by the superbacteria. Had they not been delivered their screening results on a daily basis, the study participants would have remained totally unaware of them carrying superbugs.

"It was wonderful to see how our intestinal bacteria stand up to the incomers: the great majority of all alien strains disappeared already before the end of the journey," Kantele rejoices.

Professor Jukka Corander points out that the study provides a completely new perspective to the bacterial colonization diversity in geographic regions where superbugs are endemic.

"We have earlier obtained robust modelling results concerning the stability of E. coli colonization in populations with low levels of antibiotic resistance, however, the new study conducted in Laos implies that we need to start building the model anew, so that we gain thorough understanding about the role of superbugs also in those circumstances where they colonize the majority of the people," Corander says.

Antibiotic resistance increases at an alarming rate in the tropics

The worldwide growth of antibiotic resistance is particularly alarming in tropical regions with inadequate hygiene and uncontrolled use of antibiotics. Multidrug-resistant bacteria are carried both by animals and local inhabitants. Returning from such environments, many visitors carry superbacteria to their home countries.

Increasing resistance is also being witnessed by research: the proportion of travellers carrying these bacteria is growing. Usually acquisition of ESBL or other superbacteria does not cause any symptoms. After travellers return home, the strains usually disappear over time. Carriers can, however, pass these bacteria on to others. Among a small proportion, the superbacteria cause a symptomatic infection, most typically a urinary tract infection. Treatment of infections caused by superbacteria is more challenging than of those caused by sensitive bacteria. In some cases, the infection may even turn out life-threatening.

Antibiotic use during travel further adds to the risk of carriage: favouring the resistant bacteria, antibiotic treatment makes space for newcomers.

Kantele stresses the grave threat increasing resistance poses to healthcare worldwide.

"Antibiotics are not only needed to treat infections, but they also enable high-risk operations such as major surgery and organ transplants, where they are given to prevent infections," she says.

This study was conducted as a collaboration between University of Helsinki and Helsinki University Hospital, Swiss Tropical and Public Health Institute, Universities of Basel and Zurich, University of Oslo, Sanger Institute, Universities of Birmingham and Oxford, London School of Hygiene, and Mahosot Hospital in Vientiane, Laos. In Finland, the study was supported by the Sigrid Jusélius Foundation, a Governmental subsidy for Health Science research, and the Finnish Cultural Foundation.

http://nyti.ms/3qYxHn0

A New Coronavirus Variant Is Spreading in New York, Researchers Report

The variant contains a mutation thought to help the virus dodge the immune system, scientists said.

By Apoorva Mandavilli

A new form of the coronavirus is spreading rapidly in New York City, and it carries a worrisome mutation that may weaken the effectiveness of vaccines, two teams of researchers have found.

The new variant, called B.1.526, first appeared in samples collected in the city in November. By the middle of this month, it accounted for about one in four viral sequences appearing in a database shared by scientists. One study of the new variant, led by a group at Caltech, was posted online on Tuesday. The other, by researchers at Columbia University, was published on Thursday morning.

Neither study has been vetted by peer review nor published in a scientific journal. But the consistent results suggest that the variant's spread is real, experts said.

"It's not particularly happy news," said Michel Nussenzweig, an immunologist at Rockefeller University who was not involved in the new research. "But just knowing about it is good because then we can perhaps do something about it."

Dr. Nussenzweig said he was more worried about the variant in New York than the one quickly spreading in California. Yet another contagious new variant, discovered in Britain, now accounts for about 2,000 cases in 45 states. It is expected to become the most prevalent form of the coronavirus in the United States by the end of March.

Researchers have been scrutinizing the genetic material of the virus to see how it might be changing. They examine genetic sequences of virus taken from a small proportion of infected people to chart the emergence of new versions.

The Caltech researchers discovered the rise in B.1.526 by scanning for mutations in hundreds of thousands of viral genetic sequences in a database called GISAID. "There was a pattern that was recurring, and a group of isolates concentrated in the New York region that I hadn't seen," said Anthony West, a computational biologist at Caltech.

He and his colleagues found two versions of the coronavirus increasing in frequency: one with the E484K mutation seen in South Africa and Brazil, which is thought to help the virus partially dodge the vaccines; and another with a mutation called S477N, which may affect how tightly the virus binds to human cells.

By mid-February, the two together accounted for about 27 percent of New York City viral sequences deposited into the database, Dr. West said. (For the moment, both are grouped together as B.1.526.)

The Columbia University researchers took a different approach. They analyzed 1,142 samples from patients at their medical center. They found that 12 percent of people with the coronavirus had been infected with the variant that contains the mutation E484K.

Patients infected with virus carrying that mutation were about six years older on average and more likely to have been hospitalized. While the majority of patients were found in neighborhoods close to the hospital — particularly Washington Heights and Inwood — there were several other cases scattered throughout the metropolitan area, said Dr. David Ho, director of the Aaron Diamond AIDS Research Center at Columbia University and a co-leader of the study.

"We see cases in Westchester, in the Bronx and Queens, the lower part of Manhattan and in Brooklyn," Dr. Ho said. "So it seems to be widespread. It's not a single outbreak."

The team also identified six cases of the variant that pummeled Britain, two infections with a variant identified in Brazil, and one case of the variant that took over in South Africa. The latter two had not been reported in New York City before, Dr. Ho said.

The university investigators have alerted the authorities in New York State and in the city, as well as the Centers for Disease Control and Prevention, Dr. Ho said. He and his colleagues plan to sequence about 100 viral genetic samples a day to monitor the variants' rise.

Other experts said the sudden appearance of coronavirus variants was worrying.

"Given the involvement of E484K or S477N, combined with the

fact that the New York region has a lot of standing immunity from the spring wave, this is definitely one to watch," said Kristian Andersen, a virologist at the Scripps Research Institute in San Diego, who was not involved in the new research efforts.

The E484K mutation has independently cropped up in many different parts of the world, an indication that it offers the virus a significant advantage.

"Variants that have an advantage are going to rise pretty fast in frequency, especially when numbers are coming down over all," said Andrew Read, an evolutionary microbiologist at Penn State University.

Dr. Ho's team reported in January that the monoclonal antibodies made by Eli Lilly, and one of the monoclonal antibodies in a cocktail made by Regeneron, are powerless against the variant identified in South Africa.

And several studies have now shown that variants containing the E484K mutation are less susceptible to the vaccines than was the original form of the virus. The mutation interferes with the activity of a class of antibodies that nearly everyone makes, Dr. Nussenzweig said.

"People who have recovered from the coronavirus or who have been vaccinated are very likely to be able to fight this variant off, there's no doubt about that," he said. But "they may get a little bit sick from it." They may also infect others and keep the virus circulating, which might delay herd immunity, he added.

But other experts were slightly more optimistic. "These things are a little bit less well controlled by vaccine, but it's not orders of magnitude down, which would terrify me," Dr. Read said.

As the virus continues to evolve, the vaccines will need to be tweaked, "but in the scheme of things, those aren't huge worries compared to not having a vaccine," Dr. Read said. "I'd say the glass is three-quarters full, compared to where we were last year."

http://bit.ly/3uw8ylI

Chimpanzees unite against a common enemy

Humans become more cohesive and cooperative with their own if threatened by other groups. This propensity is shared with chimpanzees

In the face of threats from other groups, humans become more cohesive and cooperative with their own, an association that Charles Darwin suggested could be an evolved capacity. Now a research group at Kyoto University has demonstrated experimentally for the first time that this propensity is shared with chimpanzees, one of our closest relatives.

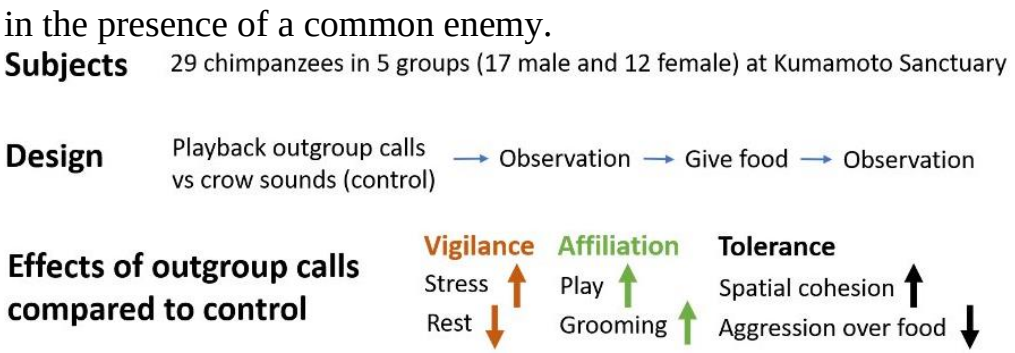
"Despite the importance of understanding how humans can be cooperative with their in-group and still carry out acts of extreme out-group aggression, there has so far been little study on whether the association between these behaviors holds in non-human primates," says first author James Brooks.

Building on field research that suggested chimpanzees were more cohesive in days and months when they had out-group encounters, the team tested the direct relation between out-group threat and in-group cohesion by simulating an out-group encounter and observing the subjects' behavior.

Five groups of chimpanzees listened to vocalizations of unfamiliar individuals, along with a control of crow vocalizations. The team found that subjects who heard the out-groups became more vigilant and stressed, but instead of translating this into in-group tension, the chimpanzees drew closer to one another, engaged in more affiliative behaviors, and were less aggressive when given limited food compared to the control group.

This suggests that in chimpanzees, as well as in humans, competition between groups fosters cohesion, and further that intergroup competition in human evolution may have led to our ability to maintain cooperation and tolerant relations in large groups

in the presence of a common enemy.



Chimpanzees showed elevated vigilance and stress but more social cohesion and tolerance within their own group **Credit: James Brooks/Kyoto University**

"This is the first experimental evidence that humans share this propensity with chimpanzees," explains study supervisor Shinya Yamamoto, "but it remains to be tested whether this is due to both species' strong evolutionary history of intergroup competition or a more common trait shared with other great apes."

The team is currently studying whether the same pattern is observed in bonobos—humans' other closest relatives—that are known for not committing lethal out-group aggression.

The paper "Uniting against a common enemy: Outgroup threat promotes ingroup cohesion in chimpanzees" will appear 24 February 2021 in the journal *PLOS ONE*.

"Uniting against a common enemy: Outgroup threat promotes ingroup cohesion in chimpanzees" PLOS ONE (2021). journals.plos.org/plosone/arti ... journal.pone.0246869

https://go.nature.com/3uylaJ2

Rich countries should tithe their vaccines

Game theory suggests that donating doses can help nations of all income levels.

Gavin Yamey

As I write this, 191 million vaccination shots against COVID-19 have been administered; more than three quarters were given in just 10 nations that account for 60% of the global gross domestic product. In some 130 nations with 2.5 billion people, not a single shot has been administered. High-income countries represent only 16% of the world's population, but they have purchased more than half of all COVID-19 vaccine doses.

The US$4 billion that the White House pledged towards equitable vaccine distribution this month is a huge help in paying for doses for poorer nations. Reframing how vaccine deals are structured — and explained to the public in rich countries — could make this pledge even more powerful.

I live in the United States, so even though I am at low risk, I will be able to get vaccinated well ahead of many health workers and high-risk people in poorer nations.

This is unfair, and will prolong the pandemic. When SARS-CoV-2 transmission is wildly uncontrolled, the virus has more scope to evolve into dangerous variants. A COVID-19 outbreak anywhere could become an outbreak everywhere.

To help, rich countries should tithe their vaccine supply to poorer places and negotiate direct purchasing deals with vaccine manufacturers to increase supplies.

Many public-health workers strived to avoid the disparities we are seeing now. We knew that rich nations had hoarded vaccines during past outbreaks, such as the 2009 swine-flu pandemic. So, dozens of us working in global health tried — in long weekly Zoom calls for many months — to at least mitigate the hoarding and put a global sharing mechanism for COVID-19 vaccines in place. The result was COVID-19 Vaccines Global Access (COVAX) — co-led by Gavi, the Vaccine Alliance; the Coalition for Epidemic Preparedness Innovations; and the World Health Organization. It is a first-of-its-kind 'buyers' pool' in which richer nations can collectively purchase vaccines, fund vaccine development and manufacturing and ensure that some of the supply will go to poorer countries.

Although around 190 nations have joined COVAX, about 3 dozen

rich nations ended up buying most of their doses by way of direct deals with vaccine companies rather than through the COVAX pool. COVAX still expects to secure some 2 billion doses by the end of 2021, but richer countries have already bought 5.8 billion doses, often purchased before clinical trials were completed, through bilateral deals. COVAX is still getting pushed to the back of the queue.

What to do now? Richer nations should share their doses, stat. Perhaps for every nine doses they administer, they can donate one dose to COVAX. This falls far short of 'equitable', but it is within what is possible. This will help beyond dimming the chance of an outbreak from an imported variant that hoarded vaccines might have reduced efficacy against.

One analysis of vaccine nationalism (see go.nature.com/37wr), in which people in rich nations receive immediate vaccination and poorer nations are left behind for years, suggested that the global economy could lose US$9 trillion. Rich nations, whose exports would be suppressed, would bear half the cost. Disruption of global supply chains that provide parts for industry would continue.

Some nations are taking the lead. Norway is the first rich nation to have pledged to donate doses to the COVAX pool in parallel with vaccinating its citizens (the United Kingdom plans to donate superfluous doses after all its citizens have been vaccinated).

My colleagues and I used game theory to project what would happen if rich nations reconfigured their purchasing deals to increase the global vaccine supply (D. McAdams *et al. BMJ Glob. Health* **5**, e003627; 2020). Currently, each vaccine purchase is a zero-sum game. But deals could include provisions that require vaccine makers to share knowledge and technology to boost production by other manufacturers. As a real-world example, the Serum Institute of India can manufacture the AstraZeneca–University of Oxford vaccine, providing doses for low- and middle-income countries.

An advanced purchase agreement might also finance risky investments that would speed up vaccine manufacturing. If one candidate fails in trials, the facility could be used for a different, successful vaccine, with a portion of the doses going to poorer countries. These deals create what economists call 'positive spillovers'. With such collaboration, global vaccine distribution would no longer be a zero-sum game.

Some in rich countries might push back against sharing doses, arguing that a government needs to put its own citizens first and that no politician would risk giving doses away. But public polling in many of these nations shows that citizens want their governments to be more collaborative. A UK poll found that almost two-thirds of the public does not want rich countries to be prioritized for COVID-19 vaccination over poorer countries. And if the rich world continues to hoard vaccines, the global pandemic will drag on for perhaps as long as seven more years.

Another argument is that many poorer countries — such as Mongolia and Vietnam — have already curtailed their COVID-19 outbreaks using non-pharmaceutical interventions such as testing, contact tracing and mask-wearing. It is unfair to penalize nations that have used these measures by denying them vaccines. How will citizens respond to public-health advice in the next pandemic if they think it will deprive them of vaccine access?

It is in everybody's interests to act collectively to boost vaccinations. It is self-defeating to act otherwise.

Nature ***590***, *529 (2021) doi: https://doi.org/10.1038/d41586-021-00470-9*

http://bit.ly/3kxJHJF

A Baby Sick With COVID-19 in Washington Had 51,000 Times More Viral Particles

A new coronavirus variant has emerged.

Gabby Landsverk, Business Insider

A very sick newborn, treated at Children's National Hospital in Washington, D.C., was found to have not only a new variant of the novel coronavirus, but a viral load 51,418 times higher than other young patients, according to the *Washington Post*.

The new variant was identified recently when the researchers sequenced the genome of the virus from the baby, who was treated in September and recovered, reported the Post's Ariana Eunjung Cha.

It's not clear how common or how risky this new variant might be. The database found eight other cases of this variant in the US mid-Atlantic region, according to a pre-print study, which has not yet been peer-reviewed, on coronavirus variations in children.

The variant, researchers said, has a different type of spike protein structure that may make it more infectious.

It's not clear whether this new variant explains the huge number of viral particles detected in the infant's nose.

"It could be a complete coincidence," Roberta DeBiasi, chief of infectious disease for the Children's National Hospital, told the Post. "But the association is pretty strong. If you see a patient who has exponentially more virus and it's a completely different variant, it is probably related."

Many questions remain about how the coronavirus affects children

Children are less likely to have severe cases of COVID-19, according to national data. Very young children may be less likely to infect other people when they get sick, although the CDC still suggests that everyone could potentially spread the disease.

But researchers still don't fully understand all the implications of coronavirus for children and babies.

In the past five months, the number of pediatric coronavirus cases has gone up "dramatically," according to the American Academy of Pediatrics and the Children's Hospital Association.

Severe cases of COVID-19 in children are rare, but do exist, and have been linked to serious and long-term side effects, including brain damage.

And we do know that some children are more vulnerable than others – the death rate of children of color is far higher than that of their white peers. As of February 11, 241 children have died of COVID-19 and the vast majority have been Black, Hispanic, or American Indian or Native Alaskan.

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Did teenage 'tyrants' outcompete other dinosaurs?

Offspring of enormous carnivorous dinosaurs may have fundamentally re-shaped their communities by out-competing smaller rival species

Paleo-ecologists from The University of New Mexico and at the University of Nebraska-Lincoln have demonstrated that the offspring of enormous carnivorous dinosaurs, such as Tyrannosaurus rex may have fundamentally re-shaped their communities by out-competing smaller rival species.

The study, released this week in the journal *Science*, is the first to examine community-scale dinosaur diversity while treating juveniles as their own ecological entity.

"Dinosaur communities were like shopping malls on a Saturday afternoon—jam-packed with teenagers" explained Kat Schroeder, a graduate student in the UNM Department of Biology who led the study. "They made up a significant portion of the individuals in a species and would have had a very real impact on the resources available in communities."

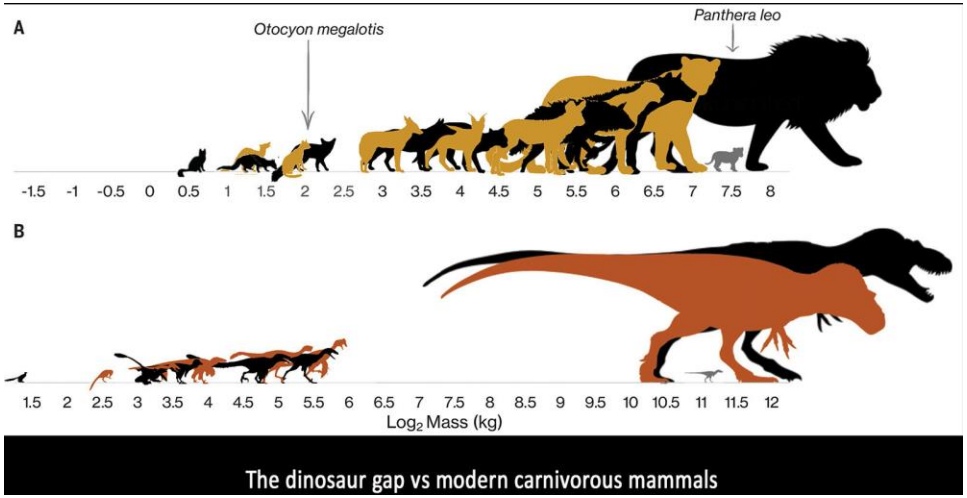
Because they were born from eggs, dinosaurs like T. rex necessarily were born small—about the size of a house cat. This meant as they grew to the size of a city bus, these "megatheropods," weighing between one and eight tons, would have changed their hunting patterns and prey items. It's long been suspected by paleontologists

that giant carnivorous dinosaurs would change behavior as they grew. But how that might have affected the world around them remained largely unknown.

"We wanted to test the idea that dinosaurs might be taking on the role of multiple species as they grew, limiting the number of actual species that could co-exist in a community," said Schroeder.

The number of different types of dinosaurs known from around the globe is low, particularly among small species.

"Dinosaurs had surprisingly low diversity. Even accounting for fossilization biases, there just really weren't that many dinosaur species," said Felisa Smith, professor of Biology at UNM and Schroeder's graduate advisor.



The Dinosaur Gap vs. Modern Carnivores illustrates the gap between prehistoric dinosaurs and modern carnivores. **Credit: UNM Biology Department**

To approach the question of decreased dinosaur diversity, Schroeder and her coauthors collected data from well-known fossil localities from around the globe, including over 550 dinosaur species. Organizing dinosaurs by mass and diet, they examined the number of small, medium and large dinosaurs in each community.

They found a strikingly clear pattern:

"There is a gap—very few carnivorous dinosaurs between 100-1000kg [200 pounds to one ton] exist in communities that have megatheropods," Schroeder said. "And the juveniles of those megatheropods fit right into that space."

Schroeder also notes that looking at dinosaur diversity through time was key. Jurassic communities (200-145 million years ago) had smaller gaps and Cretaceous communities (145-65 million years ago) had large ones.

"Jurassic megatheropods don't change as much ? the teenagers are more like the adults, which leaves more room in the community for multiple families of megatheropods as well as some smaller carnivores," Schroeder explained. "The Cretaceous, on the other hand, is completely dominated by Tyrannosaurs and Abelisaurs, which change a lot as they grow."

To tell whether the gap was really caused by juvenile megatheropods, Schroeder and her colleagues rebuilt communities with the teens taken into account. By combining growth rates from lines found in cross-sections of bones, and the number of infant dinosaurs surviving each year based on fossil mass-death assemblages, the team calculated what proportion of a megatheropod species would have been juveniles.

Schroeder explained that this research is important because it (at least partially) elucidates why dinosaur diversity was lower than expected based on other fossil groups. It also explains why there are many more very large species of dinosaurs than small, which is the opposite of what would be expected. But most importantly, she added, it demonstrates the results of growth from very small infants to very large adults on an ecosystem.

"Dinosaurs have been a life-long passion. I was, and still very much am a 'dinosaur kid.' My interest in dinosaur diversity came about when I realized that no one was really looking at dinosaurs the way

we look at modern mammals and birds," Schroeder said. "There's a ton to be gained from applying the methods of modern and paleo-ecology to dinosaurs. Fortunately, we're now in an age of dinosaur research where a lot of information is available digitally, so the big data-intensive questions of ecology are now becoming more plausible for dinosaur paleontology."

More information: *K. Schroeder el al., "The influence of juvenile dinosaurs on community structure and diversity," Science (2021). science.sciencemag.org/cgi/doi ... 1126/science.abd9220*

http://bit.ly/3sxapoK

Model identifies risk of serious complications following surgery

A web-based tool developed by Jefferson researchers predicts individualized risk for stroke, other grave post-surgical complications.

PHILADELPHIA - Heart attack, kidney failure, stroke. These are just a few of the life-threatening complications that patients are at risk for following surgery. Now Jefferson researchers have developed an easy-to-use, web-based tool that predicts the risk of post-surgical complications such as kidney failure and stroke. The model may help medical professionals put preventive measures in place before the need for emergency intervention.

"We need to be able to assess the risk of life-threatening, post-surgical complications so we can then come up with individualized ways to reduce those complications," says Sang Woo, MD, a clinical associate professor of medicine at Thomas Jefferson University who led the new research.

The need for better predictive risk models became clear to Dr. Woo after a patient suffered kidney failure following surgery and required medical intervention like dialysis. Another patient suffered a stroke following surgery to treat a fractured hip and suddenly needed emergency brain surgery.

"Seeing how much suffering those patients had gone through, I wanted to figure out what we could have done differently to prevent these life-threatening complications," Dr. Woo says.

Risk calculators that doctors currently rely on mainly assess for cardiac risks, such as heart attack or cardiac arrest. They do not provide risk assessment of other major complications like stroke, and doctors have not really paid much attention to risk assessment for kidney failure, Dr. Woo says.

"We wanted to assist doctors to be able to assess the risk of stroke, in addition to traditional risks," he says.

To develop a predictive model that was accurate and easy for clinicians to use, Dr. Woo drew on expertise in analyzing big data sets and machine learning, and collaborated with a multidisciplinary Jefferson research team including a surgeon, cardiologist, nephrologists and hospitalists.

"Often times we do the research and publish a research paper that is too complex to translate to the bedside," Dr. Woo says. "My goal from the beginning was to come up with a new model that is very practical and useful and that can be incorporated into routine patient care."

Now, in two recent studies, Dr. Woo and colleagues show that the model effectively predicts the risk of life-threatening, post-surgical complications. In a study published online December 29, 2020 in the research journal *Kidney360,* Dr. Woo and colleagues developed a model to assess a patient's risk of developing acute kidney injury (AKI) following surgery. AKI is a serious medical issue. More than a third of patients that required dialysis following cardiac surgery died for example.

"Identifying patients at high risk for AKI and implementing preventive measures may lower that mortality risk," Dr. Woo says.

He and colleagues analyzed data from more than 2.2 million surgical patients, of whom about 7,000 developed AKI requiring

dialysis. The analysis revealed that patients who required dialysis were older and more likely to have congestive heart failure and diabetes.

The researchers then trained the model with data from over 1.4 million patients using these and eight other predictors before testing it out on data from another set of more than 800,000 surgical patients. The model accurately predicted which patients would develop AKI.

In a second study published online in the *Journal of the American Heart Association* on January 30, 2021, Dr. Woo and colleagues used the model to predict the risk of stroke, cardiac event or death within 30 days after surgery.

For this version of the model, the researchers analyzed data from more than 1.1 million surgical patients. They used predictors such as age, history of stroke, type of surgery and other health factors that could be measured prior to surgery to build the model.

They found that the model predicted which patients would suffer a stroke, cardiac event or die within 30 days of surgery with high accuracy. The predictive power of the model was outstanding, with area under the curve (AUC)--a standard way of evaluating a model's performance--measuring 0.87 for stroke and 0.92 for mortality. The model also predicts cardiac risk (AUC 0.87) similar to or better than widely used cardiac risk models.

As a web-based tool, the model is also easy to use. Doctors conducting pre-surgery assessments can use the tool at the patient's bedside.

The new risk assessment models will benefit clinicians and patients. With the models, clinicians will be able to inform surgeons of the risks and better counsel patients, both of which will translate to improving patient care. "Now that we have a tool to assess stroke and kidney failure risk objectively, we are investigating novel ways to reduce that risk," says Dr. Woo.

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Sang H. Woo, Jillian Zavodnick, Lily Ackermann, Omar Maarouf, Jingjing Zhang, and Scott W. Cowan. (2020) "Development and Validation of a Web-based Prediction Model for Acute Kidney Injury after surgery" Kidney360. doi:10.34067/KID.0004732020

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http://bit.ly/37Mbzo3

Dogs and kids are 'in sync,' study shows

It is an image as heartwarming as any: Young children giggling as the family dog climbs all over them and licks their faces. But new research suggests the bond may be more than playful.

"The great news is that this study suggests dogs are paying a lot of attention to the kids that they live with," said study author Monique Udell, an animal behaviorist and associate professor at Oregon State University.

"They are responsive to them and, in many cases, behaving in synchrony with them, indicators of positive affiliation and a foundation for building strong bonds."

Indeed, dogs may even help children with social development, increasing physical activity, managing anxiety or providing attachment as family structures change, the researchers said.

The study recruited 30 youths aged 8 to 17, along with their family dog. About 83% of the kids and adolescents had a developmental disability.

The children were asked to walk with their off-leash dogs in a standardized way among color-coded taped lines in a large empty room.

Researchers videotaped the experiments, analyzing how much time each child and their dog were moving or stationary at the same time (what they called activity synchrony), how often they were within 3 feet of each other (proximity), and going in the same direction (orientation).

The dogs were synchronized with the children at higher rates than expected by chance: about 60% of the total time; 73% of the time when moving; and 41% of the time when stationary. They were in close proximity of each other 27% of the time and moving in the same direction 33.5% of the time.

"What we are finding is that kids are very capable of training dogs, and that dogs are paying attention to the kids and can learn from them," Udell said in a university news release.

"Sometimes we don't give children and dogs enough credit. Our research suggests that with some guidance we can provide important and positive learning experiences for our kids and our dogs starting at a much earlier age, something that can make a world of difference to the lives of both," she said.

Still, the percentages were all lower than found in previous research with adults—who had nearly 82% active synchrony and almost 73% proximity with their dogs.

"One interesting thing we have observed is that dogs are matching their child's behavior less frequently than what we have seen between dogs and adult caretakers, which suggests that while they may view children as social companions, there are also some differences that we need to understand better," Udell said.

The researchers are now studying more about synchrony and bond quality between dogs and the kids and adults in their families. This includes participation in animal-assisted interventions and increasing the child's responsibility for the dog's care.

The findings were published recently in the journal *Animal Cognition*.

More information: *The American Kennel Club shares information on how dogs and humans help each other be healthier and happier.*

SOURCE: Oregon State University, news release, Feb. 21, 2021

http://bit.ly/3pZeT5J

Vitamin B6 may help keep COVID-19's cytokine storms at bay

Vitamin B6 may help calm cytokine storms and unclog blood clots linked to COVID-19's lethality. But research on it is lacking. A Hiroshima University professor calls on fellow scientists to study its potential role

Who would have thought that a small basic compound like vitamin B6 in the banana or fish you had this morning may be key to your body's robust response against COVID-19?

Studies have so far explored the benefits of vitamins D and C and minerals like zinc and magnesium in fortifying immune response against COVID-19. But research on vitamin B6 has been mostly missing. Food scientist Thanutchaporn Kumrungsee hopes their paper published in *Frontiers in Nutrition* can be the first step in showing vitamin B6's potential in lowering the odds of patients becoming seriously ill with the coronavirus.

"In addition to washing your hands, food and nutrition are among the first lines of defense against Covid-19 virus infection. Food is our first medicine and kitchen is our first pharmacy," Kumrungsee, an associate professor at Hiroshima University's Graduate School of Integrated Sciences for Life, said.

"Recently, many scientists have published papers regarding the role of diets and nutrients in the protection against COVID-19. However, very few scientists are paying attention to the important role of vitamin B6," she added.

In their paper, she and her fellow researchers pointed out growing evidence showing that vitamin B6 exerts a protective effect against chronic illnesses such as cardiovascular diseases and diabetes by suppressing inflammation, inflammasomes, oxidative stress, and carbonyl stress.

"Coronaviruses and influenza are among the viruses that can cause

lethal lung injuries and death from acute respiratory distress syndrome worldwide. Viral infections evoke a 'cytokine storm,' leading to lung capillary endothelial cell inflammation, neutrophil infiltration, and increased oxidative stress," they said.

Kumrungsee explained that thrombosis (blood clotting) and cytokine storm (hyper inflammation) might be closely linked to the graveness of COVID-19. Cytokine storms happen when the immune system dangerously goes into overdrive and starts attacking even the healthy cells. Meanwhile, blood clots linked to COVID-19 can block capillaries, damaging vital organs like the heart, lungs, liver, and kidneys.

Vitamin B6 is a known anti-thrombosis and anti-inflammation nutrient. Deficiency in this vitamin is also associated with lower immune function and higher susceptibility to viral infections.

"Vitamin B6 has a close relationship with the immune system. Its levels always drop in people under chronic inflammation such as obesity, diabetes, and heart diseases. We can see from the news that obese and diabetic people are at high risk for COVID-19," Kumrungsee said.

"Thus, our attempt in this paper is to shed light on the possible involvement of vitamin B6 in decreasing the severity of COVID-19."

The associate professor said she is looking forward to clinical trials that would test their hypothesis.

"It is of great interest to examine if vitamin B6 exerts protection against novel types of virus infection and pneumonia which will be encountered in the future. At present, there is few information regarding the protective role of nutrients against pneumonia and lung diseases," she said.

"After COVID-19, we should develop the area of nutrition for lung diseases such as pneumonia and lung cancer."

http://bit.ly/3dUWgNQ

Statin use associated with increased survival in severe COVID-19

Approximately 50% less likely to die if hospitalized for COVID-19

New York, NY - People who took statins to lower cholesterol were approximately 50% less likely to die if hospitalized for COVID-19, a study by physicians at Columbia University Vagelos College of Physicians and Surgeons and NewYork-Presbyterian has found.

"Our study is one of the larger studies confirming this hypothesis and the data lay the groundwork for future randomized clinical trials that are needed to confirm the benefit of statins in COVID-19," says Aakriti Gupta, MD, a cardiologist at NewYork-Presbyterian/Columbia University Irving Medical Center and one of the co-lead authors of the study.

"If their beneficial effect bears out in randomized clinical trials, statins could potentially prove to be a low-cost and effective therapeutic strategy for COVID-19," adds co-lead author Mahesh V. Madhavan, MD, also a cardiologist at NewYork-Presbyterian/Columbia University Irving Medical Center.

Why Look at Statins?

Gupta, Madhavan, and the study's leadership group are cardiologists who cared for hospitalized COVID-19 patients in the spring and summer of 2020 when the first wave of the pandemic swept through New York City.

"We observed that patients who got very sick and required hospitalization had high rates of hyperinflammation and clotting," says Elaine Wan, MD, the Esther Aboodi Assistant Professor of Medicine in Cardiology and Cardiac Electrophysiology and a cardiac electrophysiologist at NewYork-Presbyterian/Columbia University Irving Medical Center, one of the study's senior authors.

"As cardiologists, statins naturally came to mind," Gupta says. "In addition to their well-known cholesterol-lowering effect, statins are

known for their anti-inflammatory, anticoagulant and immunomodulatory properties."

Study Analyzed Data from Electronic Health Records

Based on their observations, the authors looked at outcomes for 2,626 patients with COVID-19 who were admitted to a quaternary academic medical center in Manhattan during the first 18 weeks of the pandemic. The researchers compared 648 patients who regularly used statins before developing COVID-19 to 648 patients who did not use statins. Patients in each group were matched so that there were no significant differences in demographics, comorbidities, or use of other medications at home.

50% Fewer Deaths among Statin Users

Among the statin users, 96 (14.8%) died in the hospital within 30 days of admission compared with 172 (26.5%) of patients who did not use statins.

When other differences among the patients were factored in, the researchers found that statin use was significantly associated with a 50% reduction in in-hospital mortality (within 30 days). Patients on statins also tended to have lower levels of C-reactive protein, a marker of inflammation.

Statin use was not associated with a statistically significant decrease in the use of invasive mechanical ventilation (18.6% in statin users vs. 21.9%), days on a ventilator (13.5 vs 12.8), or length of hospital stay (7 vs 7).

Comparison with Other Studies

Other studies and meta-analyses from China have also suggested a survival benefit from statins among COVID-19 patients. However, these results may not apply to patients in Western countries who generally have more cardiovascular disease.

The current study is one of the larger studies confirming the association. Smaller retrospective studies out of North America and Europe have found similar results.

Randomized Clinical Trials Needed

Although the study compared closely matched participants and adjusted for other variables, as a retrospective analysis, unknown factors could explain the results.

"Only randomized controlled clinical trials can evaluate the benefits of statins in COVID-19 patients," says senior author Sahil A. Parikh, MD, associate professor of medicine and a cardiologist at NewYork-Presbyterian/Columbia University Irving Medical Center. Several randomized trials are underway, including studies to determine if statins can prevent hospitalization in outpatients, and lower the risk of death when given to hospitalized patients.

One of the study's authors, Behnood Bikdeli, MD, a former cardiology fellow at Columbia now a fellow in vascular medicine at Brigham and Women's Hospital, is leading a randomized clinical trial looking at the impact of statins in hospitalized ICU patients in Iran.

The study, titled "Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19," was published Feb. 26 in Nature Communications. All other authors are affiliated with Columbia and NewYork-Presbyterian unless otherwise noted: Timothy J. Poterucha, Ersilia M. DeFilippis, Jessica A. Hennessey, Bjorn Redfors (Columbia, NewYork-Presbyterian, and Sahlgrenska University Hospital, Sweden), Christina Eckhardt, Behnood Bikdeli (Columbia, NewYork-Presbyterian, and Brigham and Women's), Jonathan Platt, Ani Nalbandian, Pierre Elias, Matthew J. Cummings, Shayan N. Nouri, Matthew Lawlor, Laruen S. Ranard, Jianhua Li, Claudia Boyle, Raymond Givens, Daniel Brodie, Harlan M. Krumholz (Yale), Gregg W. Stone (Icahn School of Medicine), Sanjum S. Sethi, Daniel Burkhoff, Nir Uriel, Allan Schwartz, Martin B. Leon, and Ajay J. Kirtane.

Competing interests of the authors can be found in the paper.

http://bit.ly/3q6jiE8

Genes identified that increase the risk of obesity but also protect against disease

Range of genes linked to both elevated levels of body fat, and offering protection from some negative health impacts of obesity

People living with obesity tend to have unhealthy glucose and lipid levels in their blood, as well as high blood pressure. As a result,

they are more at risk of cardiovascular and metabolic diseases. But scientists have observed that up to 45% of people living with obesity have healthy blood pressure and glucose and lipid levels, and therefore may not be at high risk of disease. The reason why this group of people with obesity remain healthy, has been poorly understood.

But now a team of researchers - led by scientists at the University of Copenhagen and Icahn School of Medicine at Mount Sinai, New York - have identified a range of genes that are linked to both elevated levels of body fat, as well as offering protection from some of the negative health impacts of obesity. The results were published in the journal *Nature Metabolism*.

Associate Professor Tuomas Kilpeläinen from the Novo Nordisk Foundation Center for Basic Metabolic Research (CBMR) at the University of Copenhagen says the findings shed new light on the biology that may disconnect higher level of body fat from higher risk of diabetes and heart disease.

"The identified genes seem to benefit our health by helping to maintain a healthy fat tissue. Some of the genes may offer targets for the development of new therapies that lower the risk of diabetes and heart disease by improving the health of our fat tissue," says Tuomas Kilpeläinen.

The scientists made the discovery by analyzing data from hundreds of thousands people who had been assessed for their body fat and disease risk markers. They identified 62 sections of the genome that were significantly associated with both high levels of body fat and lower risk of cardiometabolic diseases. Further analyses showed that the genes had a range of functions in the body, including the regulation and development of fat cells, distribution of body fat, as well as energy regulation and inflammation.

Staff Scientist Lam Opal Huang from CBMR carried out the computational analyses that identified the genes.

"We used a data-driven approach in this study, which led us to find new genes associated with fat tissue health, instead of the known obesity genes associated with central nervous system, which control satiety and are typically linked to unhealthy obesity," says Lam Opal Huang.

According to Professor Ruth Loos from the Icahn School of Medicine at Mount Sinai, this new knowledge is a step toward a more nuanced approach to treating obesity.

"Clearly, obesity is a complex disease and not every individual with excess body weight is equally at risk of developing cardiometabolic diseases. Knowing which genes protect people from developing diabetes and cardiovascular disease will eventually help us better diagnose and treat individuals with obesity."

http://bit.ly/3ksqMGO

Ancient Egyptian manual reveals new details about mummification

Oldest surviving manual on mummification yet discovered

Based on a manual recently discovered in a 3,500-year-old medical papyrus, University of Copenhagen Egyptologist Sofie Schiødt has been able to help reconstruct the embalming process used to prepare ancient Egyptians for the afterlife. It is the oldest surviving manual on mummification yet discovered.

In ancient Egypt, embalming was considered a sacred art, and knowledge of the process was the preserve of very few individuals. Most secrets of the art were probably passed on orally from one embalmer to the other, Egyptologists believe, so written evidence is scarce; until recently, only two texts on mummification had been identified.

Egyptologists were therefore surprised to find a short manual on embalming in a medical text that is primarily concerned with herbal medicine and swellings of the skin. The manual has recently been edited by Schiødt.

"Many descriptions of embalming techniques that we find in this papyrus have been left out of the two later manuals, and the descriptions are extremely detailed. The text reads like a memory aid, so the intended readers must have been specialists who needed to be reminded of these details, such as unguent recipes and uses of various types of bandages. Some of the simpler processes, e.g. the drying of the body with natron, have been omitted from the text," Sofie Schiødt explains.

The papyrus contains new evidence of the procedure for embalming the deceased's face, where the face is covered with a piece of red linen and aromatic substances. **Credit: Ida Christensen, University of Copenhagen**

She adds: "One of the exciting new pieces of information the text provides us with concerns the procedure for embalming the dead person's face. We get a list of ingredients for a remedy consisting largely of plant-based aromatic substances and binders that are cooked into a liquid, with which the embalmers coat a piece of red linen. The red linen is then applied to the dead person's face in order to encase it in a protective cocoon of fragrant and anti-bacterial matter. This process was repeated at four-day intervals."

Although this procedure has not been identified before, Egyptologists have previously examined several mummies from the same period as this manual whose faces were covered in cloth and resin. According to Sofie Schiødt, this would fit well with the red linen procedure described in this manuscript.

Four was the key number

The importance of the Papyrus Louvre-Carlsberg manual in reconstructing the embalming process lies in its specification of the process being divided into intervals of four, with the embalmers actively working on the mummy every four days.

- A ritual procession of the mummy marked these days, celebrating the progress of restoring the deceased's corporeal integrity, amounting to 17 processions over the course of the embalming period. In between the four-day intervals, the body was covered with cloth and overlaid with straw infused with aromatics to keep away insects and scavengers, Sofie Schiødt says.

Section of the papyrus that deals with swellings of the skin. **Credit: The Papyrus Carlsberg Collection, University of Copenhagen**

The Papyrus Louvre-Carlsberg

The manuscript, which Schiødt has been working on for her Ph.D. thesis, is the Papyrus Louvre-Carlsberg—so called because one half of the papyrus belongs to the Louvre Museum in Paris and the other half is part of the University of Copenhagen's Papyrus Carlsberg Collection. The two parts of the papyrus originally belonged to two private collectors, and several sections of it are still missing. Based on the palaeography—that is, the sign forms—the six meter long papyrus is dated to approximately 1450 BC, which means that it predates the only two other examples of embalming texts by more than a thousand years.

The bulk of the papyrus, which is the second-longest medical papyrus surviving from ancient Egypt, deals with herbal medicine and skin illnesses. Specifically, it contains the earliest-known herbal treatise, which provides descriptions of the appearance, habitat, uses, and religious significance of a divine plant and its seed as well as a lengthy treatise on swellings of the skin, which are seen as illnesses sent forth by the lunar god Khonsu.

The embalming process

The embalming, which was performed in a purpose-built workshop erected near the grave, took place over 70 days that were divided into two main periods—a 35-day drying period and a 35-day

wrapping period.

During the drying period, the body was treated with dry natron both inside and outside. The natron treatment began on the fourth day of embalming after the purification of the body, the removal of the organs and the brain, and the collapsing of the eyes.

The second 35-day period was dedicated to the encasing of the deceased in bandages and aromatic substances. The embalming of the face described in the Papyrus Louvre-Carlsberg belonged to this period.

The entire 70-day embalming process was divided into intervals of 4 days, with the mummy being finished on day 68 and then placed in the coffin, after which the final days were spent on ritual activities allowing the deceased to live on in the afterlife.

Sofie Schiødt's Ph.D. thesis: Medical Science in Ancient Egypt: A translation and interpretation of Papyrus Louvre-Carlsberg (PLouvre E 32847 + PCarlsberg 917)

http://bit.ly/3bKkBDl

Plastic bottles holding 2.3 litres are least harmful to the planet

Using plastic bottles that contain the most liquid for the lowest packaging weight could help reduce plastic waste.

By Ibrahim Sawal

Plastic pollution is a huge problem for the world, with much plastic waste reaching the oceans where it can affect marine life.

In recognition of this, many researchers are developing strategies to tackle the plastic waste problem. Now, Rafael Becerril-Arreola at the University of South Carolina and his colleagues have come up with a relatively simple method to make a difference: change the packaging size to maximise its capacity for a given weight of plastic.

"We realised we could establish a relationship between supermarket beverage sales and plastic waste," says Becerril-Arreola. "I saw the opportunity to create an impact, and I took it."

Becerril-Arreola and his team focused on polyethylene terephthalate (PET), the most common material in plastic bottles. They weighed 187 empty bottles of different sizes from bestselling drink brands to determine the weight of plastic required to produce a bottle of a given capacity. They also compared this against PET waste and drink sales in Minnesota between 2009 and 2013, as the state government there reliably collects waste statistics and its bottled drink consumption is close to the US national average.

The researchers found that the most efficient bottles – those with the greatest capacity relative to the weight of plastic used to make the bottle – had a volume between 0.5 and 2.9 litres. Bottles of this size are typically bought for on-the-go use or social gatherings. Bottles that were smaller (under 0.4 litres) or larger (over 3 litres) used more plastic in relation to each bottle's capacity.

The highest efficiency was seen with bottles with a volume of 2.3 litres. The data from Minnesota supported this: PET waste was lower during periods when, for reasons that were unclear, the proportion of bottles of about 2.3 litres sold was unusually high. In contrast, during periods in which unusually high proportions of smaller bottles were sold, waste seemed to increase.

The team then calculated what could happen if there were a shift in sales in the US towards bottles with a volume nearer 2.3 litres using the national data on PET waste. Becerril-Arreola says that PET generates around 740,000 tonnes of waste each year in the US, and that a 20 per cent shift to bottles closer to 2.3 litres in size could reduce that waste by about 9000 tonnes a year.

Becerril-Arreola says he hopes these findings encourage consumers to switch to more efficient bottles to help reduce plastic waste. "It's going to be tricky," he says. "It's a matter of awareness. We cannot expect corporations to make plastic bottles more efficient themselves."

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http://bit.ly/3kurAo0

Roman chariot unearthed 'almost intact' near Pompeii

The four-wheel processional chariot was missed by looters who tunneled by on either side

An ornate Roman chariot has been discovered "almost intact" near Italy's buried city of Pompeii, the archaeological park announced on Saturday, calling it a discovery with "no parallel" in the country.

The four-wheeled processional carriage was found in the portico to stables where the remains of three horses were unearthed in 2018, including one still in its harness. Pompeii was buried in boiling lava when Mount Vesuvius erupted in 79 AD, killing between 2,000 and 15,000 people.

"A large ceremonial chariot with four wheels, along with its iron components, beautiful bronze and tin decorations, mineralised wood remains and imprints of organic materials (from the ropes to the remains of floral decoration), has been discovered almost intact," a statement issued by the archaeological park said.

"This is an exceptional discovery... which has no parallel in Italy thus far—in an excellent state of preservation."

The excavation site is known as the Civita Giuliana, a suburban villa that lies just a few hundred metres from the ancient city of Pompeii. The excavation is part of a programme aimed at fighting illegal activity in the area, including tunnel digging to reach artefacts that can be sold on illicit markets.

Looters missed the room where the chariot had lain for almost 2,000 years, tunnelling by on both sides, the park's statement said.

Specialists took great care to unearth the vehicle, for example by pouring plaster into voids "to preserve the imprint of any organic material" that had decomposed, it added.

The park said this had allowed it to emerge well preserved down to the imprints of ropes, "thus revealing the chariot in all of its complexity".

Parts of the chariot have been preserved in fine detail

"Pompeii continues to amaze with all of its discoveries, and it will continue to do so for many years yet, with 20 hectares (50 acres) still to be excavated," Culture Minister Dario Franceschini was quoted as saying.

'Parades and processions'

"It is an extraordinary discovery for the advancement of our knowledge of the ancient world," added Massimo Osanna, outgoing director of the park.

"What we have is a ceremonial chariot, probably the Pilentum referred to by some sources, which was employed not for everyday use or for agricultural transport, but to accompany community festivities, parades and processions."

Pompeii's remarkably well-preserved remains have slowly been uncovered by teams of archaeological specialists. It is Italy's third most visited tourist site, drawing more than 3.9 million visitors in 2019. The ancient city was closed after the coronavirus struck, and only reopened on January 18.

http://bit.ly/3e8IsQb

Thousands of Human Skeletons Show Us The Evolutionary War Between Man And Disease

Ancient skeletons reveal how the human body evolves to fight disease,

David Nield

As the world wrestles with a global pandemic, a study of tens of thousands of ancient skeletons has revealed how the human body evolves to fight disease, and how the diseases also evolve to

become less deadly over time. Its conclusions could teach experts more about how we'll adapt to cope with diseases in the future.

The researchers behind the new study say that it shows how germs mutate to replicate and ensure survival across as many human hosts as possible – but that this behaviour also then reduces the severity of the disease over time. In the end, the harmful microorganisms or pathogens end up reaching a sort of truce with the human body.

Leprosy, tuberculosis, and treponematoses (a group of diseases including syphilis) were the diseases analysed in the research. They can all leave marks on bones and teeth that indicate infection, and thanks to the human remains and the medical records that are available, they can be traced back as far as 200 generations.

"Each of these three diseases shows a decline in prevalence resulting from co-adaptation that is mutually beneficial for the disease and human host," says anthropologist Maciej Henneberg, from Flinders University in Australia.

"In the last 5,000 years, before the advent of modern medicine, skeletal signs of tuberculosis become less common, skeletal manifestations of leprosy in Europe declined after the end of the Middle Ages, while skeletal signs of treponematoses in North America declined, especially in the last years before contact with invading Europeans."

The researchers looked at three previous studies of the three diseases, covering 69,379 skeletons in total. Across the studies looked at, the ages of these skeletons varied from as far back as 7250 BCE right up until the present day.

Not all of these skeletons were from people with tuberculosis, treponematoses, or leprosy, and not all of the skeletons from people who did have these diseases would have shown physical signs on the bones. While this means the new study isn't a strict epidemiological meta-analysis, it does mean that the sample size was large enough for the team to make some useful speculations.

None of the three diseases kills their human hosts immediately, which helps the pathogens live on and spread. But the statistically significant decline in the prevalence of tuberculosis, treponematoses, or leprosy over time suggests that either humans became more immune or tolerant or that the disease became less damaging. "From an evolutionary perspective, it makes sense for a pathogen to cause less harm to the host on which it depends for its survival so high levels of transmission appear to be a temporary evolutionary trait which reduces as time goes on when we look at leprosy, tuberculosis and syphilis," says anthropologist Teghan Lucas, from Flinders University.

While there are some caveats to mention – such as the different ways the three studies reported their respective results, and the need to consider other factors that can affect disease spread besides those covered here – it's an interesting overview of the progress of diseases over time.

The COVID-19 coronavirus has only been with us a short time, but we've already seen the viruses mutating and changing in order to ensure its survival and to reach more human hosts. Even as vaccinations get the spread of the virus under control, experts will have to keep a close eye on how it evolves in the future.

The new research is part of the growing field of palaeopathology, the study of ancient human diseases through evidence such as skeletons, mummified remains, ancient documents and literature, and art. "Palaeopathology is becoming an increasingly popular discipline which allows diseases which manifest on hard tissues to be studied in past populations because the diseases preserved for as long as the skeletal remains exist," says Lucas. "Due to the preservation of pathological signs on skeletons, it is possible to trace the process of co-evolution of the three major infectious diseases as far back as specimens have been found." The research has been published in *PLOS One*.