https://bit.ly/2VcFIWB

The four horsemen of the COVID-19 pandemic

Overpopulation, globalization, hyperconnectivity and increasingly limited and centralized supply chains

It is clear that we must prioritize identifying and alleviating the conditions that made the Covid-19 pandemic possible. Even as it rages, scientists are already asking if it is more than just a virus, but rather a symptom emerging from something much deeper, a nonlinear dynamical system of coupled pathologies underlying a veneer of "progress" in an increasingly fragile, volatile, hyperconnected world.

A new article by Kang Hao Cheong and Michael C. Jones published in *BioEssays* describes the convergence of four broad, but easily identifiable systemic, pathologically networked conditions, or "four Horsemen", that are hurtling civilization towards potential self-destruction in which a pandemic is only one of many possible triggers. The "four Horsemen" of overpopulation, globalization, hyperconnectivity and increasingly limited and centralized supply chains are the broad parameters underlying the probability space of catastrophe.

"The Covid-19 pandemic has exposed critical pathologies lurking within the dynamical global system of commerce, governance, and public health," said Cheong, from the Singapore University of Technology and Design.

From this heuristic framework a pandemic can metastasize into other vital domains, such as economic and geopolitical stability and other 2nd and 3rd order, multiplicative effects that could snowball into unprecedented catastrophe.

"Even if Covid-19 is not the proximal cause of global catastrophe this time, like the rogue iceberg that slashed the Titanic, it is a blow sufficiently unsettling to awaken us to the fact that we are sailing into a dangerous sea that is increasingly crowded with icebergs," said Jones, a co-author of the article.

In this increasingly complex and chaotic landscape, manoeuvres such as colossal financial bailouts to avoid ruin by the Covid-19 iceberg can turn the ship straight into a bigger "iceberg", or, more likely, into a chain of collisions to the point that catastrophic failure is virtually inevitable. From the standpoint of decision making, as long as these conditions are not resolved, catastrophe should be considered an inevitable endpoint from the nonlinear dynamics.

"A proper understanding of this explosive risk landscape points towards a solution: a massive change of global course based on the precautionary principle and informed by biological principals," observed Cheong.

"Biological theory and complexity science will play a major role in guiding the paradigmatic transformations required to defuse the time bomb. We will have to construct sustainable social institutions and behaviors that imitate life, rather than systems that defy the principles of the living state, in which living things both anticipate and avoid ruin to achieve persistence," said Jones.

You can read more about the article found at: Kang Hao Cheong, Michael C. Jones. "Introducing the 21st Century's New Four Horsemen of the Coronapocalypse," BioEssays (2020). DOI: https://doi.org/10.1002/bies.202000063

https://bit.ly/3bVJDOq

Hereditary mutation that drives aggressive head and neck, and lung cancers in Asians

New knowledge derived from the study opens up opportunities for personalised treatment against the disease

Researchers from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS) have uncovered a genetic variant in a gene called MET that is responsible for more aggressive growth of head and neck, and lung cancers. A further probe into the finding revealed therapeutic

strategies that could potentially target this genetic alteration, thereby paving the way for clinicians to develop better and more effective treatments for cancer patients of such profile.

The study, published in prestigious scientific journal *Nature Communications* on 25 March 2020, was conducted in close collaboration with clinicians from the National University Cancer Institute, as well as researchers from the National Cancer Centre Singapore and the Bioinformatics Institute at the Agency for Science, Technology and Research, Singapore.

The MET gene encodes for a cancer promoting protein that relays growth, survival and transmission of signals in cancer cells. In the study led by Professor Goh Boon Cher and Dr Kong Li Ren from CSI Singapore, the team of researchers identified a form of MET protein, which showed ethnic preference with higher incidence among Asians, and is associated with poorer prognosis in patients diagnosed with head and neck squamous cell carcinoma or lung squamous cell carcinoma. Even though the MET variant does not seem to predispose an individual to cancer, it leads to more aggressive growth of cancers that have already developed.

Unlike other MET mutants, this genetic variant also does not appear to be inhibited by existing MET-blocking drugs that have been developed and approved in the clinical setting, prompting the researchers to conduct further investigation on the mechanism behind the genetic alteration.

Leveraging the research team's multi-disciplinary expertise and state-of-the-art molecular modelling, the team found that the single amino-acid change in the MET receptor from the genetic alternation leads to preferential strong binding to another cancer promoting protein, HER2. Both proteins then work cooperatively to drive cancer aggression and enable cancer cells to survive therapies involving MET-blocking drugs.

"The mechanism of this MET variant is novel and unreported. This finding contributes to the growing evidence of the role of genetic variants in affecting clinical outcome, and underscores the importance of diving deep into our genetic inheritance in cancer research," said Dr Kong, Research Fellow at CSI Singapore who initiated the study.

Knowledge of this unique mechanism also facilitated the team in identifying several HER2 inhibitors capable of blocking cancer progression caused by this genetic alteration using laboratory models.

Prof Goh, Deputy Director and Senior Principal Investigator at CSI Singapore, said, "Our study represents a conceptual advancement to cancer research, as we have shown that it is possible to block the activity of a cancer-driving gene by administrating a targeted therapy directed not against the mutant protein in question, but rather, a corresponding protein with which it binds to. The remarkable anti-tumour responses observed in our experimental models, coupled with the availability of FDA-approved HER2 inhibitors also presents a huge opportunity for clinicians to improve disease outcome of this genetic alteration via precision medicine."

The research team is now translating the findings to a clinical trial where patients tested positive for this MET variant gene are treated with suitable medications that have shown effectiveness in the laboratory.

https://bit.ly/3c1KrBm

Compound in fruit peels halts damage and spurs neuronal repair in multiple sclerosis

Ursolic acid, abundant in fruit peels and some herbs, both prevents and repairs neurons in animal models of multiple sclerosis

Philadelphia - Multiple sclerosis (MS), characterized by increasing muscle weakness and paralysis, has a number of treatments that

help stall progression of the disease when used early on in the disease. But the current treatments can hardly reverse damage that has already occurred in brain cells called neurons. New research suggests that a compound found in the peels of fruits such as apples and prunes, and some herbs, can reduce further damage to neurons, and also help rebuild the protective sheaths covering neurons, reversing the damage.

"Although the evidence is preliminary - our data is from animal models of disease - it's encouraging to see a compound that both halts and repairs damage in MS, in the lab," says Guang-Xian Zhang, PhD, co-senior author and Professor of Neuroscience at the Sidney Kimmel Medical College at Thomas Jefferson University. The study was published in the *Proceedings of the National Academy of Sciences (PNAS)* on Monday April 6th.

"There is additional work we must do to test the safety of this compound, ursolic acid" says co-senior author A.M. Rostami, MD, PhD, chair of the department of Neurology at the Vickie and Jack Farber Institute for Neuroscience - Jefferson Health. "But this is a great new lead for disease treatment."

The researchers used a lab-grade purified form of ursolic acid in mice that had established MS disease. "Many experiments have looked at mice in the acute phase, when disease is just starting or at the peak," says Dr. Zhang. "Instead, we tested whether this compound was effective in chronic disease, once there has already been chronic damage to tissues of central nervous system."

Drs. Zhang, Rostami, together with first author Yuan Zhang and colleagues used an established mouse model of multiple sclerosis that develops the disease slowly over the course of its life, mimicking human disease. At about day 12, the mouse begins the acute phase of the disease, when signs of MS, partial paralysis, appear, and when currently-available medications are most effective. The researchers, however, started treating mice at day 60, - a far more advanced stage of the disease when chronic tissue damage has been formed in brain and spinal cords, which needs to be repaired and regenerated.

Researchers treated the mice for 60 days, and began to see an improvement at day 20 of treatment. The mice which were paralyzed at the start of the experiment, regained the ability to walk around again, although with weakness, after treatment.

"It's not a cure, but if we see a similar response in people, it would represent a significant change in quality of life. And most significantly, it's a reversal, which we really haven't seen before with other agents at such a late stage of disease," says Dr. Zhang.

The researchers also investigated just how ursolic acid acted on cells. They observed that it suppressed Th17 cells - a type of immune cell that is one of the main drivers of the pathological autoimmune response in MS. Many currently active therapies appear to suppress Th17. But the Jefferson researchers showed that the compound could activate precursor cells to mature into much needed myelin-sheath-making cells, called oligodendrocytes.

"This maturation effect is the most crucial," says Dr. Zhang. "Myelin-sheath-making oligodendrocytes are depleted in MS. And the stem cells that produce new oligodendrocytes are dormant and unable to mature. This compound helps activate those stem cells into making new oligodendrocytes, and is likely responsible for the reversal of symptoms we saw."

The next steps for the investigators include testing the compound for safety. Although ursolic acid is available as a dietary supplement, it could be toxic at high doses. "There are still a number of tests to complete before the first clinical trials," says Dr. Rostami. "However, we are moving quickly with this promising approach."

This study was supported by the NIH, USA (Grants NS099594 and AI135601). Drs. Yuan Zhang and Xing Li were partly supported by Chinese Foundations (Grants 81771345, 31970771 and KF2019001).

Article reference: *Yuan Zhang, Xing Li, Bogoljub Ciric, Mark T. Curtis, Wan-Jun Chen, Abdolmohamad Rostami, and Guang-Xian Zhang, "A dual effect of ursolic acid to the treatment of multiple sclerosis through both immunomodulation and direct remyelination," PNAS, DOI: 10.1073/pnas.2000208117, 2020.*

https://bit.ly/2JT30f8

Potential early biomarker to track development of non-alcoholic fatty liver disease

Biomarker in humans tied to the development of NAFLD that might help doctors detect early stages of the disease

Boston - Fatty liver disease not associated with alcohol consumption, which is called Nonalcoholic Fatty Liver Disease or NAFLD, affects more than one billion people worldwide. Even in children the numbers are overwhelming, with up to 80 percent of pediatric patients who are considered obese affected worldwide. People with NAFLD can progress to a severe form known as nonalcoholic steatohepatitis (NASH), which puts patients at higher risk for cirrhosis or liver cancer.

With no definitive treatment options or early detection methods yet discovered, researchers have been hard at work to identify early biomarkers of this disease. "This becomes also especially important in the context of diabetes because individuals with Type 2 diabetes are much more susceptible to this disease," says Rohit N. Kulkarni, MD, PhD, Section Head, Senior Investigator, Islet Cell and Regenerative Biology, Joslin Diabetes Center, and Professor of Medicine, Harvard Medical School.

But recent research from Dr. Kulkarni's lab at Joslin has uncovered a biomarker in humans tied to the development of NAFLD that might help doctors detect early stages of the disease. The researchers also determined that this biomarker, a protein known as "neuronal regeneration related protein" (or NREP), plays a significant role in the regulation of a pathway that is currently being reviewed in clinical trials as a treatment option for the disease. The study was published today in *Journal of "Clinical Investigation*."

"We identified NREP as a new biomarker for NAFLD that is involved in the regulation of liver fat metabolism and in a process called fibrosis that occurs during the progression of the fatty liver disease that may lead to cirrhosis and liver cancer" says Dario F. De Jesus, MSc, PhD, a postdoctoral research fellow in the Kulkarni Lab at Joslin and lead author on the study.

Previous studies had indicated genetics played a large role in who got NAFLD. But other evidence suggests that environmental factors such as the parental health status are also at play. "One of the causative factors that has been suggested is the parental influence in the offspring, in the sense that if either the mother or the father [or particularly both] has metabolic syndrome (a medical condition associated with obesity, high blood glucose, high cholesterol, and elevated insulin levels) then the chances of the offspring developing this disease is greater," says Dr. Kulkarni.

Dr. Kulkarni's research team and collaborators tested this hypothesis first in animal models in their recently published study. They used two groups of mice; one group had a genetic modification to have the markers of metabolic syndrome. Another group was not genetically modified. They studied the offspring from these groups in three different categories: either one of the parents had metabolic syndrome, both parents did, or neither did. Then they selected genetically normal offspring from each of these parents and fed them either a normal diet or a high caloric diet rich in fat to mimic obesity, and monitored their development.

"When the offspring were fed a normal diet, they did not experience much change in body fat percentage. But when the offspring [of parent groups affected by metabolic syndrome] were fed a slightly high fat diet, their body fat content went up dramatically in comparison with the offspring of the healthy parents," says Dr. Kulkarni.

When they looked in more depth at where the body fat accumulated, they saw a striking increase of fat in the liver. These offspring also had increased cholesterol and triglycerides in the liver.

They took a deep dive into the genetic pathways that were active in the healthy offspring versus the offspring that developed NAFLD. They noticed the protein NREP was reduced in the unhealthy offspring. This was the first time NREP was linked to liver metabolism. They then either increased (e.g. overexpressed) or decreased (e.g. knocked down) NREP in culture dishes to study this newly discovered function.

"When we decreased NREP levels in human liver cells, the cholesterol pathway and markers associated with the development of fibrosis went up resembling what happens during the progression of NAFLD" says Dr. Kulkarni.

They wanted to see if this association of lower levels of NREP with NAFLD was also true in humans. They collaborated with researchers in Finland who had a large database of information from patients in various stages of the liver disease to better understand the correlation with NREP levels.

"We detected this protein really clearly and we could show a pattern that tracks the progression of the disease. So, this is really exciting," says Dr. Kulkarni. In other words--as soon as NAFLD started, NREP circulating levels got lower, suggesting NREP is an early biomarker of NAFLD.

In this study, they also showed that NREP modulates a protein called ATP citrate lyase (or ACLY). ACLY is actively being investigated in clinical trials as a possible treatment for NAFLD. This means that the discovery of NREP's role in NAFLD not only yields a useful biomarker for tracking disease course, it can also help further the development of a treatment.

As a follow-up, they plan to specifically track the pathways by which parental metabolic syndrome modifies how NREP is expressed in offspring. But for now, they have a valuable biomarker to track NAFLD in the general population.

"We can really begin to consider, in the clinic, using this protein as a biomarker to identify those individuals in that risk window. We can also track those who already have low NREP but don't have the disease, with the assumption that when it is low, then they're much more susceptible and should be followed up very carefully," says Dr. Kulkarni. "That gives an important perspective for extra, personalized care."

The research team included Dario F. De Jesus, Kazuki Orime, Dorota Kaminska, Tomohiko Kimura, Giorgio Basile, Chih-Hao Wang, Larissa Haertle, Renzo Riemens, Natalie K. Brown, Jiang Hu, Ville Männistö, Amélia M. Silva, Ercument Dirice, Yu-Hua Tseng, Thomas Haaf, and Jussi Pihlajamäki,

This study was funded in part by the National Institutes of Health.

https://bit.ly/3e4w7d3

Successful MERS vaccine in mice may hold promise for COVID-19 vaccine

Vaccine fully protects mice against a lethal dose of MERS, a close cousin of the SARS-CoV2

Researchers at the University of Iowa and the University of Georgia have developed a vaccine that fully protects mice against a lethal dose of MERS, a close cousin of the SARS-CoV2 coronavirus that causes COVID-19.

The vaccine uses a harmless virus to deliver a MERS coronavirus protein into cells to generate an immune response, and may hold promise for developing vaccines against other coronaviruses diseases, including COVID-19.

The team led by Paul McCray, MD, at the UI Carver College of Medicine, and Biao He, PhD, at the University of Georgia College of Veterinary Medicine, tested a MERS vaccine candidate in mice engineered to be susceptible to the MERS coronavirus. The vaccine is an innocuous parainfluenza virus (PIV5) carrying the "spike" protein that MERS uses to infect cells. All the vaccinated mice

survived a lethal dose of the MERS coronavirus. The results of the study were published April 7 in the journal *mBio*.

"Our new study indicates that PIV5 may be a useful vaccine platform for emerging coronavirus diseases, including SARS-CoV-2, the virus causing the ongoing COVID-19 pandemic," says McCray, UI professor of pediatrics. "Using the same strategy, vaccine candidates based on PIV5 expressing the spike protein of SARS-CoV-2 have been generated. We are planning more studies in animals to test the ability of PIV5-based vaccines in preventing disease caused by SARS-CoV-2."

MERS (Middle East Respiratory Syndrome) and COVID-19 are both caused by coronaviruses. MERS is deadlier and is fatal in about one third of known cases, but there have been only 2,494 cases since 2012, when the virus first emerged. In contrast, there have been over 1.25 million confirmed cases of COVID-19 worldwide since it first emerged in late 2019 in Wuhan, China, and almost 70,000 people have died from the disease.

The study found that just one, relatively low dose of the vaccine given to the mice intranasally (inhaled through the nose) was sufficient to fully protect all the treated mice from a lethal dose of MERS coronavirus.

When the researchers analyzed the immune responses generated by the vaccine, they found that both antibodies and protective T cells were produced. However, the antibody response was quite weak and it seems most likely that the vaccine's protective effect is due to the T cell response in the mouse lungs.

The researchers note several factors that make PIV5 expressing a coronavirus spike protein an appealing platform for vaccine development against emerging coronaviruses. First, PIV5 can infect many different mammals, including humans, without causing disease. PIV5 is also being investigated as a vaccine for other respiratory diseases including respiratory syncytial virus (RSV) and influenza. Second, the fact that a low dose of the vaccine was sufficient to protect the mice might be beneficial for creating enough vaccine for mass immunization. And finally, the vaccine in the current study was the most effective MERS vaccine to date in animal models of the disease.

In addition to McCray, who also holds an appointment the UI Department of Microbiology and Immunology, and He, who is a professor of infectious disease at the University of Georgia, the research team included Kun Li, Christine Wohlford-Lenane, David Meyerholz, Rudragouda Channappanavar, and Stanley Perlman at the UI; and Zhuo Li and Dong An at the University of Georgia.

The research was funded in part by grants from the National Institutes of Health and the Cystic Fibrosis Foundation. McCray is supported by the Roy J. Carver Charitable Trust. Biao He is supported by endowment of Fred C. Davison Distinguished University Chair in Veterinary Medicine.

https://bit.ly/2JTwjOB

Love The Smell of Rain? There's an Ulterior Motive Behind The Lure of Petrichor

If you've lived outside a major city, the smell is instantly recognisable – the earthy scent of petrichor as rain hits dry soil.

Jacinta Bowler

Now, new research has uncovered why it's not just us humans who are attracted to this incredibly pleasant odour.

That luscious smell we can detect after rain comes from an organic compound called geosmin, which is produced by microbes, including the bacteria genus *Streptomyces*.

We also know that *Streptomyces* releases geosmin when they die, and that humans and other creatures are particularly attuned to it. The question, of course, is - why does this happen?

An international team of researchers set out to explain why bacteria produce geosmin, and whether any other creatures were able to enjoy the smell as much as we do.

"To investigate possible roles of geosmin and other *Streptomyces* volatile organic compounds in the context of soil ecosystems, we asked whether the smell of *Streptomyces* spp. might attract soil-

dwelling arthropods," the international team of researchers wrote in their new paper. And that's exactly what they found.

"In a network of field traps baited with *Streptomyces coelicolor* colonies, we found significant attraction of springtails (Collembola) compared with control traps."

The team did a number of experiments both in the field and in the lab to see the effects of geosmin and another compound called 2-methylisoborneol (2-MIB) on forest creatures, particularly springtails - tiny arthropods with a tail-like appendage, which live in organic materials such as leaf litter on a forest floor.

Turns out that springtails are big fans of geosmin. They can sense it with their antennae, are attracted to it, and will feed on the *Streptomyces* producing it.

But why would a bacterium go to so much effort just to be slurped up by an arthropod? Although producing a nice smell to get eaten might sound like a bad time for most, *Streptomyces* actually has a plan.

Streptomyces acts, in a lot of ways, like a fungus. It looks a lot like a filamentous fungus, and when it is ready to reproduce, it creates spores, which can spread newborn bacteria far and wide.

But it does need a vector for that spread, which is where the springtails come in.

"[A springtail] feeds on the *Streptomyces* colonies and disseminates spores both via faecal pellets and through adherence to its hydrophobic cuticle," the team explains.

"The results indicate that geosmin and 2-MIB production is an integral part of the sporulation process, completing the *Streptomyces* life cycle by facilitating dispersal of spores by soil arthropods."

Next time you smell the rain, you can enjoy the fact that what you're smelling is an entire circle of life in its own little way.

The research has been published in *Nature*.

https://bit.ly/3c33Gud

Common coronaviruses are highly seasonal, with most cases peaking in winter months

Four coronaviruses cause common respiratory infections that are sharply seasonal and appear to transmit similarly to influenza

Of the seven coronaviruses known to infect people, four cause common respiratory infections that are sharply seasonal and appear to transmit similarly to influenza, according to a new study by University of Michigan School of Public Health researchers.

The study authors say it is not possible to determine whether SARS-CoV-2 coronavirus, which causes COVID-19 disease, will behave likewise. But they hope their findings will help investigators better prepare for what's to come during the COVID-19 pandemic. Their study appears in the *Journal of Infectious Diseases*.

"Even though the seasonal coronaviruses found in Michigan are related to SARS-CoV-2, we do not know whether that virus will behave like the seasonal coronaviruses," said Arnold Monto, the Thomas Francis Collegiate Professor of Epidemiology at the U-M School of Public Health. "Only time will tell if SARS-CoV-2 will become a continuing presence in the respiratory infection landscape, continue with limited circulation as with MERS, or like SARS, disappear from humans altogether."

The researchers note that while coronaviruses have long been recognized as human respiratory pathogens, human coronaviruses have historically been detected in mild respiratory illnesses; when animal coronaviruses spill over to humans, however, they can cause severe disease. Severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012 both emerged when a coronavirus jumped from an animal to people. The COVID-19 pandemic is believed to have started in the same way.

Monto and colleagues used data from the Household Influenza Vaccine Evaluation study, an ongoing longitudinal investigation of

respiratory illnesses in households with children in the Ann Arbor area. For the last 10 years, between 890 to 1,441 individuals from several hundred households participated in the study. The continuing study is now tracking the occurrence of SARS-CoV-2 and its potential presence in Michigan households.

In 2010, the study began tracking the occurrence of four typically mild human coronaviruses (OC43, 229E, HKU1 and NL63). The researchers looked at frequency, seasonality and household transmission characteristics of the 993 infections caused by those coronaviruses. They found:

- ***Overall, 9% of adult cases and 20% of cases in children were associated with doctor visits. On average, 30% of influenza cases require a doctor visit.***
- ***When year-round surveillance occurred, most coronavirus cases were detected between December and April/May, and peaked in January/February. Only 2.5% of the cases occurred between June and September.***
- ***The highest infection frequency was in children under age 5.***
- ***Of the 993 infections, 260 were acquired from an infected household contact.***
- ***The serial interval between index and household-acquired cases ranged from 3.2 to 3.6 days; secondary infection risk ranged from 7.2% to 12.6% by type.***
- ***Cases in children under age 5 and adults over age 50 were more likely to be classified as severe.***

Monts and colleagues say that the coronaviruses studied are sharply seasonal in Michigan and appear, based on serial interval and secondary infection risk, to have similar transmission potential to that of the influenza A (H3N2) virus in the study population. They say the results are not indicative of how SARS-CoV-2 will behave.

In a separate ongoing study, the researchers are using samples collected before the COVID-19 pandemic to explore community introduction of SARS-CoV-2. Preliminary results show no evidence that SARS-CoV-2 was present in the community before March.

The study was funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, through grants R01 AI097150 and R56 AI097150.

Study: Coronavirus occurrence and transmission over 8 years in the HIVE cohort of households in Michigan

https://bit.ly/2V9wCdi

Hangover drug shows wider benefits in USC research

Hangover drug not only soothes pounding headaches but also triggers profound changes that protect the liver

A well-known hangover drug not only helps soothe pounding headaches but also triggers profound changes that protect the liver, USC scientists report in new findings that could help prevent alcohol-related harm.

The study focuses on dihydromyricetin (DHM), also known as ampelopsin, an over-the-counter herbal remedy. When researchers at the USC School of Pharmacy sought to understand how it works, their investigation revealed a sequence of metabolic changes responsible not only for easing headaches but also benefitting the liver.

"We know DHM helps the body to metabolize alcohol faster, but how does it work? We found it activates a cascade of mechanisms that erase alcohol from the body very quickly," said Jing Liang, a research professor of clinical pharmacy and the corresponding author of the study. The study appears today in *Alcoholism: Clinical and Experimental Research*.

The findings support the utility of DHM as a dietary supplement to offset acute alcohol-related effects as well as long-term risks. In addition, the authors say the substance likely has wider applications to help people cope with binge drinking, alcoholism and liver damage.

Alcohol use disorders constitute the most common form of substance abuse. About 88,000 people die of alcohol-related deaths

annually -- the third leading preventable cause of death in the United States, according to the U.S. Centers for Disease Control and Prevention. Globally, alcohol consumption contributes to 3 million deaths each year and is responsible for 5.1% of the global burden of disease, according to the World Health Organization. There is no effective therapeutic agent for the disorder without major side effects.

Meanwhile, excessive alcohol consumption is a significant cause of chronic liver disease, accounting for nearly half of the cirrhosis-associated deaths in the United States, according to the study.

DHM is derived from fruit from the Japanese raisin tree (Hovenia dulcis) *玄圃梨*, which is native to Japan, Korea and Southeast Asia and now commercially grown. It's been used in China for liver ailments for 500 years, but how the substance works is unclear.

To better understand what the drug does inside the body, the scientists fed 36 mice a daily diet of alcohol for two months, gradually increasing doses to 30% of their total food intake for an average of 39.4 g/kg of ethanol per day per mouse. Then, they assessed their livers for injury and markers of stress.

The researchers focused on the liver, Liang said, because when you take a drink, alcohol circulates through the bloodstream. Though the alcohol affects the brain, it is metabolized primarily by the liver, which is significantly harmed by long-term, high levels of alcohol consumption.

"It's like stepping on a tack; your brain says it hurts. During a hangover, the fogginess in your brain is an acute reaction to what's going on in your body," said Daryl Davies, a study co-author and professor of clinical pharmacy in the USC School of Pharmacy.

Among other significant effects, the scientists found that DHM:

- ***Triggered the liver to produce more ethanol-gobbling enzymes, including alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH).***
- ***Boosted the efficiency of ADH and ALDH, enabling the enzymes to convert ethanol into simpler forms the body can eliminate easier.***
- ***Reduced lipid (fat) accumulation in liver tissue. Heavy doses of alcohol can negatively affect the liver's metabolism, leading to an accumulation of fat, increased stress and the eventual progression to liver diseases such as cirrhosis.***
- ***Reduced inflammatory agents, called cytokines. Excessive alcohol leads to the release of cytokines in the liver, which contributes to cellular damage to the liver and other organs.***

"In total, these findings support the utility of DHM as a dietary supplement to reduce ethanol-induced liver injury via changes in lipid metabolism, enhancement of ethanol metabolism and suppressing inflammation responses to promote liver health," the study said. "This line of research suggests that DHM acts on multiple pathways to promote liver health and counteract ethanol injury."

Davies, who is also director of the Alcohol and Brain Research Laboratory at USC, said the findings also help explain how DHM works as a hangover treatment. The liver converts alcohol into an aldehyde with properties like formaldehyde, which contribute to headache and nausea. Since it takes about one hour for the body to metabolize one drink, a night of heavy drinking causes the liver to keep churning out the chemicals that make people feel woozy for so long.

"We now know what [DHM] is doing and how it's doing it mechanically, activating a cascade of energy-regulating mechanisms that speed metabolism of ethanol and its byproducts," said Joshua Silva, a doctoral student at the USC School of Pharmacy and study co-author.

The findings have important implications for helping prevent liver damage and harm from alcohol abuse.

For example, binge drinkers could use DHM for its liver protection properties, extending the function of the organ long enough for the person to get help and stop their bad drinking habit. "We may not be able to fix their problem overnight, but we can give them step-by-step improvements to help them drink less and gain health protection," Davies said.

Binge drinking is a serious problem for young adults, especially college students. About 37% of students engage in binge drinking -- five or more drinks on a single occasion for men or four or more drinks for women -- and about 10% engage in heavy alcohol use -- binge drinking on 5 or more days in the past month. Those rates are much higher than among non-college peers, according to a recent survey by the National Institutes of Health.

Excessive alcohol consumption significantly contributes to higher rates of alcohol-related liver disease at a younger age.

Excessive drinking has high social and economic costs, leading to heart disease, high blood pressure, unplanned pregnancies, violence and vehicle crashes. The CDC estimates the total economic cost at $249 billion annually.

DHM could potentially help patients who go to the doctor with early warning signs of liver damage. The substance could be used to help restore and prolong their liver function and delay the onset of liver disease while waiting for a transplant. DHM could also prove useful for liver transplant patients to help the new organ perform better so patients could enjoy a better quality of life.

"There's hope here. It could be a new lease on life for a lot of people," Davies said.

The study authors are Joshua Silva, Xin Yu, Renita Moradian, Carson Folk, Maximilian H. Spatz, Phoebe Kim, Adil A. Bhatti, Daryl L. Davies and Jing Liang of the USC School of Pharmacy.

The work was supported by funding and grants from the National Institutes of Health - National Institute on Alcohol Abuse and Alcoholism (R01AA022448), USC Good Neighbors Campaign, USC School of Pharmacy, American Foundation for Pharmaceutical Education, and More Labs.

https://bit.ly/39Zt8zf

Researcher discovers early, complex brain surgery in ancient Greece

Very serious trauma cases been treated surgically or orthopedically by a very experienced physician/surgeon with great training in trauma care

New research from Adelphi University has revealed the first forensically-assessed archeological discovery of remains of a group of domineering mounted archer-lancers and their kin of the Eastern Roman Empire from the turbulent ProtoByzantine period, which spanned the fourth to seventh centuries.

Ectocranial view of palaeopathological specimen: a) red arrow points to orifice on the mastoid process, and b) surgical preparation dimensions peripheral to trephination. **Anagnostis P. Agelarakis/Adelphi University**

Ten skeletal remains—four women and six men likely of high social standing—were discovered in the Paliokastro site on Thasos island in Greece. Their bones illuminated their physical activities, traumas, and even a complex form of brain surgery.

"The burial place and architecture of the funerary monumental church and the construction of the graves is spectacular," said lead researcher and anthropologist Anagnostis Agelarakis, Ph.D., who added that it indicates the high social standing of the individuals buried there.

The advanced preservation of their remains and the impressive location and architecture of the funerary monumental church where they were buried exhibit their high status in the region.

"According to the skeleto-anatomic features of the individuals, both men and women lived physically demanding lives," said Agelarakis, professor of anthropology in Adelphi's Department of History.

"The very serious trauma cases sustained by both males and females had been treated surgically or orthopedically by a very experienced physician/surgeon with great training in trauma care. We believe it to have been a military physician."

As for the brain surgery, Agelarakis suggests that "even despite a grim prognosis, an extensive effort was given to this surgery for this male. So, it's likely that he was a very important individual to the population at Paliokastro."

Agelarakis and his colleagues were able to derive medical and surgical data, as well as paleopathological data, on this "extraordinary head and neck surgery and the great efforts of the surgeon." It was determined that the likely cause for the surgical intervention was infection and that archer died shortly after or during surgery. "The surgical operation is the most complex I have ever seen in my 40 years of working with anthropological materials," Agelarakis said.

"It is unbelievable that it was carried out, with most complicated preparations for the intervention, and then the surgical operation itself which took place, of course, in a pre-antibiotic era."

The results are described in a new book, "Eastern Roman Mounted Archers and Extraordinary Medico-Surgical Interventions at Paliokastro in Thasos Island during the ProtoByzantine Period: The Historical and Medical History Records and the Archaeo-Anthropological Evidence," by Archaeopress, Access Archaeology.

More information: *Anagnostis P. Agelarakis. Eastern Roman Mounted Archers and Extraordinary Medico-Surgical Interventions at Paliokastro in Thasos Island during the ProtoByzantine Period: The Historical and Medical History Records and the Archaeo-Anthropological Evidence.*
http://www.archaeopress.com/ArchaeopressShop/Public/download.asp?id=%7BA3ADBD32-B3DD-4A70-8916-54E9E666FC71%7D

https://bit.ly/3e8zTSQ

False memories of crime appear real when retold to others

People are no better than chance at identifying when someone else is recounting a false or real memory of a crime, according to a new UCL study.

The findings, published in *Frontiers in Psychology*, build on a previous study that was the first to successfully implant false memories of committing a crime - involving either assault or assault with a weapon that resulted in police contact.

Study author Dr Julia Shaw (UCL Psychology & Language Sciences) said: "Everyone thinks that they couldn't be tricked into believing they have done something they never did, and that if someone were telling them about a false memory, they would be able to spot it. But we found that actually, people tend to be quite susceptible to having false memories, and they sound just like real memories."

For the previous study, published in 2015, Dr Shaw and a colleague invited young adults into a study about emotional memories, and also spoke with a member of their family to learn about events from the participants' early adolescence, in as much detail as possible.

The researchers spoke to the participants about their past, and used leading questions and suggestive tactics, as well as visualisation techniques to convince the participants that they were helping them recover a forgotten memory - while in fact they were implanting a false memory that the participant had committed a crime when they were young, such as theft or assault.

"We were essentially doing exactly 'what not to do' when conducting a police interview," explained Dr Shaw.

The 2015 study reported that the majority of participants developed a false memory of committing a crime, and the participants consistently reported that the false memories felt incredibly real.

The current research involves two studies that used videos from the 2015 study, of the study participants recounting their false memories of a crime, which they believed to be real. The new participants watched those videos and were asked if the person was describing an event that actually happened or not.

Participants were only 53% accurate (no better than chance) at identifying false memories of committing a crime. These results were replicated in the second study. Even when participants were explicitly told that one of the memories they watched was false, their judgment was still no better than tossing a coin.

In addition to incorrectly believing false memories to be true, participants were just as likely to watch someone recount a genuine memory, and then misidentify it as false, once the research team told them that some of the videos would feature false memories. In other words, many true memories looked like false memories.

"Legal professionals and police officers need to realise how easy it is to manipulate someone's memories. Judges in particular should never assume that they can tell when someone has a false memory, and should consider the entire process to see if there was any risk of contamination of a defendant or witness' memories," Dr Shaw said.

"The findings really highlight how important it is to ensure that criminal proceedings are done right. The questioning process should be evidence-based, to reduce the risk of implanting false memories in people being questioned by the police."

https://bit.ly/2y9H3pb

Revolutionary new method for dating pottery sheds new light on prehistoric past

New method was proven to date sites incredibly accurately, even to within a human life span

A team at the University of Bristol has developed a new method of dating pottery which is allowing archaeologists to date prehistoric finds from across the world with remarkable accuracy.

The exciting new method, reported in detail today in the journal *Nature*, is now being used to date pottery from a range of key sites up to 8,000 years old in Britain, Europe and Africa.

Pottery and the dating game

Archaeological pottery has been used to date archaeological sites for more than a century, and from the Roman period onwards can offer quite precise dating. But further back in time, for example at the prehistoric sites of the earliest Neolithic farmers, accurate dating becomes more difficult because the kinds of pottery are often less distinctive and there are no coins or historical records to give context. This is where radiocarbon dating, also known as 14C-dating, comes to the rescue. Until now, archaeologists had to radiocarbon date bones or other organic materials buried with the pots to understand their age. But the best and most accurate way to date pots would be to date them directly, which the University of Bristol team has now introduced by dating the fatty acids left behind from food preparation.

Professor Richard Evershed from the University of Bristol's School of Chemistry led the team. He said: "Being able to directly date archaeological pots is one of the "Holy Grails" of archaeology. This new method is based on an idea I had going back more than 20 years and it is now allowing the community to better understand key archaeological sites across the world.

"We made several earlier attempts to get the method right, but it wasn't until we established our own radiocarbon facility in Bristol that we cracked it. There's a particular beauty in the way these new technologies came together to make this important work possible and now archaeological questions that are currently very difficult to resolve could be answered."

How the method works

The trick was isolating individual fat compounds from food residues, perhaps left by cooking meat or milk, protected within the

pores of prehistoric cooking pots. The team brought together the latest high resolution nuclear magnetic resonance spectroscopy and mass spectrometry technologies to design a new way of isolating the fatty acids and checking they were pure enough for accurate dating.

The team then had to show that the new approach gave dates as accurate as those given by materials commonly dated in archaeology, such as bones, seeds and wood. To do this the team looked at fat extracts from ancient pottery at a range of key sites in Britain, Europe and Africa with already precise dating which were up to 8,000 years old.

From the famous Sweet Track site in Somerset and several sites in the Alsace region of France, to the World Heritage site of Çatalhöyük in central Turkey and the famous rock shelter site of Takarkori in Saharan Africa, the new method was proven to date sites incredibly accurately, even to within a human life span.

Professor Alex Bayliss, Head of Scientific Dating at Historic England, who undertook the statistical analyses, added: "It is very difficult to overstate the importance of this advance to the archaeological community. Pottery typology is the most widely used dating technique in the discipline, and so the opportunity to place different kinds of pottery in calendar time much more securely will be of great practical significance."

Using the pottery calendar to better understand London's pre-history

In London, England, the new dating method has been used on a remarkable collection of pottery found in Shoreditch, thought to be the most significant group of Early Neolithic pottery ever found in the capital. The extraordinary trove, comprising 436 fragments from at least 24 separate vessels weighing nearly 6.5 kilos in total, was discovered by archaeologists from MOLA (Museum of London Archaeology).

The site appeared to date from the time when the first farmers came to Britain but accurately dating it was difficult until the Bristol team, using their new dating method on traces of milk fats extracted from the pots, showed the pottery was 5,500 years old. The team were able to date the pottery collection to a window of just 138 years, to around 3600BC.

The results indicate that around 5600 years ago the area around what is now Shoreditch High Street was used by established farmers who ate cow, sheep or goat dairy products as a central part of their diet. These people were likely to have been linked to the migrant groups who were the first to introduce farming to Britain from Continental Europe around 4000 BC - just 400 years earlier.

Jon Cotton, a consultant prehistorian working for MOLA, said: "This remarkable collection helps to fill a critical gap in London's prehistory. Archaeological evidence for the period after farming arrived in Britain rarely survives in the capital, let alone still in-situ. This is the strongest evidence yet that people in the area later occupied by the city and its immediate hinterland were living a less mobile, farming-based lifestyle during the Early Neolithic period."

The results from this site are a prime example of where pottery survives in circumstances that other organic materials do not, so using this revolutionary new method will unlock important information about our prehistoric past.

https://bit.ly/2UZUyko

Amazonian crops domesticated 10,000 years ago

International team gathers evidence from 'forest islands'.

Southwest Amazonia has been confirmed as one of the earliest centres of plant domestication in the world.

From their arrival 10,000 years ago, human inhabitants in what is now Llanos de Moxos in northern Bolivia created thousands of artificial forest islands as they tamed wild plants to produce food, a new study shows.

They began growing manioc and squash, a development the researchers suggest is as significant as the cultivation of rice in China, grains and pulses in the Middle East, maize, beans and squash in Mesoamerica, and potatoes and quinoa in the Andes.

The international team undertook a large-scale analysis of 61 archaeological sites identified by remote sensing, retrieving samples from 30 forest islands and carrying out archaeological excavations in four of them.

Forest islands in Llanos de Moxos, Bolivia. **Umberto Lombardo**

Their findings are published in the journal *Nature*.

"Archaeologists, geographers and biologists have argued for many years that southwestern Amazonia was a probable centre of early plant domestication because many important cultivars like manioc, squash, peanuts and some varieties of chilli pepper and beans are genetically very close to wild plants living here," says lead author Umberto Lombardo, from the University of Bern, Switzerland.

"However, until this recent study, scientists had neither searched for, nor excavated, old archaeological sites in this region that might document the pre-Columbian domestication of these globally important crops."

The forest islands remained above water level even when the savannah area flooded during the wet season, allowing trees and plants to grow. This shows that small-scale communities began to shape the Amazon 8000 years earlier than previously thought, the researchers say.

They documented the earliest evidence in the Amazon of manioc (10,350 years ago), squash (10,250) and maize (6850)

The plants were no doubt chosen because they were carbohydrate-rich and easy to cook, and they likely provided a considerable part of the calories consumed by the first inhabitants of the region, supplemented by fish and some meat.

"Genetic and archaeological evidence suggests there were at least four areas of the world where humans domesticated plants around 11,000 years ago, two in the Old World and two in the New World," says co-author Jose Iriarte from the University of Exeter, UK. "This research helps us to prove southwest Amazonia is likely the fifth."

https://wb.md/34yffY2

Parasite Drug Shows Early Promise Against COVID-19 in Vitro

An inexpensive drug used to treat parasitic infections killed the coronavirus that causes COVID-19 in less than 48 hours in a laboratory setting, Australian researchers say.

Kathleen Doheny

The drug, ivermectin, has been used widely used for decades. It was introduced as a veterinary drug in the 1970s. Doctors also prescribe it to treat head lice, scabies, and other infections caused by parasites.

According to a report published online in the journal *Antiviral Research*, the drug quickly prevented replication of SARS-CoV-2, the virus that causes COVID-19. The study has been peer-reviewed and accepted for publication, although it is not yet a "definitive" version of record.

Researchers infected cells with SARS-CoV-2, then exposed them to ivermectin. "We showed that a single dose of ivermectin could kill COVID-19 in a petri dish within 48 hours, indicating potent antiviral activity," says study co-author David Jans, PhD, a professor of biochemistry and molecular biology at Monash University in Melbourne.

Even at 24 hours, "there was a really significant reduction" in the virus, study leader Kylie Wagstaff, PhD, a senior research fellow in biochemistry and molecular biology at Monash University, said in a

statement. But experts say more testing is needed to know if it works well in people and if it's safe to use.

"No One Should Try to Self-Medicate"

"The main way we think ivermectin works is to target a key molecule of our cells that we think helps the virus to proliferate," Jans says. "By stopping this, the virus replicates more slowly, and so our immune system has a better chance to mount the antiviral response and kill the virus." Giving this or any antiviral drug early is thought to give the body the best chance of beating infection, he says.

In other studies, the researchers say, the drug has been shown to work against dengue fever and to limit infections similar to COVID-19, such as the West Nile virus.

The drug is "safe at relatively high doses, widely available, and relatively cheap, too," Jans says. The next step is more research to find the best dose for fighting COVID-19. Then researchers can begin testing in people, he says. "It is important to stress that no one should try to self-medicate with versions of ivermectin that are for veterinary purposes or head lice." The only safe way to get ivermectin is by prescription from a doctor, he says.

U.S. Experts Weigh In

The new study "certainly piqued our interest," says Jill Weatherhead, MD, an assistant professor of adult and pediatric infectious diseases at Baylor College of Medicine in Houston. Her clinic uses the medicine to treat intestinal parasites found in international travelers or immigrants.

The important caveat, says Weatherhead, who reviewed the study but was not involved in the research, is that it was done in a lab. But "at this point, any lead we have should be investigated," she says. "What we really need to know is, could you translate that concentration [of the drug used in the lab study] into human studies and have it be safe?"

"The results are promising," agrees Katherine Seley-Radtke, PhD, a professor of chemistry and biochemistry at the University of Maryland, Baltimore County. She holds patents on compounds that are also being studied for COVID-19.

"Ivermectin," she says, "has shown effectiveness against other viruses, despite being an anti-parasitic drug." The drug is worthy of further study, Seley-Radtke says, but she calls the findings "very preliminary."

Sources:

Antiviral Research: "The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro."

Katherine Seley-Radtke, PhD, professor of chemistry and biochemistry, University of Maryland, Baltimore County.

Jill Weatherhead, MD, assistant professor of adult and pediatric infectious diseases, Baylor College of Medicine, Houston.

David Jans, PhD, professor of biochemistry and molecular biology, Monash University, Melbourne, Australia.

Editor's note: *Find the latest COVID-19 news and guidance in Medscape's Coronavirus Resource Center.*

https://bit.ly/2RvFKbj

Elaborately decorated eggs predate Easter by thousands of years

If you wanted to impress a Bronze or Iron Age chieftain, jewelry wouldn't cut it. You'd present them with an elaborately carved ostrich eggshell

By Michael Price

If you wanted to make an impression on a high-ranking Bronze or Iron Age chieftain, mere jewelry or gems wouldn't cut it. Instead, you'd present them with an egg—an elaborately carved and embellished ostrich eggshell, to be exact. Such oologic offerings have been found inside the tombs of Mediterranean and Middle Eastern elites who lived from about 2500 to 500 B.C.E., equally thrilling and perplexing archaeologists. Who made them, and how did they wind up in the hands of ancient nobility?

To crack the case, a team of archaeologists and museum curators took a closer look at decorated eggshells in the collection of the British Museum, which includes five prized eggs in outstanding condition.

***Jononmac46* (CC BY-SA 3.0)**

The intact eggs were all discovered in a burial site known as the Isis Tomb in Vulci, Italy, that was uncovered in 1839 by Napoleon Bonaparte's brother, Prince Lucien. The tomb dates to about 600 B.C.E. and was filled with other luxury items, including gold jewelry and bronze dinnerware. All five of the ostrich eggs were painted, and four were engraved with repeating geometric patterns (as seen above), animal motifs, and chariots and soldiers.

On other, fragmented pieces found in about a dozen other burial sites around the Mediterranean and Middle East, the researchers used stable isotope analysis—a technique that matches chemical markers in bones and teeth to specific regions—to trace the eggs' origins. Researchers already suspected they were made by Assyrian and Phoenician craftworkers, and the isotope analysis bore that out. But they found that even within the same tomb, eggshells came from several different regions, indicating a more complex supply chain than previously thought, the researchers report today in *Antiquity*. A scanning electron microscope also revealed the engravers used a multitude of tools and techniques, underlining the intense effort and skill that went into making these ovular ornaments.

https://bit.ly/2RuP3Ia

Newly engineered enzyme can break down plastic to raw materials

The resulting chemicals can be used to make brand-new bottles.

John Timmer

Plastics have a lot of properties that have made them fixtures of modern societies. They can be molded into any shape we'd like, they're tough yet flexible, and they come in enough variations that we can tune the chemistry to suit different needs. The problem is that they're tough enough that they don't break down on their own, and incinerating them is relatively inefficient. As a result, they've collected in our environment as both bulk plastics and the seemingly omnipresent microplastic waste.

For natural materials, breaking down isn't an issue, as microbes have evolved ways of digesting them to obtain energy or useful chemicals. But many plastics have only been around for decades, and we're just now seeing organisms that have evolved enzymes to digest them. Figuring they could do one better, researchers in France have engineered an enzyme that can efficiently break down one of the most common forms of plastic. The end result of this reaction is a raw material that can be reused directly to make new plastic bottles.

An unwanted PET

The plastic in question is polyethylene terephthalate, or PET. PET has a variety of uses, including as thin films with very high tensile strength (marketed as mylar). But its most notable use is in plastic drink bottles, which are a major component of environmental plastic waste. PET was first developed in the 1940s, and the first living organism that can break down and use the carbon in PET was described in 2016—found in sediment near a plastic recycling facility, naturally.

While microbes like this could solve the plastic waste issue, they don't make plastics any more sustainable since the carbon backbone of PET ends up being broken down completely. That means we have to constantly supply new material to replace PET containers as they're broken down—material that currently comes from petrochemicals. The French team was interested in creating a

circular PET process, in which existing material gets broken down in a way that allows it to be immediately reused to make new PET products.

PET is a long collection of carbon rings linked by oxygen and carbon atoms. To break it down in a way that allows recycling, these carbon-oxygen links haven't been broken, releasing a large collection of rings that can then be re-linked. The microbes that currently digest PET break down that ring as well, making them unsuitable for recycling.

But a number of enzymes that can break the links in PET have already been identified. These all function to break down the waxy coating on the surfaces of leaves, called "cutin" (making these enzymes cutinases). These provided the starting materials for the new work. To begin with, the researchers took a panel of cutinases and tested their activities in breaking down PET. The one with the highest activity turned out to have a name that indicated where it was originally found: in a compost pile (it's called "leaf-branch compost cutinase").

I’m melting

To understand the researchers' next steps, we have to understand a bit about PET itself. While all versions of PET have the same chemical formula, the material can solidify into two forms: a tightly packed crystalline form and a more loose, disordered form. Most materials made of PET have different amounts of these two forms, as their ratios can allow manufacturers to tune the material's properties. The tight packing of the crystalline form, however, makes it difficult to digest for even the most efficient enzyme. Fortunately, there's a partial solution: heating any form of PET causes some of the crystalline PET to melt into a disordered form, allowing more of it to be digested.

That, unfortunately, creates a problem, as the enzymes themselves often melt and are inactivated at the temperatures involved (65°C, or 150°F). In addition, these enzymes evolved to break down a different polymer and wouldn't be expected to work as well on PET, which is chemically distinct from anything on plants' leaves. These were the two big hurdles faced by the researchers.

To get the enzyme to work better on PET, the researchers looked up the cutinase structure and ran chemical simulations to figure out where PET would interact with the enzyme. They found it fit into a groove on the enzyme's surface that included the location where the PET would be cut. To improve PET's fit into this groove, the researchers created a large panel of mutant versions of the enzyme that, in different combinations, changed every single amino acid on the inside of the groove. While most of these nearly eliminated the enzyme's activity, a few actually improved it and were used for further studies.

The second problem was the issue of the enzyme's ability to tolerate high temperatures. Here, studies with related enzymes provided a hint: many were stabilized by interacting with a metal ion that holds two parts of the enzyme together. Starting with the original version of the enzyme, the researchers engineered in two amino acids that could form a chemical bond between those two parts (for those who know biochemistry, that's a disulfide bridge). This version was more stable at high temperatures than the original one.

By combining all these changes, the researchers created two versions that they then tested on PET obtained by shredding drink bottles.

Cheap and effective

Given this source of PET, the original enzyme could digest about half in 20 hours. The researchers' best modified version only needed 15 hours to hit 85 percent digestion. Optimizing the conditions, they were able to hit 90 percent breakdown of PET in under 10 hours. While there was still some crystalline PET left over, they found that they could take 1,000kg of PET waste and produce

863kg of raw materials from it. Put in different terms, their redesigned enzyme is more efficient at digesting PET than our digestive enzymes are at breaking down starches.

They then used this raw material to make new PET products using standard industrial reactions. The new product's ability to withstand pressure was only 5 percent off from the value measured for PET made from standard chemical sources. Appearance wise, it was within 10 percent of the PET produced the regular way.

How much would using recycled PET cost compared to starting with petrochemical feedstocks? The authors estimate that, if the protein can be made for about $25 a kilogram, then the cost of the process will end up being about 4 percent of what you can get with for the PET made from it. While that might not be as cheap as petrochemicals—especially now, after oil prices have collapsed—it's going to be relatively immune to future price shocks and is far more sustainable.

Nature, 2020. DOI: 10.1038/s41586-020-2149-4 (About DOIs).

https://bit.ly/2XviSw3

The mysterious connection between the coronavirus and the heart

Doctors say some patients with COVID-19 can have heart damage.

By Yasemin Saplakoglu - Staff Writer

The novel coronavirus mainly attacks the lungs. But doctors have been increasingly reporting cases of another battlefield raging within the body: the heart.

More than 1 in 5 patients develop heart damage as a result of COVID-19 in Wuhan, China, one small study published March 27 in the journal JAMA Cardiology suggested. While some of these patients have a history of heart conditions, others do not. So what's going on?

Cardiologists say several scenarios could be unfolding: The heart may struggle to pump blood in the absence of enough oxygen; the virus may directly invade heart cells; or the body, in its attempt to eradicate the virus, may mobilize a storm of immune cells that attack the heart.

"We know that this is not the only virus that affects the heart," said Dr. Mohammad Madjid, an assistant professor at McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth). The risk of developing heart attacks, for example, is thought to increase about sixfold when a person is infected with the flu virus, according to a study published in 2018 in the New England Journal of Medicine.

What's more, during most influenza epidemics, more patients die from heart complications than from pneumonia, according to a review published March 27 in the journal JAMA Cardiology. Viral infections can disrupt blood flow to the heart, cause irregular heartbeats and heart failure, according to the review.

So while it doesn't "come as a surprise," that novel coronavirus called SARS-CoV-2 can lead to heart damage, it may be occurring more frequently in these patients than it does in people infected with other viruses, Madjid, the lead author of the review, told Live Science.

The double-edged sword

The virus might be directly attacking the heart.

"We're seeing cases of people who don't have an underlying heart disease," who are getting heart damage, said Dr. Erin Michos, the associate director of preventive cardiology at Johns Hopkins School of Medicine. Heart damage isn't typical in mild cases of COVID-19, and tends to occur more often in patients who have severe symptoms and are hospitalized, she said.

Though the virus predominantly affects the lungs, it is circulating in the bloodstream; that means the virus could directly invade and attack other organs, including the heart, Michos told Live Science.

Both heart cells and lung cells are covered with surface proteins known as angiotensin-converting enzyme 2 (ACE2) — these molecules serve as "doorways" for the virus to enter cells. But this enzyme is a "double-edged sword," she said. On one hand, the ACE2 molecule acts as a gateway for the virus to enter the cell and replicate, but on the other hand, it normally serves a "protective" function, Michos said.

When tissues in the body are damaged — either by an invading virus such as SARS-CoV-2 or by other means, the body's natural healing response involves releasing inflammatory molecules, such as small proteins called cytokines, into the bloodstream. But paradoxically, too much inflammation can actually make things worse. The ACE2 enzyme acts as an anti-inflammatory, keeping immune cells from inflicting more damage on the body's own cells.

But when the virus latches onto ACE2 proteins, these proteins get knocked out of commission, possibly reducing the anti-inflammatory protection that they give. So the virus may be acting as a double-whammy by damaging cells directly and preventing the body from protecting tissues from inflammatory damage.

"If the heart muscle is inflamed and damaged by the virus, the heart can't function," she said.

The novel coronavirus might also indirectly damage the heart. In this scenario, the patient's immune system winds up "going haywire," Michos said. This scenario has played out in some really sick patients who have highly elevated inflammatory markers — or proteins that signal high levels of inflammation in the body.

This is called a "cytokine storm," Michos said. Cytokine storms damage organs throughout the body, including the heart and liver, she added. It's not clear why some people have such an elevated response compared with others, but some people could be genetically prone to it, she added.

And then you have patients who have underlying heart disease who are at higher risk of developing severe symptoms of COVID-19 — and higher risk of mortality. "You can imagine, if their heart already has difficulty working … they don't have the capacity to meet this challenge" of not having enough oxygen because their lungs aren't working as well.

So COVID-19 can "exacerbate" underlying heart disease, Michos said. A new study, published April 3 in the journal Circulation, described four cases of heart damage among COVID-19 patients in New York, some with underlying conditions. (Michos is on the editorial board for the journal Circulation.)

Treatments and complications

Cardiologists identify heart damage using a blood test for a protein called troponin. When heart cells are injured, they leak troponin into the bloodstream. But "it's sometimes not that easy," to figure out what kind of heart damage a patient is having, Michos said.

"We are really seeing different cardiac involvement," Michos said. So it matters "what's causing the heart damage because you would treat it differently."

For example, if the virus is directly invading the heart, the patient may need antiviral medications. If instead the immune system is causing heart damage, the patient might need immunosuppressants. Right now, no direct treatments target COVID-19, and most of the treatment being used currently involves supportive care such as providing more oxygen.

What's more, people who have high blood pressure or other underlying heart conditions commonly take ACE inhibitors or angiotensin receptor blockers (ARBs) — medications that widen blood vessels, therefore increasing the amount of blood the heart pumps and lowering blood pressure.

Cardiologists are hotly debating whether people should stop or start taking those medications if they're at high risk for COVID-19. (One

paper suggested the drugs could be harmful, while some clinical trials are assessing the use of ARBs to reduce the severity of COVID-19, Live Science previously reported.)

It's really hard to tease out whether having more ACE2 is helpful or harmful, as these proteins are how the virus enters the cells, but also known to protect the cells against injury, Michos said.

The current consensus is that if patients are already taking these medications, they should stay on them, she said. "Patients taking ACE-[inhibitors] and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician," according to a statement from the American Heart Association, the Heart Failure Society of America and the American College of Cardiology.

Experts from Australia and New Zealand similarly said they strongly recommend patients with hypertension, heart failure and cardiovascular disease who are already on these medications keep using them, according to a study preprint published on April 3 in The Medical Journal of Australia.

Complicating matters, certain drugs that are currently under investigation for treating COVID-19, including hydroxychloroquine - the drug that President Trump has said is a game-changer - could cause heart damage, those experts said. Now, the goal is to figure out if there's a genetic or biochemical reason some people are more prone to heart damage from COVID-19 - and to figure out what drugs work best "to protect the heart from injury," Michos said.

https://wb.md/3eewEcI

Toilets May Pose Risk for Spreading COVID-19

Introducing one other potential means of its spread: the toilet.

David A. Johnson, MD

Hello. I'm Dr David Johnson, professor of medicine and chief of gastroenterology at Eastern Virginia Medical School in Norfolk, Virginia.

As the COVID-19 pandemic continues to ravage the United States and the world at large, the reasons behind its rapid epidemiologic spread remain astoundingly unknown. We don't really have a good answer for why most patients develop this disease. Recent data from the Centers for Disease Control and Prevention indicate that approximately 25% of infected patients may not have clinical signs or symptoms, meaning gastrointestinal (GI) or the classic respiratory illness, but may still be viral shedders. A percentage of patients with an asymptomatic prelude may also have viral shedding for about 2 to 3 days before they then develop the more classic respiratory illness.

In light of the puzzling nature of this epidemiologic spread, we've adapted social distancing. However, I want to talk about one other potential means of its spread: the toilet.

As we know, GI diseases can be transmitted via the fecal-oral route. Now researchers looking at hospitals in Wuhan, China, that treated COVID-19-positive patients have provided valuable new data on its transmission. They found that although the intensive care units were good at containing the spread of the virus outside of the patients' rooms, there was a high concentration of the virus in the air samples taken from the patients' toilets.

What are the implications of that finding? Droplets of SARS-CoV-2, which causes the disease COVID-19, can be spread and live in the air for up to 3 hours, and be disseminated to hard surface areas where they can live up to 3 to 4 days. That is quite concerning when you consider that flushing a toilet can create an aerosolized plume of these viral particles, which can then spread elsewhere within proximity. We know that toothbrushes left in proximity to the toilet gain viral spread quite rapidly, mirroring levels observed in the toilet itself. That same thing can occur for cell phones, which many people take with them into the bathroom. However, this mode of transmission has not been well studied as it relates to COVID-19.

We do have available evidence with another coronavirus, the severe acute respiratory syndrome (SARS). Researchers looked at the Amoy Gardens apartment complex in Hong Kong, which experienced a large community outbreak of SARS during the 2003 epidemic. Using airflow dynamics studies, they were able to retrospectively track the spread of the virus from one individual patient—the index case—to other residents of the complex. They reported that the patient's toilet exhaust fan, which created a negative pressure effect, vented into the apartments above and also to the outside. They linked this to 187 cases in the complex with available data. This analysis suggests that the SARS virus was able to be transmitted by microdroplets through inhalation, touch, and potentially fecal-oral routes.

We can and should practice social distancing, taking a step back so we're 6 feet away from each other. But what do we do to address concerns that the toilet microbiome may put us at risk for COVID-19?

Certainly, hospitals caring for these patients need to pay close attention to toilet cleansing and determine whether there are venting systems that expel air from the toilet via a negative pressure effect. It also raises questions about the use of toilets in the public domain. Six-feet social distancing means I can see you, you can see me, and we can stay apart. But if I use a toilet, there's no way of knowing whether it was used prior by a symptomatic or asymptomatic viral carrier or shedder.

The aerosolization effect that can occur in toilets, leading to microdroplets that can be inhaled or persist on surface areas, raises some real concerns regarding epidemiologic spread. It may also be helpful in understanding why this rapid spread can occur when not linked to known contact with those positive for COVID-19.

Turning our attention to the toilets is something we need to do. It's very prudent for those caring for patients in the hospital. And for those who are out of the hospital and trying to stay healthy, consider avoiding public-domain toilets.

We don't have the answers yet, but there are some evidence-based steps that I encourage you to consider.

I'm Dr David Johnson. Thanks again for listening.

This transcript has been edited for clarity.

David A. Johnson, MD, a regular contributor to Medscape, is professor of medicine and chief of gastroenterology at Eastern Virginia Medical School in Norfolk, Virginia, and a past president of the American College of Gastroenterology. His primary focus is the clinical practice of gastroenterology. He has published extensively in the internal medicine/gastroenterology literature, with principal research interests in esophageal and colon disease, and more recently in sleep and microbiome effects on gastrointestinal health and disease.

https://bit.ly/2Vjk0QZ

Stone Age String Strengthens Case for Neandertal Smarts

Our extinct cousins had fiber technology. Stop calling them dumb already

By Kate Wong

Fibers twisted together to form string might not sound like bleeding-edge technology. But with string, or cordage, one can make bags, nets, rope and clothing. We use it to lace our shoes, floss our teeth, suspend bridges, transmit electrical power—the list goes on and on. Naturally, archaeologists have been eager to trace the origins of this pivotal innovation. But doing so is a difficult business because ancient string was made from perishable materials that have mostly been lost to time.

Now archaeologists who have been excavating a rock shelter in France have recovered a fragment of string that could push back the known record of this technology by tens of thousands of years. What is more, the artifact appears to be the handiwork of Neandertals, adding to mounting evidence that our extinct cousins were cleverer than they have been given credit for.

Until recently, the oldest direct evidence of string technology came from a site called Ohalo II in Israel and the famed Lascaux Cave in France. The bits of preserved string found at these sites date to 19,000 and 17,000 years ago, respectively, and were made by early members of our own species. But there were hints that fiber technology might have deeper roots in *Homo sapiens* culture. Impressions of woven fabric have been found on fired clay from sites in Moravia dating back as far as 28,000 years ago. And ivory artifacts from sites in Germany that may have been used for spinning plant fibers are up to 40,000 years old.

In 2013 archaeologist Bruce Hardy of Kenyon College and his colleagues reported that they had found plant fibers that looked as though they had been twisted to form string in excavations at the Abri du Maras rock shelter in southeastern France, which once harbored Neandertals. But with only individual fibers to go on, as opposed to actual string showing them twisted together, the case was far from airtight.

Photograph of the cord fragment taken by digital microscopy (the fragment is approximately 6.2 mm long and 0.5 mm wide). **Credit © C2RMF**

In the new study, published today in *Scientific Reports*, Hardy and his co-authors describe a 6.2-millimeter-long fragment of string that their team found at the same rock shelter —in a layer dated to between 52,000 and 41,000 years ago, when Neandertals occupied the site. Analyses of the fragment show that it is made of fibers that were probably harvested from the inner bark of a conifer tree. The fibers were twisted clockwise to form yarn, and then three lengths of the yarn were twisted in the opposite direction to make string.

Exactly what the string was used for is uncertain. But it was found adhering to a sharp-edged stone flake, leading the authors to suggest that it might have been applied to attach the flake to a handle of some sort. Alternatively, they suppose, the string might have had nothing to do with the stone flake and instead have been part of a net or bag.

Specific usage aside, the manufacture of the string attests to cognitive sophistication in Neandertals, Hardy and his colleagues contend. Harvesting the fibers would have required intimate knowledge of the growth and seasonality of the trees. And producing string after one has the raw material is itself mentally demanding, requiring the maker to keep track of multiple, sequential operations at the same time. Considering these findings, along with discoveries of different advanced technologies and even art at other Neandertal sites, “it is difficult to see how we can regard [Neandertals] as anything other than the cognitive equals of modern humans,” Hardy and his co-authors write.

Outside researchers are intrigued by the new work. “I’m not 100 percent convinced” that the find is, in fact, a piece of string, says archaeologist Marie Soressi of Leiden University in the Netherlands, noting that she finds the photographs that accompany the team’s paper “difficult to understand.” But the new work constitutes “by far the best evidence” that the Neandertals at Abri du Maras made string, she says.

In Soressi’s view, the most exciting aspect of the study is not what it demonstrates about Neandertals’ sophistication—we already know their technology was very complex, she observes—but instead what it reveals about preservation. The previous record holder for the oldest known string remains came from a site that had been exposed to groundwater for a long time. Such waterlogged sites tend to preserve perishable materials, such as plant fibers, quite well. The new work by Hardy and his colleagues “supports the idea that microscopic residues of strings are preserved in nonwaterlogged rock-shelter deposits of Neandertal age,” Soressi observes. Perishable objects account for much of the material

culture of humans. Yet most of what archaeologists know about prehistoric humans, including the Neandertals, comes from the durable bones and stone tools they left behind. The ability to recover traces of the perishable materials our ancient predecessors used stands to reveal their lives in a whole new light.

https://bit.ly/2UZovBq

Now metal surfaces can be instant bacteria killers

Bacterial pathogens can live on surfaces for days. What if frequently-touched surfaces such as doorknobs could instantly kill them off?

West Lafayette, Ind. -- Bacterial pathogens can live on surfaces for days. What if frequently touched surfaces such as doorknobs could instantly kill them off?

Purdue University engineers have created a laser treatment method that could potentially turn any metal surface into a rapid bacteria killer - just by giving the metal's surface a different texture.

In a study published in the journal *Advanced Materials Interfaces*, the researchers demonstrated that this technique allows the surface of copper to immediately kill off superbugs such as MRSA.

"Copper has been used as an antimicrobial material for centuries. But it typically takes hours for native copper surfaces to kill off bacteria," said Rahim Rahimi, a Purdue assistant professor of materials engineering. "We developed a one-step laser-texturing technique that effectively enhances the bacteria-killing properties of copper's surface."

The technique is not yet tailored to killing viruses such as the one responsible for the COVID-19 pandemic, which are much smaller than bacteria.

Since publishing this work, however, Rahimi's team has begun testing this technology on the surfaces of other metals and polymers that are used to reduce risks of bacterial growth and biofilm formation on devices such as orthopedic implants or wearable patches for chronic wounds.

Giving implants an antimicrobial surface would prevent the spread of infection and antibiotic resistance, Rahimi said, because there wouldn't be a need for antibiotics to kill off bacteria from an implant's surface. The technique might apply to metallic alloys that also are known to have antimicrobial properties.

Metals such as copper normally have a really smooth surface, which makes it difficult for the metal to kill bacteria by contact.

The technique developed by Rahimi's team uses a laser to create nanoscale patterns on the metal's surface. The patterns produce a rugged texture that increases surface area, allowing more opportunity for bacteria to hit the surface and rupture on the spot. A YouTube video is available at https://youtu.be/3vFFdNXsoN0.

Researchers in the past have used various nanomaterial coatings to enhance the antimicrobial properties of metal surfaces, but these coatings are prone to leach off and can be toxic to the environment.

"We've created a robust process that selectively generates micron and nanoscale patterns directly onto the targeted surface without altering the bulk of the copper material," said Rahimi, whose lab develops innovative materials and biomedical devices to address health care challenges.

The laser-texturing has a dual effect: The technique not only improves direct contact, but also makes a surface more hydrophilic. For orthopedic implants, such a surface allows bone cells to more strongly attach, improving how well the implant integrates with bone. Rahimi's team observed this effect with fibroblast cells.

Due to the simplicity and scalability of the technique, the researchers believe that it could easily be translated into existing medical device manufacturing processes.

The work was funded in part by Purdue's School of Materials Engineering and the Wabash Heartland Innovation Network. This research was performed at the Birck Nanotechnology Center in Purdue's Discovery Park.

https://bit.ly/3aY2GHI

Experimental Drug Has Broad Spectrum Antiviral Activity against Multiple Coronaviruses

Orally bioavailable prodrug has broad spectrum antiviral activity against zoonotic coronaviruses

An orally bioavailable prodrug called EIDD-2801 (β-D-N^4-hydroxycytidine-5'-isopropyl ester) has broad spectrum antiviral activity against SARS-CoV-2, MERS-CoV, SARS-CoV, and related zoonotic coronaviruses in primary human airway epithelial cells, according to a new study published in the journal *Science Translational Medicine*. The study also found that, when used as a prophylactic, EIDD-2801 can prevent severe lung injury in infected mice.

EIDD-2801 is an orally available form of the antiviral compound EIDD-1931 (β-D-N^4-hydroxycytidine). It can be taken as a pill and can be properly absorbed to travel to the lungs.

When given as a treatment 12 or 24 hours after infection has begun, EIDD-2801 can reduce the degree of lung damage and weight loss in mice. This window of opportunity is expected to be longer in humans, because the period between coronavirus disease onset and death is generally extended in humans compared to mice.

"This new drug not only has high potential for treating COVID-19 patients, but also appears effective for the treatment of other serious coronavirus infections," said study senior author Professor Ralph Baric, a virologist at the University of North Carolina at Chapel Hill.

Compared with other potential COVID-19 treatments that must be administered intravenously, EIDD-2801 can be delivered by mouth as a pill.

In addition to ease of treatment, this offers a potential advantage for treating less-ill patients or for prophylaxis — for example, in a nursing home where many people have been exposed but are not yet sick.

"We are amazed at the ability of EIDD-1931 and EIDD-2801 to inhibit all tested coronaviruses and the potential for oral treatment of COVID-19," said study co-author Dr. Andrea Pruijssers, an antiviral scientist at the Vanderbilt University Medical Center.

In 2019, the researchers reported that EIDD-1931 blocked the replication of a broad spectrum of coronaviruses. They also performed the preclinical development of remdesivir, another antiviral drug currently in clinical trials of patients with COVID-19.

In the new study, they demonstrated that viruses that show resistance to remdesivir experience higher inhibition from EIDD-1931.

"Viruses that carry remdesivir resistance mutations are actually more susceptible to EIDD-1931 and vice versa, suggesting that the two drugs could be combined for greater efficacy and to prevent the emergence of resistance," said study co-author Dr. George Painter, from Emory University and the Drug Innovation Ventures at Emory (DRIVE).

Clinical studies of EIDD-2801 in humans are expected to begin later this spring. If they are successful, the drug could not only be used to limit the spread of SARS-CoV-2, but also could control future outbreaks of other emerging coronaviruses.

"With three novel human coronaviruses emerging in the past 20 years, it is likely that we will continue to see more," said study first author Dr. Timothy Sheahan, from the University of North Carolina at Chapel Hill. "EIDD-2801 holds promise to not only treat COVID-19 patients today, but to treat new coronaviruses that may emerge in the future."

Timothy P. Sheahan et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Science Translational Medicine, published online April 6, 2020; doi: 10.1126/scitranslmed.abb5883

https://bit.ly/2xmpnqv

Scientists use the Tokyo Skytree to test Einstein's theory of general relativity

To make new ultraprecise measurements of the time dilation effect predicted by Einstein's theory of general relativity.

In another verification of the validity of Einstein's theory of general relativity, published in *Nature Photonics*, scientists from the RIKEN Center for Advanced Photonics and Cluster for Pioneering Research, with colleagues, have used two finely tuned optical lattice clocks, one at the base and one on the 450-meter observatory floor of Tokyo Skytree, to make new ultraprecise measurements of the time dilation effect predicted by Einstein's theory of general relativity.

Einstein theorized that the warping of time-space by gravity was caused by massive objects. In line with this, time runs more slowly in a deep gravitational field than in a shallower one. This means that times runs slightly more slowly at the base of the Skytree tower than at the top.

The difficulty with actually measuring the change in how quickly clocks run in different gravity field is that the difference is very small. Performing a stringent test of the theory of relativity requires either a very precise clock or a large difference in height. One of the best measurements so far has involved large and complex clocks such as those developed by the RIKEN group, which can measure a difference of around a centimeter in height. Outside the laboratory, the best tests have been taken by satellites, with altitudes that are thousands of kilometers different. Such space experiments have constrained any violation of general relativity to about 30 parts per million, a tremendously precise measurement that essentially shows Einstein to be correct.

The scientists from RIKEN and their collaborators took up the task of developing transportable optical lattice clocks that could make comparably precise tests of relativity, but on the ground. The ultimate purpose, however, is not to prove or disprove Einstein. According to Hidetoshi Katori of RIKEN and the University of Tokyo, who led the group, "Another major application of ultraprecise clocks is to sense and utilize the curvature of spacetime by gravity. Using it, clocks can distinguish small differences in altitude, allowing us to measure ground swelling in places such as active volcanoes or crustal deformation, or to define the reference for height. We wanted to demonstrate that we could conduct these accurate measurements anywhere outside the laboratory, with transportable devices. This is the first step toward making ultraprecise clocks into real-world devices."

The key to the engineering feat was to miniaturize the laboratory-sized clocks into transportable devices and to make them insensitive to environmental noises such as temperature changes, vibrations, and electromagnetic fields. Each of the clocks was enclosed in a magnetic-shield box, around 60 centimeters on each side. The various laser devices and electronic controllers required for trapping and interrogating the atoms confined in a lattice were housed in two rack-mountable boxes. The two clocks were connected by an optical fiber to measure the beat note. In parallel, the scientists conducted laser ranging and gravity measurement to independently evaluate the difference of gravitational field for the two clocks.

The figure they attained for violations of general relativity was another validation of Einstein's theory, like others before. What is key about the experiment, according to Katori, is that they demonstrated this to a precision comparable to the best space-based measurements, but using transportable devices operating on the ground. In the future, the group plans to compare clocks hundreds of kilometers apart to monitor the long-term uplift and depression

of the ground, one of the potential applications of ultraprecise clocks.

More information: *Masao Takamoto et al, Test of general relativity by a pair of transportable optical lattice clocks, Nature Photonics (2020).* [DOI: 10.1038/s41566-020-0619-8](DOI: 10.1038/s41566-020-0619-8)

https://bit.ly/34BveVj

With ventilators running out, doctors say the machines are overused for Covid-19

If the iconoclasts are right, putting coronavirus patients on ventilators could be of little benefit to many and even harmful to some.

By Sharon Begley @sxbegle

Even as hospitals and governors raise the alarm about a shortage of ventilators, some critical care physicians are questioning the widespread use of the breathing machines for Covid-19 patients, saying that large numbers of patients could instead be treated with less intensive respiratory support.

If the iconoclasts are right, putting coronavirus patients on ventilators could be of little benefit to many and even harmful to some.

What's driving this reassessment is a baffling observation about Covid-19: Many patients have blood oxygen levels so low they should be dead. But they're not gasping for air, their hearts aren't racing, and their brains show no signs of blinking off from lack of oxygen.

That is making critical care physicians suspect that blood levels of oxygen, which for decades have driven decisions about breathing support for patients with pneumonia and acute respiratory distress, might be misleading them about how to care for those with Covid-19. In particular, more and more are concerned about the use of intubation and mechanical ventilators. They argue that more patients could receive simpler, noninvasive respiratory support, such as the breathing masks used in sleep apnea, at least to start with and maybe for the duration of the illness.

"I think we may indeed be able to support a subset of these patients" with less invasive breathing support, said Sohan Japa, an internal medicine physician at Boston's Brigham and Women's Hospital. "I think we have to be more nuanced about who we intubate."

That would help relieve a shortage of ventilators so critical that states are scrambling to procure them and some hospitals are taking the unprecedented (and largely untested) step of using a single ventilator for more than one patient. And it would mean fewer Covid-19 patients, particularly elderly ones, would be at risk of suffering the long-term cognitive and physical effects of sedation and intubation while being on a ventilator.

None of this means that ventilators are not necessary in the Covid-19 crisis, or that hospitals are wrong to fear running out. But as doctors learn more about treating Covid-19, and question old dogma about blood oxygen and the need for ventilators, they might be able to substitute simpler and more widely available devices.

An oxygen saturation rate below 93% (normal is 95% to 100%) has long been taken as a sign of potential hypoxia and impending organ damage. Before Covid-19, when the oxygen level dropped below this threshold, physicians supported their patients' breathing with noninvasive devices such as continuous positive airway pressure (CPAP, the sleep apnea device) and bilevel positive airway pressure ventilators (BiPAP). Both work via a tube into a face mask.

In severe pneumonia or acute respiratory distress unrelated to Covid-19, or if the noninvasive devices don't boost oxygen levels enough, critical care doctors turn to mechanical ventilators that push oxygen into the lungs at a preset rate and force: A physician threads a 10-inch plastic tube down a patient's throat and into the lungs, attaches it to the ventilator, and administers heavy and long-

lasting sedation so the patient can't fight the sensation of being unable to breathe on his own.

In this video, we look at how ventilators work, and how they are used to treat patients with Covid-19.

But because in some patients with Covid-19, blood-oxygen levels fall to hardly-ever-seen levels, into the 70s and even lower, physicians are intubating them sooner. "Data from China suggested that early intubation would keep Covid-19 patients' heart, liver, and kidneys from failing due to hypoxia," said a veteran emergency medicine physician. "This has been the whole thing driving decisions about breathing support: Knock them out and put them on a ventilator."

To be sure, many physicians are starting simple. "Most hospitals, including ours, are using simpler, noninvasive strategies first," including the apnea devices and even nasal cannulas, said Greg Martin, a critical care physician at Emory University School of Medicine and president-elect of the Society of Critical Care Medicine. (Nasal cannulas are tubes whose two prongs, held beneath the nostrils by elastic, deliver air to the nose.)

"It doesn't require sedation and the patient [remains conscious and] can participate in his care. But if the oxygen saturation gets too low you can achieve more oxygen delivery with a mechanical ventilator."

The question is whether ICU physicians are moving patients to mechanical ventilators too quickly. "Almost the entire decision tree is driven by oxygen saturation levels," said the emergency medicine physician, who asked not to be named so as not to appear to be criticizing colleagues.

That's not unreasonable. In patients who are on ventilators due to non-Covid-19 pneumonia or acute respiratory distress, a blood oxygen level in the 80s can mean impending death, with no room to give noninvasive breathing support more time to work. Physicians are using their experience with ventilators in those situations to guide their care for Covid-19 patients. The problem, critical care physician Cameron Kyle-Sidell told Medscape this week, is that because U.S. physicians had never seen Covid-19 before February, they are basing clinical decisions on conditions that may not be good guides.

"It's hard to switch tracks when the train is going a million miles an hour," said Kyle-Sidell, who works at a New York City hospital. "This may be an entirely new disease," making ventilator protocols developed for other conditions less than ideal.

As doctors learn more about the disease, however, both frontline experience and a few small studies are leading him and others to question how, and how often, mechanical ventilators are used for Covid-19.

The first batch of evidence relates to how often the machines fail to help. "Contrary to the impression that if extremely ill patients with Covid-19 are treated with ventilators they will live and if they are not, they will die, the reality is far different," said geriatric and palliative care physician Muriel Gillick of Harvard Medical School.

Researchers in Wuhan, for instance, reported that, of 37 critically ill Covid-19 patients who were put on mechanical ventilators, 30 died within a month.

In a U.S. study of patients in Seattle, only one of the seven patients older than 70 who were put on a ventilator survived; just 36% of those younger than 70 did. And in a study published by JAMA on Monday, physicians in Italy reported that nearly 90% of 1,300 critically ill patients with Covid-19 were intubated and put on a ventilator; only 11% received noninvasive ventilation. One-quarter died in the ICU; 58% were still in the ICU, and 16% had been discharged.

Older patients who do survive risk permanent cognitive and respiratory damage from being on heavy sedation for many days if not weeks and from the intubation, Gillick said.

To be sure, the mere need for ventilators in Covid-19 patients suggests many in the studies were so critically ill their chances of survival were poor no matter what care they received.

But one of the most severe consequences of Covid-19 suggests another reason the ventilators aren't more beneficial. In acute respiratory distress syndrome, which results from immune cells ravaging the lungs and kills many Covid-19 patients, the air sacs of the lungs become filled with a gummy yellow fluid. "That limits oxygen transfer from the lungs to the blood even when a machine pumps in oxygen," Gillick said.

As patients go downhill, protocols developed for other respiratory conditions call for increasing the force with which a ventilator delivers oxygen, the amount of oxygen, or the rate of delivery, she explained. But if oxygen can't cross into the blood from the lungs in the first place, those measures, especially greater force, may prove harmful. High levels of oxygen impair the lung's air sacs, while high pressure to force in more oxygen damages the lungs.

In a letter last week in the American Journal of Respiratory and Critical Care Medicine, researchers in Germany and Italy said their Covid-19 patients were unlike any others with acute respiratory distress. Their lungs are relatively elastic ("compliant"), a sign of health "in sharp contrast to expectations for severe ARDS." Their low blood oxygen might result from things that ventilators don't fix. Such patients need "the lowest possible [air pressure] and gentle ventilation," they said, arguing against increasing the pressure even if blood oxygen levels remain low. "We need to be patient."

"We need to ask, are we using ventilators in a way that makes sense for other diseases but not for this one?" Gillick said. "Instead of asking how do we ration a scarce resource, we should be asking how do we best treat this disease?"

Researchers and clinicians on the front lines are trying. In a small study last week in Annals of Intensive Care, physicians who treated Covid-19 patients at two hospitals in China found that the majority of patients needed no more than a nasal cannula. Among the 41% who needed more intense breathing support, none was put on a ventilator right away. Instead, they were given noninvasive devices such as BiPAP; their blood oxygen levels "significantly improved" after an hour or two. (Eventually two of seven needed to be intubated.) The researchers concluded that the more comfortable nasal cannula is just as good as BiPAP and that a middle ground is as safe for Covid-19 patients as quicker use of a ventilator.

"Anecdotal experience from Italy [also suggests] that they were able to support a number of folks using these [non-invasive] methods," Japa said.

To be "more nuanced about who we intubate," as she suggests, starts with questioning the significance of oxygen saturation levels. Those levels often "look beyond awful," said Scott Weingart, a critical care physician in New York and host of the "EMCrit" podcast. But many can speak in full sentences, don't report shortness of breath, and have no signs of the heart or other organ abnormalities that hypoxia can cause.

"The patients in front of me are unlike any I've ever seen," Kyle-Sidell told Medscape about those he cared for in a hard-hit Brooklyn hospital. "They looked a lot more like they had altitude sickness than pneumonia."

Because U.S. data on treating Covid-19 patients are nearly nonexistent, health care workers are flying blind when it comes to caring for such confounding patients. But anecdotally, Weingart said, "we've had a number of people who improved and got off CPAP or high flow [nasal cannulas] who would have been tubed

100 out of 100 times in the past." What he calls "this knee-jerk response" of putting people on ventilators if their blood oxygen levels remain low with noninvasive devices "is really bad. … I think these patients do much, much worse on the ventilator."

That could be because the ones who get intubated are the sickest, he said, "but that has not been my experience: It makes things worse as a direct result of the intubation." High levels of force and oxygen levels, both in quest of restoring oxygen saturation levels to normal, can injure the lungs. "I would do everything in my power to avoid intubating patients," Weingart said.

One reason Covid-19 patients can have near-hypoxic levels of blood oxygen without the usual gasping and other signs of impairment is that their blood levels of carbon dioxide, which diffuses into air in the lungs and is then exhaled, remain low. That suggests the lungs are still accomplishing the critical job of removing carbon dioxide even if they're struggling to absorb oxygen. That, too, is reminiscent of altitude sickness more than pneumonia. The noninvasive devices "can provide some amount of support for breathing and oxygenation, without needing a ventilator," said ICU physician and pulmonologist Lakshman Swamy of Boston Medical Center.

One problem, though, is that CPAP and other positive-pressure machines pose a risk to health care workers, he said. The devices push aerosolized virus particles into the air, where anyone entering the patient's room can inhale them. The intubation required for mechanical ventilators can also aerosolize virus particles, but the machine is a contained system after that.

"If we had unlimited supply of protective equipment and if we had a better understanding of what this virus actually does in terms of aerosolizing, and if we had more negative pressure rooms, then we would be able to use more" of the noninvasive breathing support devices, Swamy said.

https://bit.ly/3cay8CJ

Would-be coronavirus drugs are cheap to make

Most drugs in clinical trials against COVID-19, such as chloroquine phosphate, can be made cheaply.

By Robert F. Service

With a vaccine for the novel coronavirus still likely a year or more away, the first weapon against the virus could be one of the drugs now in clinical trials with COVID-19 patients. A new analysis out today shows that many of these drugs, which are currently manufactured or in development to treat other diseases, can be made for $1 a day per patient, or less. If any prove effective against the novel coronavirus, a coordinated international effort will be needed to ensure they are made affordable for people worldwide, the researchers argue.

Scientists worldwide are conducting clinical trials on at least a dozen potential treatments for COVID-19. Some compounds have been on the market for decades, such as chloroquine and hydroxychloroquine used to combat malaria and lupus. That makes it relatively straightforward to estimate the minimum cost of making them, says Andrew Hill, a drug pricing specialist at the University of Liverpool.

For the new analysis, out today in the *Journal of Virus Eradication*. Hill and colleagues reprised a strategy he previously used to estimate the cost of drugs to treat HIV and hepatitis C. They started with an India-mandated database that includes the cost per kilogram of active pharmaceutical ingredients (APIs) shipped in and out of the country, a major hub for generic drug production. To those figures, they added in additional costs for formulating APIs into medicines, packaging, and a 10% markup for the companies manufacturing the drugs. For eight of the nine candidate COVID-19 treatments analyzed the estimated cost was under $1.50 per day per person treated and from $0.30 to $31 for a full course of treatment.

The bottom line is clear, Hill says. “All of these drugs are fundamentally really cheap to make.” (Hill’s team was unable to estimate the cost of one compound, Tocilizumab, a monoclonal antibody used to treat rheumatoid arthritis, because it is currently made only in small quantities.)

Today, however, these drugs aren’t always cheap to buy. They retail for between $0.20 and $510 per course in countries that strictly hold down drug costs, such as India and Pakistan, but between $19 to $18,610 per course in the United States, Hill and his colleagues report.

Jessica Burry, a pharmacist with Doctors Without Borders, worries that high pricing of COVID-19 treatments would amount to rationing, putting them off-limits for poorer patients and countries. “Rationing drugs because of high prices and limited supply will only serve to prolong the pandemic,” says. “What good is a lifesaving drug if you can’t afford it?”

Hill notes that most of the drugs his group evaluated are off patent, and thus could be manufactured cheaply by generic drugmakers. But some of the antivirals in the COVID-19 clinical trials are proprietary. As the debate over drug pricing for coronavirus drugs is already heating up, one flashpoint is remdesivir, a drug from Gilead Sciences that appears to inhibit an RNA-copying polymerase the new coronavirus uses to replicate. Hill’s team estimates that 1 day’s supply of the drug could be manufactured for $0.93.

Manufacturing cost of potential coronavirus drugs

Though most drugs currently in clinical trials to fight COVD-19 can be made cheaply, they can sell for hundreds of times the price.

But patent protection and limited supplies could send its price soaring, some groups fear. On 30 March, Doctors Without Borders and nearly 150 other civil society organizations sent an open letter to Gilead CEO Daniel O’Day asking “that Gilead take immediate actions to ensure rapid availability, affordability, and accessibility of its experimental therapy remdesivir for the treatment of COVID-19.” The authors implored Gilead to forgo patent protection for the drug and allow generic manufacturers to add to the supply. Gilead’s Corporate Affairs and General Counsel Brett Pletcher responded today that Gilead is already ramping up production sharply. The company is also exploring a partnership with UNICEF to distribute the drug globally, Pletcher wrote the groups in a letter made public by the company.

Drug	Estimated cost price (course)	Estimated cost price (day)
Remdesivir (10 days)	$9	$0.93
Favipiravir (14 days)	$20	$1.45
Lopinavir/ritonavir (14 days)	$4	$0.28
Hydroxychloroquine (14 days)	$1	$0.08
Chloroquine (14 days)	$0.30	$0.02
Azithromycin (14 days)	$1.40	$0.10
Sofosbuvir/daclatasvir (14 days)	$5	$0.39
Pirfenidone (28 days)	$31	$1.09

A. Hill et al., Journal of Virus Eradication, 2020

One model for distributing a coronavirus drug quickly and cheaply comes from ongoing parallel efforts to provide HIV and tuberculosis drugs, run by the Global Fund and the U.S. President’s Emergency Plan for AIDs Relief. Each organization pools financial contributions from governments worldwide or U.S. government agencies, respectively, and use the money to negotiate cheap prices for generic drugs that are then distributed to countries in need—an approach that has been hailed for saving tens of millions of lives. David Nash, a physician and pharmaceutical industry expert at Jefferson College of Population Health, says that model could work with coronavirus as well. “I would not reinvent the wheel here.” Nash says international drug pricing experts should begin setting up

such an initiative to mass produce and distribute coronavirus medications, adding that they should move fast. “We ought to start the conversation now in anticipation of the results of the clinical trials.”

https://bit.ly/2wwiGSf

Brown hares and chickens were treated as 'gods,' not food when they arrived in Britain, research shows

Archaeological evidence shows that the first brown hares and chickens to arrive in Britain were buried with care and intact.

There is no signs of butchery on bones examined and the ongoing research suggests the two animals were not imported for people to eat.

Work by experts from the Universities of Exeter, Leicester and Oxford is revealing when brown hares, rabbits and chickens were introduced to Britain, and how they became incorporated into modern Easter traditions.

The team has previously analyzed the earliest rabbit bone to be found in the country, which dates to the first/second century AD. New radiocarbon dates for bones found on sites in Hampshire (Houghton Down, Weston Down, Winnal Down and Winklebury Camp) and Hertfordshire (Blackhorse Road) suggests brown hares and chickens were introduced to Britain even earlier, arriving simultaneously in the Iron Age, between the fifth and the third century BC.

The discovery of buried skeletons fits historical evidence that neither animal was eaten until the Roman period, which began hundreds of years later.

Julius Caesar's De Bello Gallico says: "The Britons consider it contrary to divine law to eat the hare, the chicken, or the goose. They raise these, however, for their own amusement and pleasure."

The third-century AD author, Dio Cassius reported that Queen Boudicca released a live hare in order to divine the outcome of her battle with the Romans, calling upon the goddess Andraste to secure their victory.

During the Roman period, both species were farmed and eaten, and rabbits were also introduced. But in AD 410 the Roman Empire withdrew from Britain causing economic collapse. Rabbits became locally extinct, while populations of chickens and brown hares crashed. Due to their scarcity at this time, chickens and hares regained their special status.

Professor Naomi Sykes, from the University of Exeter, who is leading the research, said: "Easter is an important British festival, yet none of its iconic elements are native to Britain. The idea that chickens and hares initially had religious associations is not surprising as cross-cultural studies have shown that exotic things and animals are often given supernatural status.

"Historical accounts have suggested chickens and hares were too special to be eaten and were instead associated with deities—chickens with an Iron Age god akin to Roman Mercury, and hares with an unknown female hare goddess. The religious association of hares and chickens endured throughout the Roman period.

"However archaeological evidence shows that, as their populations increased, they were increasingly eaten, and hares were even farmed as livestock. Rather than being buried as individuals, hare and chicken remains were then disposed of as food waste."

After the Romans had left Britain, people stopped hunting hares and this may explain why archaeologists have found few remains of the animal until the medieval period. By contrast, chicken populations increased. This is likely because, in the sixth century Saint Benedict forbade the consumption of meat from four-legged animals during fasting periods such as Lent. His rules were widely adopted in the tenth and eleventh centuries, increasing the popularity of chickens and eggs as fast-day foods.

Historical and archaeological evidence show rabbits were reintroduced to Britain as an elite food during the thirteenth century AD. Rabbits were increasingly common in the nineteenth-century landscape, likely contributing to their replacement of the hare as the Easter Bunny when the festival's traditions were reinvigorated during the Victorian period.

These new findings have emerged just as the country has gone into lockdown, so the team has created an Easter craft activity that can be printed out and made at home. The activity is inspired by the results and from artifacts recorded by the Portable Antiquities Scheme.

https://wb.md/2yWElUD

COVID-19 and Diabetes: Patterns Emerge

Those with diabetes are actually not at increased risk for catching the novel coronavirus, but once they become infected, they may do less well

Anne L. Peters, MD

This transcript has been edited for clarity.

Here is another update on what we know about COVID-19 in people with diabetes. The data that we have suggest that people with diabetes are actually not at increased risk for catching the novel coronavirus, but once they become infected, they may do less well, particularly if they're in an ICU setting.

However, we don't know if there are any differences between people with type 1 versus type 2 diabetes, or between people whose diabetes is well controlled versus less well controlled. We do know that younger people as a whole do better than older people. The more comorbidities present, such as cardiovascular disease and chronic kidney disease, the higher the risk for mortality and doing poorly.

Historically, we've believed that people with higher glucose levels are likely to be at greater risk for infection than those with more normal glucose levels. This is because high glucose levels can inhibit white cell function. We obviously want our patients to be as well controlled as possible in order to help them do better.

Some Patterns Emerge

I have now seen patients with diabetes who have been infected with COVID-19 and heard cases of many others. No one in my personal practice with type 1 diabetes has developed COVID-19, but I have seen a number of people with type 2 diabetes who have had it.

What I know for sure is that I can't predict this virus. I have had people with every known risk factor for a poor outcome do incredibly well, and those with fewer risk factors do worse than I expected. I've seen families in whom everybody was infected, and families where only one member became ill.

However, some patterns have emerged. Unscientifically, I divide my patients into three groups of illness severity: mild, moderate, and severe. Mild is when COVID-19 is a slightly annoying head cold and nothing more. Moderate is where people feel miserable; they're feverish, they have muscle pain, they have headaches, their lungs hurt, they cough, and they feel wretched—but they don't need to be in the hospital and they survive. Then there are the severe cases; these patients are hospitalized, and some of them end up in the ICU.

In terms of diabetes management, it's the moderate category where we really have to do our most aggressive outpatient care. We don't want these patients to end up in the hospital. The biggest issue I deal with is dehydration. My patients are febrile and they're often anorexic, not wanting to eat or drink much, so I really have to encourage hydration.

I've also seen patients with glucose levels lower than normal, which is different from what I'm used to seeing in patients with infection. Glucose monitoring is incredibly important in patients with COVID-19.

Changes to Medications

My first step in all patients who are on an SGLT2 inhibitor is to stop the drug at the first sign of symptoms. I've had a lean person with type 2 diabetes on an SGLT2 inhibitor go into diabetic ketoacidosis (DKA) when they developed COVID-19, so this is very important. This patient had already stopped their SGLT2 inhibitor for a day when they became quite ill.

Other practitioners, such as my dear friend, Dr Irl Hirsch, suggest that we stop SGLT2 inhibitor therapy in all people with type 1 diabetes who are using them off-label because it increases the risk for DKA. I haven't done that in my patients except for those who I feel are on too low a dose of insulin or who seem to be at higher risk for DKA than others. For my patients who are able to test for ketones and connect with me, I've kept them on their SGLT2 inhibitor, but I suggest monitoring this on a case-by-case basis.

In my patients with type 1 diabetes, I make sure that they are prepared with glucose-containing fluids at home, and that they're able to give injected insulin. I also make sure that they have ketone test strips at home and some sort of antiemetic so they can keep down fluids.

Preparing a Hospital Kit

There has been an issue in hospitals where patients on insulin drips can't get hourly blood glucose readings because the staff doesn't have enough personal protective equipment to go in and out of patient rooms to do the testing. Patients must be prepared to do self-monitoring of glucose levels in the hospital if they happen to end up hospitalized. I encourage patients with type 1 diabetes and those with type 2 diabetes on insulin to prepare a kit that they could bring with them to the hospital. This kit includes testing supplies (if people are doing self-monitoring of blood glucose) and sensors (if people are on a sensor).

People need to remember such details as bringing charger cables for their iPhones, iPads, and anything else they may need to help self-monitor their glucose levels if hospitalized. This is particularly important now because family members aren't allowed into hospitals to bring the pieces that someone may have forgotten at home.

In people with type 2 diabetes who are on insulin secretagogues and/or insulin, I have needed to lower the dose of medication, and in some cases, to stop it. Again, self-monitoring is important.

As patients recover from their COVID-19 infections, they may still not feel much like eating and have relative anorexia. There have been some cases where I have held the GLP-1 receptor agonist therapy for a week or two after the illness has resolved to make sure my patients return to their fully normal baseline state.

The most important advice I give patients is to reach out to us, their healthcare team, if they need us. None of us want anyone to go to the hospital, but there are patients who develop DKA and can't keep down fluids, and they need to be hospitalized. Patients shouldn't wait, because the DKA may become even more severe by the time they're admitted.

We all need to keep in mind that most people are going to be okay, with or without diabetes—although, tragically, some will die. As a healthcare provider, I am encouraging my patients to use this time to take extra good care of themselves, to learn to optimize their diabetes control when not being distracted by going out to social events, dinner, or work.

I think we are helping our patients establish a new baseline that will hopefully translate into sustained health over time. Please be sure to take care of yourselves, your families, and your patients. Be well.

Anne L. Peters, MD, is a professor of medicine at the University of Southern California (USC) Keck School of Medicine and director of the USC clinical diabetes programs. She has published more than 200 articles, reviews, and abstracts, and three books, on diabetes, and has been an investigator for more than 40 research studies. She has spoken

internationally at over 400 programs and serves on many committees of several professional organizations.

https://wb.md/3ejQqDk

Presymptomatic or Asymptomatic? ID Experts on Shifting Terminology

Experts discussed the shift in thinking between the two terms, and addressed racial disparities surrounding COVID-19

Megan Brooks

Asymptomatic or presymptomatic for COVID-19? Experts with the Infectious Diseases Society of America (IDSA) discussed the shift in thinking between the two terms at a media briefing Friday.

They also addressed racial disparities surrounding COVID-19, and announced new IDSA guidelines for diagnosis and treatment of the illness.

Regarding the shifting thinking on symptoms and transmission of the novel coronavirus, when it comes to presymptomatic or asymptomatic, "pre" is really the right terminology, Carlos del Rio, MD, professor of medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia, said during the briefing, because it's not that people are asymptomatic but that they develop symptoms later and start transmitting the virus 24 to 48 hours before they develop symptoms.

"Clearly, this plays a role in transmission," with some studies suggesting that 6% to 12% of transmissions occur during this presymptomatic stage, he explained.

Jeanne Marrazzo, MD, MPH, director of the Division of Infectious Diseases at University of Alabama at Birmingham, noted that early in the COVID-19 pandemic, the presymptomatic phase "could have been missed because we didn't realize the wide ranging symptoms this disease has." This is turning out to be a "very interesting" virus with "fascinating" symptoms, she told reporters on the call.

The virus seems to have capacity to affect far more than just the respiratory tract. Initially, however, it was viewed "very much like a classic respiratory viral infection. As a result, a lot of people were refused testing because they were not showing the classic signs" of respiratory infection, Marrazzo noted.

It's now clear that the range of symptoms is quite different, she said. Notably, loss of smell seems to be "very characteristic and very specific to this infection. I can't think of another common viral infection that causes loss of smell before you start to see other things," Marrazzo said.

Data also suggest that gastrointestinal symptoms are common with COVID-19. Early data suggest that diarrhea probably occurs in about one third of patients. Some people have reported abdominal pain as the first sign, she said.

"Now that we know about the more wide range of symptoms associated [with COVID-19], we are being much more open to considering people perhaps having this infection. There is a lower index of suspicion and much lower threshold for diagnostic testing," Marrazzo said, adding that there are still many barriers to testing and getting test results.

Stark Racial Disparities Need Greater Understanding

The second major topic of discussion at the briefing was the growing realization of racial disparities in COVID-19. "Racial disparities in our country are not new but racial disparities in this disease are pretty stark," del Rio said.

"We live in a country where disparities have really colored a lot of what our diseases are, from HIV to diabetes to hypertension, and it's not surprising that we are seeing this now with COVID-19."

Marrazzo noted that, in Alabama, around 20% of the population is African American, yet almost 40% of COVID-19 deaths are occurring in this population. "The most stark statistics are coming

out of Illinois and Michigan, where less than around 15% of the population is African American and yet 70% of the deaths are occurring in that group," she said.

Both del Rio and Marrazzo agreed that understanding the racial differences in COVID-19 deaths is going to require a lot of analysis in the coming months.

Part of it likely reflects the challenge of social distancing in urban areas, Marrazzo said. "Social distancing is a luxury afforded by having a really big space, and space is money."

The other long-standing challenge of unequal access to healthcare also likely plays a role, she said. This includes missing out on preventive health appointments and screenings, which can translate into more comorbidities, particularly hypertension.

The evolving evidence about the virus, and the stark conditions that frontline clinicians face, make this an especially challenging public health crisis, del Rio said.

"Taking care of these patients is incredibly taxing and my hat is off to physicians, residents, nurses, everybody working on this in the hospitals because they are really doing a yeoman's work," he said.

"These are not easy patients to take care of. Not only are [the frontline clinicians] providing care, they are caring for the patient and providing a comfort and someone to listen to when family can't be present," del Rio emphasized.

New Guidelines

The IDSA just released new guidelines for diagnosis and treatment of COVID-19.

"We are learning new things every day about this virus. Things are rapidly changing, and as we learn new things we have to adapt and make changes," del Rio said.

del Rio noted that the guildelines "will evolve and change as more information comes out."