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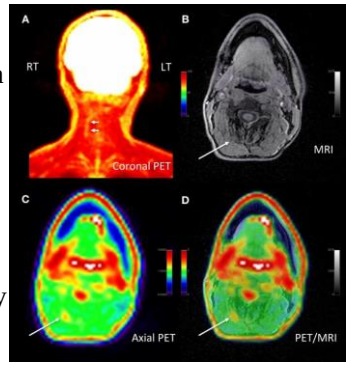
New PET/MRI approach pinpoints chronic pain location, alters management

Molecular imaging approach utilizing 18F-FDG PET and MRI precisely identifies location of pain generators in chronic pain sufferers



A new molecular imaging approach utilizing 18F-FDG positron emission tomography (PET) and magnetic resonance imaging (MRI) can precisely identify the location of pain generators in chronic pain sufferers, often precipitating a new management plan for patients. This research was presented at the Society of Nuclear Medicine and Molecular Imaging 2020 Annual Meeting.

***Molecular imaging approach utilizing 18F-FDG PET and MRI precisely identifies location of pain generators in chronic pain sufferers Adult male with decades of right neck pain, discomfort and tightening following birth injury. The patient had failed multiple standard therapeutic maneuvers before presenting for 18F-FDG PET/MR imaging. Images shows abnormally elevated FDG uptake (white arrows; SUVmax = 1.2) observed in a linear pattern in the space in the posterolateral right neck, between the oblique capitis inferior and the semispinalis capitis muscles, where the greater occipital nerve resides. By comparison, the same region on the contralateral, asymptomatic side of the neck has an SUVmax = 0.7. This result encouraged a surgeon to explore the area. The surgeon ultimately found a collection of small arteries wrapped around the nerve in this location. The small arteries underwent lysis by the surgeon and the patient reported tremendous relief of symptoms. (A) Coronal thick slab MIP of 18F-FDG PET. (B) Axial LAVA FLEX MRI through the cervical spine. (C) Axial PET at the same slice as the axial MRI. (D) Fused axial PET/MRI.* Cipriano, et al., Stanford University, CA.**

Pain is the most common reason to seek medical attention, and those who suffer from it outnumber those who suffer from cancer, heart disease and diabetes combined. According to the National Center for Complementary and Integrative Health, chronic pain affects nearly 50 million adults in the United States and costs the nation's healthcare system as much as $635 billion in total expenses, including imaging and treatment costs.

"In the past few decades, we have confirmed that anatomic-based imaging approaches, such as conventional MRI, are unhelpful in identifying chronic pain generators," said Sandip Biswal, MD, musculoskeletal radiologist and associate professor of radiology at Stanford University School of Medicine in Stanford, California. "We know that 18F-FDG PET has the ability to accurately evaluate increased glucose metabolism that arises from to acute or chronic pain generators. As such, in our study we examined PET/MRI as a potential solution to determine the exact molecular underpinnings of one's pain."

In the study, 65 chronic pain patients underwent 18F-FDG PET/MRI from head to foot. Maximum standardized uptake values and target-to-background ratios were measured using image analysis software. PET/MR images were evaluated by two radiologists to determine if increased 18F-FDG uptake occurred in the site of symptoms or in other areas of the body. Imaging results were then discussed with the referring physician, who determined whether a change in the pain management plan would follow.

Increased uptake of 18F-FDG in affected nerves and muscle was identified at the site of pain and other areas of the body in 58 out of 65 patients. This resulted in a mild modification of management plan (e.g., additional diagnostic test) for 16 patients and a significant modification for 36 patients (e.g., new invasive procedure suggested or ordered). In total, new management plans

were implemented for 40 out of 65 patients, which had not been anticipated by the referring physician.

"The results of this study show that better outcomes are possible for those suffering from chronic pain," said Biswal. "This clinical molecular imaging approach is addressing a tremendous unmet clinical need, and I am hopeful that this work will lay the groundwork for the birth of a new subspecialty in nuclear medicine and radiology. Using this approach will require knowledge and expertise not only in nuclear medicine but also in musculoskeletal imaging, neuroradiology and potentially other fields, such as body imaging and pediatric radiology, where pain syndromes are important clinical problems."

Abstract 399. "18F-FDG PET/MRI of patients with chronic pain alters management," Peter Cipriano, Daehyun Yoon, Ian Carroll, Catherine Curtin, Vivianne Tawfik, Yingding Xu, and Sandip Biswal, Stanford University, Stanford, California. SNMMI's 67th Annual Meeting, July 11-14, 2020.

All 2020 SNMMI Annual Meeting abstracts can be found online at http://jnm.snmjournals.org/content/61/supplement_1.toc.

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Pancreatic cancer hides from the immune system by destroying the cell's danger signal

Stopping the cancer cells from degrading the signal shrunk the tumors

Allison J Matthews

There is an entire branch of our immune system that has evolved to recognize when something is wrong inside a cell, and it revolves around a group of proteins called MHC-I.

MHC-I is a little pedestal that cells use to display their proteins for immune cells called T-cells to inspect. If everything is normal and healthy, the proteins on the MHC-I pedestal won't cause any alarm, and the cell is allowed to continue happily growing and dividing. However, if something in the cell has gone awry – whether that is viral infection, bacterial infection, or cancer – what gets displayed on the MHC-I can signal a problem. In that case, a T-cell will immediately kill the cell to nip the problem in the bud.

more T-cells flooded the area around the tumor, and that this was correlated with a significant decrease in tumor size and weight

In a perfect world, this would work every time and our immune system could always stop cancer in its tracks. But some cancers are able to avoid detection by the immune system by not producing MHC-I at all.

A recent paper led by scientists at the NYU School of Medicine and the University of California - San Francisco showed that pancreatic cancer cells recycle and degrade MHC-I complexes so fast that there are almost none on the cell surface to signal that something is wrong.

To try to increase the amount of MHC-I present on the surface of cancerous cells, the researchers treated pancreatic cancers of mice with chloroquine, which prevents the cells from degrading MHC-I complexes. When this was combined with immunotherapy, they saw that more T-cells flooded the area around the tumor, and that this was correlated with a significant decrease in tumor size and weight. This discovery has the potential to improve treatment for cancers that were previously resistant to immunotherapy, making it a promising new strategy to combat them.

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Drug linked to 45% lower risk of dying among COVID-19 patients on ventilators

Patients who received single intravenous dose of tocilizumab were also more likely to leave the hospital or be off ventilator within a month, despite double the risk of additional infection

Critically ill COVID-19 patients who received a single dose of a drug that calms an overreacting immune system were 45% less likely to die overall, and more likely to be out of the hospital or off

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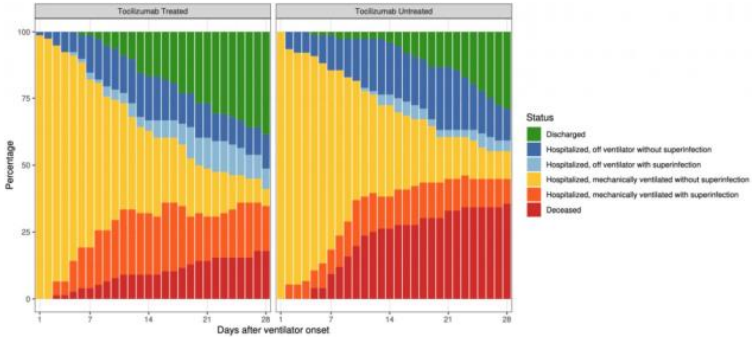
a ventilator one month after treatment, compared with those who didn't receive the drug, according to a new study by a team from the University of Michigan. The lower risk of death in patients who received intravenous tocilizumab happened despite the fact that they were also twice as likely to develop an additional infection, on top of the novel coronavirus.

The study is published in the peer-reviewed journal *Clinical Infectious Diseases* after being available as a preprint last month.

It suggests a benefit from timely and targeted efforts to calm the "cytokine storm" caused by the immune system's overreaction to the coronavirus. Tocilizumab, originally designed for rheumatoid arthritis, has already been used to calm such storms in patients receiving advanced immunotherapy treatment for cancer.



This graph shows the outcomes over time for the COVID-19 patients on ventilators treated with and without tocilizumab at Michigan Medicine, the University of Michigan's academic medical center. The data are from an observational study that looked back at patient data from March and April, after the hospital's pharmacy guidelines early in the pandemic gave physicians information about the potential benefits and risks of prescribing the drug. **University of Michigan/Clinical Infectious Diseases**

The researchers base their conclusions on a thorough look back at data from 154 critically ill patients treated at Michigan Medicine, U-M's academic medical center, during the first six weeks of the pandemic's arrival in Michigan from early March to late April. The analysis looked at patients' records through late May.

During that time, when little was known about what would help COVID-19 patients on ventilators, about half of the studied patients received tocilizumab and half did not. Most received it within the 24-hour period surrounding their intubation.

This created a natural opportunity for comparing the two groups' outcomes in an observational study, though clinical trials are still needed to truly see if the drug provides a benefit, the authors say.

Promising result

Lead author Emily Somers, Ph.D., Sc.M., an epidemiologist who has studied both rheumatologic and immunologic diseases, says the research team went into their analysis uncertain whether they would find a benefit, a risk, or no clear effect associated with tocilizumab in the patients with life-threatening COVID-19. But they knew it was a critically important question that they were uniquely positioned to answer at that point in the pandemic.

"One role of epidemiology is to rigorously evaluate real-world data on treatment effects, especially when evidence from clinical trials is not available. We kept trying to prove ourselves wrong as signals of benefit emerged in the data, both because of the immediate implications of these data, and in part because of concern about the supply of the medication for other patients," she says. "But the difference in mortality despite the increase in secondary infection is quite pronounced, even after accounting for many other factors."

Somers is an associate professor in the U-M Medical School's Department of Internal Medicine and member of the U-M Institute for Healthcare Policy and Innovation. She co-leads the COVID-19 Rapid Response Registry, which is supported by the Michigan Institute for Clinical and Health Research.

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The paper's co-first author is Gregory Eschenauer, Pharm.D., a clinical pharmacist at Michigan Medicine and clinical associate professor at the U-M College of Pharmacy. He and senior author Jason Pogue, Pharm.D., are members of the Michigan Medicine Antimicrobial Stewardship Program.

The ASP group developed treatment guidelines provided to Michigan Medicine physicians in mid-March that identified tocilizumab as a potentially beneficial therapy for the most severely ill COVID-19 patients. Those guidelines also pointed out its risks and the lack of evidence for its use in COVID-19, and recommended a dose of 8 milligrams per kilogram.

This led some physicians to choose to use it, while others did not - setting the stage inadvertently for a natural comparison.

More research needed

Pogue, clinical professor at the U-M College of Pharmacy and an infectious disease pharmacist at Michigan Medicine, notes that more robust data released in June from a large randomized controlled trial in the United Kingdom has led him to recommend the steroid dexamethasone as the first choice to treat critically ill COVID-19 patients.

"For a retrospective, single-center study, our data are robust. But at this time, due to the lack of randomized controlled trial data and the much higher cost, we recommend reserving tocilizumab for the treatment of select patients who decompensate while on or after receiving dexamethasone or in patients where the risks of adverse events from steroid therapy outweigh the potential benefits" says Pogue. "Further studies of tocilizumab, which is more targeted than dexamethasone in addressing the hyperinflammatory process, could include combining these agents or comparing them head-to-head," he adds.

Pogue notes that a single dose of tocilizumab is roughly 100 times more expensive than a course of dexamethasone. He also notes that another drug that aims to treat cytokine storm by targeting the interleukin-6 (IL-6) receptor - one called sarilumab - appears to have failed to improve outcomes in a clinical trial in COVID-19 patients including those on ventilators.

Michigan Medicine had been participating in the sarilumab study at the time the patients in the current study were treated, but not all patients qualified because of the timing of their admission or issues around testing for COVID-19. The current study does not include any patients who received sarilumab.

If the evidence around IL-6 targeting bears out in further studies, the authors note that it will be important to select the dose and timing carefully, to address the cytokine storm without interfering with IL-6's other roles in activating the body's response to infections and its processes for repairing tissue.

More about the study

The majority of the patients were transferred to U-M from Detroit-area hospitals after diagnosis with COVID-19, and those who received tocilizumab were less likely overall to have been transferred while already on a ventilator.

By the end of the 28-day period after patients went on a ventilator, 18% of those who received tocilizumab had died, compared with 36% of those who had not. When adjusted for health characteristics, this represents a 45% reduction in mortality. Of those still in the hospital at the end of the study period, 82% of the tocilizumab patients had come off the ventilator, compared with 53% of those who didn't receive the drug.

In all, 54% of the tocilizumab patients developed a secondary infection, mostly ventilator associated pneumonia; 26% of those who didn't receive tocilizumab developed such infections. Such "superinfections" usually reduce the chance of survival for COVID-19 patients.

Hydroxychloroquine was included in the treatment guidelines for COVID-19 inpatients at Michigan Medicine for the first two and a half weeks of the study period, before being removed as evidence of its lack of benefit and risks emerged. In all, it was used in one-quarter of the patients who received tocilizumab and one-fifth of those who didn't. Similar percentages of the two patient groups received steroids, though none received dexamethasone.

The patients in the two groups were similar in most ways except for a slightly higher average age in the non-tocilizumab group, and lower rates of chronic obstructive pulmonary disease and chronic kidney disease among the tocilizumab patients.

The study was supported by the National Institutes of Health [UL1TR002240, 1K12HL133304]; the Centers for Disease Control and Prevention [U01IP000974]; and an American Society for Transplantation and Cellular Therapy New Investigator Award. The COVID-19 Rapid Response Registry is supported by the Michigan Institute for Clinical and Health Research (MICHR), and uses the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterization Protocol to standardize the clinical characterization of patients with COVID-19 so their data can be studied.

In addition to Somers, Pogue and Eschenauer, the study's authors are from several departments of the U-M Medical School, and from the U-M College of Pharmacy, School of Public Health, and MICHR. They are: Jonathan P Troost, PhD, Jonathan L Golob, MD PhD, Tejal N Gandhi, MD, Lu Wang, PhD, Nina Zhou, MS, Lindsay A Petty, MD, Ji Hoon Baang, MD, Nicholas O Dillman, PharmD, David Frame, PharmD, Kevin S Gregg, MD, Dan R Kaul, MD, Jerod Nagel, PharmD, Twisha S Patel, PharmD, Shiwei Zhou, MD, Adam S Lauring, MD PhD, David A Hanauer, MD MS, Emily Martin, PhD, Pratima Sharma, MD MS, and Christopher M Fung, MD.

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Single-dose flu drug can reduce spread within households,

A single dose of the flu drug baloxavir marboxil can reduce the spread of the illness within households, new research concludes.

A study examining 752 household contacts of 545 patients with the flu found that flu infections were much less common in household members who received the drug than among those who received a placebo. Only 1.9% of uninfected household contacts who took a single dose of baloxavir marboxil came down with the flu, compared with 13.6% of those who received the placebo.

"This trial established that baloxavir, if taken within a day or so after exposure, is highly effective for preventing influenza illness in households, a high-risk setting for virus transmission," said researcher Frederick G. Hayden, MD, of the University of Virginia School of Medicine. "The findings indicate that baloxavir prophylaxis should prove effective for prevention in other circumstances, such as outbreaks in nursing homes and healthcare facilities, although formal studies will need to be undertaken."

Reducing Influenza Spread

The double-blind study found that baloxavir marboxil, sold under the brand name Xofluza, was effective in adults, children and those at high-risk, regardless of whether they had received the flu vaccine. The frequency of adverse events, such as headaches and nausea, was similar among those who received the drug (22.2%) and those who received placebos (20.5%). There were no deaths in either group.

Hayden, a professor emeritus in UVA's Division of Infectious Diseases and International Health, was also part of a research team that published a month ago in Lancet Infectious Diseases that baloxavir treatment shortened the duration of influenza and reduced complications in adults and adolescents at high risk of complications. A single dose of the drug was as effective as a five-day course of oseltamivir (Tamiflu), the researchers concluded.

The federal Food and Drug Administration has approved baloxavir marboxil to treat flu within 2 days of symptom onset in people 12 years and older and those at high risk of developing complications.

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Its approval in 2018 marked the first novel flu drug in 20 years. The FDA is reviewing baloxavir applications for both treatment in children aged 1-11 years and for prophylaxis.

Findings Published

The researchers have published their findings in the prestigious *New England Journal of Medicine*. The study's authors were Hideyuki Ikematsu, Hayden, Keiko Kawaguchi, Masahiro Kinoshita, Menno D. de Jong, Nelson Lee, Satoru Takashima, Takeshi Noshi, Kenji Tsuchiya and Takeki Uehara. Hayden disclosed that he has received fees for serving on a data safety and monitoring board, paid to the UVA School of Medicine, from Celltrion Healthcare, GlaxoSmithKline and Vaccitech. He has served as a consultant and received travel support from F. Hoffmann-La Roche and Shionogi, and he has served as a consultant for Cidara Therapeutics, Fujifilm Corp., Genentech, Gilead Sciences, Janssen Pharmaceuticals, MediVector, Regeneron Pharmaceuticals, resTORbio, SAB Biotherapeutics, Versatope, Vir and Visterra. A full list of disclosures is included in the paper.

The research was funded by Shionogi, Japan Primary Registries Network No. JapicCTI-184180. Shionogi and the Roche Group are the developers of the drug.

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Pickled capers activate proteins important for human brain and heart health

New study reveals how a compound found in capers regulates proteins that control important bodily processes

Irvine, CA - A compound commonly found in pickled capers has been shown to activate proteins required for normal human brain and heart activity, and may even lead to future therapies for the treatment of epilepsy and abnormal heart rhythms.

Researchers from the University of California, Irvine School of Medicine have discovered that a compound named quercetin, commonly consumed when eating capers, can directly regulate proteins required for bodily processes such as the heartbeat, thought, muscular contraction, and normal functioning of the thyroid, pancreas and gastrointestinal tract.

Published in *Communications Biology*, the discovery was made by the laboratory of Geoffrey Abbott, PhD, a professor in the Department of Physiology and Biophysics at the University of California, Irvine School of Medicine. Kaitlyn Redford, a graduate student in the Abbott Lab, was first author of the study titled, "The ubiquitous flavonoid quercetin is an atypical KCNQ potassium channel activator."

The Abbott Lab found that quercetin, a plant-derived bioflavonoid, modulates potassium ion channels in the KCNQ gene family. These channels are highly influential in human health and their dysfunction is linked to several common human diseases, including diabetes, cardiac arrhythmia, and epilepsy.

Pickled capers used in this study were found to activate KCNQ channels important for normal human brain and heart activity. **Bo Abbott**

The study revealed that quercetin modulates the KCNQ channels by directly regulating how they sense electrical activity in the cell, suggesting a previously unexpected mechanism for the therapeutic properties of capers. The mechanism may extend to other quercetin-rich foods in our diet, and quercetin-based nutritional supplements.

"Now that we understand how quercetin controls KCNQ channels," said Abbott, "future medicinal chemistry studies can be pursued to create and optimize quercetin-related small molecules for potential use as therapeutic drugs."

The Abbott Lab screened plant extracts for the ability to alter activity of KCNQ channels and found that one percent extract of pickled capers activated channels important for normal human brain and heart activity. Further studies revealed the molecular

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mechanism - quercetin from the caper extract binds to a region of the KCNQ channel required for responding to electrical activity, and in doing so, tricks the channel into opening when it would normally be closed.

"Increasing the activity of KCNQ channels in different parts of the body is potentially highly beneficial," said Abbott. "Synthetic drugs that do this have been used to treat epilepsy and show promise in preventing abnormal heart rhythms."

Archaeological evidence for human caper consumption dates back as far as 10,000 years, according to archaeological findings from Mesolithic soil deposits in Syria and late Stone Age cave dwellings in the Greece and Israel. Capers have traditional been used as folk medicine for hundreds if not thousands of years and are in current use or study for their potential as anti-cancer, anti-diabetic and anti-inflammatory properties, and their possible circulatory and gastrointestinal benefits.

This study was supported by the National Institutes of Health, National Institute of General Medical Sciences and National Institute of Neurological Disorders and Stroke.

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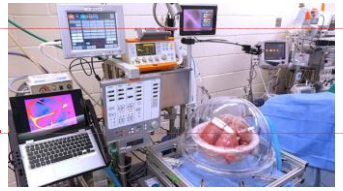
How to use a live pig to revitalize a human lung

Unusual method could increase the supply of lungs available for transplantation.



Damaged human lungs could be rejuvenated to allow for transplant into people if the organs were hooked up to a pig's circulatory system.

Human lungs can be reconditioned for transplant by connecting them to a living pig (under blue sheet). **Credit: A. E. Hozain et al./Nature Med.**

Matthew Bacchetta at Vanderbilt University in Nashville, Tennessee, Gordana Vunjak-Novakovic at Columbia University in New York City and their colleagues collected five human lungs that had been deemed unsuitable for transplantation because of acute damage. The researchers also gave immunosuppressant drugs and a component of cobra venom to five pigs to prevent the animals' immune systems from attacking the human lungs after attachment.

Next, the team connected the lungs' blood vessels to the pigs' jugular veins and allowed their blood to intermix for 24 hours. When the researchers examined the human lungs afterwards, they found that the organs' structure and function had improved enough to make them suitable for transplantation. They have not yet performed human trials.

Using this method to increase the number of healthy lungs available could cut the length of time people wait for transplants, the authors say. *Nature Med.* (2020)

https://nyti.ms/32skYQ4

World Population Could Peak Decades Ahead of U.N. Forecast, Study Asserts

The study, published in The Lancet, said an accelerated decline in fertility rates means the global population could peak in 2064 at 9.7 billion and fall to 8.8 billion by century's end.

By Rick Gladstone

United Nations demographers have been anticipating since last year that the world's population may stop growing by 2100 as fertility rates decline, projecting a peak of 10.9 billion people by century's end, compared with roughly 7.8 billion now.

But a study published on Tuesday in The Lancet, the medical journal, has challenged that forecast, with major economic and political implications. The study asserted that the global population could peak at 9.7 billion by 2064 — nearly four decades earlier — and decline to 8.8 billion by 2100.

Moreover, the study concluded, the elderly will make up a bigger chunk of the total than foreseen in the U.N. forecast, and the

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populations of at least 23 countries, including Japan, Thailand, Italy and Spain, could shrink by more than 50 percent. The study also projected significant declines in the working-age populations of China and India, the two most populous countries, portending a weakening in their global economic power.

The study's projections, if borne out, also carry significant consequences for the United States, whose economy is expected to trail China's in size by 2035. As China's working-age population declines in the second half of the century, the study said, the United States could reclaim the top spot economically by 2098 — if immigration continues to replenish the American work force.

"Continued global population growth through the century is no longer the most likely trajectory for the world's population," said Dr. Christopher Murray, director of the Institute for Health Metrics and Evaluation at the University of Washington's School of Medicine, who led the study.

Dr. Murray said the study "provides governments of all countries an opportunity to start rethinking their policies on migration, work forces and economic development to address the challenges presented by demographic change."

An important underlying reason behind the conclusions is the improvement in access to modern contraception and the education of girls and women, which the study said would "hasten declines in fertility and slow population growth."

While the most recent United Nations population forecast, made in June 2019, also noted declining fertility, the new study said the consequences would be felt much sooner and with greater impact.

John Wilmoth, director of the population division in the United Nations Department of Economic and Social Affairs, which produces the organization's projections every two years, said Tuesday that he had not yet fully read the study. But he said that it had made some assumptions about fertility, mortality and migration that helped shape the conclusions.

One of the biggest assumptions, he said in a phone interview, was that countries with low fertility rates would do nothing to raise them between now and 2100.

"It's kind of an extreme assumption to think that countries aren't going to think their way out of the problem for the next 80 years," he said.

Mr. Wilmoth also said the United Nations had been tracking population trends for 70 years and that its projections "represent a consensus view" among demographers. Still, he said, "I welcome this sort of creative inquiry about other ways of seeing these things."

The forecasting methodology used in the study found that by 2100, 183 of 195 countries would have total fertility rates — the average number of children a woman delivers over her lifetime — below the replacement level of 2.1 births. That is the level needed to prevent population decline. The study also suggested that the decline could be offset by immigration, with countries that promote liberal immigration policies better able to maintain their population and support economic growth.

Some countries with fertility rates lower than replacement level, such as the United States, Australia and Canada, would probably

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replenish their working-age populations through net immigration, the study said, although it noted uncertainty about such a forecast. The backlash in the United States against immigration, the study said, could threaten "the country's potential to sustain population and economic growth."

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Graduates of family medicine residencies are likely to enter and remain in family medicine

Characteristics of family medicine residency graduates, 1994-2017: An update

This study provides an overview of the characteristics of physicians who completed family medicine residency training from 1994 to 2017. It serves to update the only previous comprehensive national review of this kind, conducted in 1996, which covered family medicine graduates from 1969 through 1993. With only 10.9 percent of medical students entering family medicine residency training in 2016, and in light of the continuing shortage of family physicians, one goal of the new study was to determine whether family medicine residency graduates continue to practice in the field after residency. The study yielded moderately encouraging findings suggesting that family medicine residents are likely to remain in the primary care workforce.

Characteristics of Family Medicine Residency Graduates, 1994-2017: An Update
Mingliang Dai, PhD, et al American Board of Family Medicine, Lexington, Kentucky
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Vision scientists discover why people literally don't see eye to eye

Study finds visual localization and acuity varies from person to person

We humans may not always see eye to eye on politics, religion, sports and other matters of debate. But at least we can agree on the location and size of objects in our physical surroundings. Or can we?

Not according to new research from the University of California, Berkeley, recently published in the *Proceedings of the Royal Society B: Biological Sciences* journal, that shows that our ability to pinpoint the exact location and size of things varies from one person to the next, and even within our own individual field of vision.

"We assume our perception is a perfect reflection of the physical world around us, but this study shows that each of us has a unique visual fingerprint," said study lead author Zixuan Wang, a UC Berkeley doctoral student in psychology.

The discovery by Wang and fellow researchers in UC Berkeley's Whitney Laboratory for Perception and Action has ramifications for the practices of medicine, technology, driving and sports, among other fields where accurate visual localization is critical.

For example, a driver who makes even a small miscalculation about the location of a pedestrian crossing the street can cause a catastrophe. Meanwhile, in sports, an error of visual judgment can lead to controversy, if not a fiercely disputed championship loss.

Take, for example, the 2004 U.S. Open quarterfinals, in which tennis icon Serena Williams lost to Jennifer Capriati after a series of questionable line calls. An umpire incorrectly overruled a line judge who called a backhand hit by Williams as in, resulting in an apology to Williams by the U.S. Tennis Association.

"Line judges need to rule on whether the ball is outside or inside the parameters. Even an error as small as half a degree of visual angle, equal to a sub-millimeter shift on the judge's retina, may influence the result of the whole match," said Wang, a die-hard tennis fan.

Researchers sought to understand if different people see objects in their surroundings exactly the same way. For example, when glancing at a coffee cup on a table, can two people agree on its

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exact position and whether its handle is big enough to grip? The result of a series of experiments suggest not, though there's an upside.

"We may reach for a coffee mug thousands of times in our life, and through practice we reach our target," Wang said. "That's the behavioral aspect of how we train ourselves to coordinate how we act in relation to what we see."

In the first task to test visual localization, study participants pinpointed on a computer screen the location of a circular target. In another experiment looking at variations of acuity within each person's field of vision, participants viewed two lines set a minimal distance apart and determined whether one line was located clockwise or counterclockwise to the other line.

And in an experiment measuring perception of size, participants viewed a series of arcs of varying lengths and were asked to estimate their lengths. Surprisingly, people perceived the exact same arcs to be bigger at some locations in the visual field and smaller at other locations.

Overall, the results showed remarkable variations in visual performance among the group and even within each individual's field of vision. The data were mapped to show each study participant's unique visual fingerprint of perceptual distortion.

"Though our study might suggest that the source of our visual deficiencies can originate from our brain, further investigations are needed to uncover the neural basis," said Wang.

"What's also important," she added, "is how we adapt to them and compensate for our errors."

Other co-lead authors of the study are David Whitney at UC Berkeley and Yuki Murai at UC Berkeley and Osaka University in Japan.

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COVID-19 may attack patients' central nervous system

University of Cincinnati researcher says depressed mood and anxiety may be symptoms of a COVID-19 impact on the brain

Depressed mood or anxiety exhibited in COVID-19 patients may possibly be a sign the virus affects the central nervous system, according to an international study led by a University of Cincinnati College of Medicine researcher.

These two psychological symptoms were most closely associated with a loss of smell and taste rather than the more severe indicators of the novel coronavirus such as shortness of breath, cough or fever, according to the study.

"If you had asked me why would I be depressed or anxious when I am COVID positive, I would say it is because my symptoms are severe and I have shortness of breath or I can't breathe or I have symptoms such as cough or high fever," says Ahmad Sedaghat, MD, PhD, an associate professor and director of rhinology, allergy and anterior skull base surgery, in the UC College of Medicine's Department of Otolaryngology-Head and Neck Surgery.

"None of these symptoms that portended morbidity or mortality was associated with how depressed or anxious these patients were," explains Sedaghat, also a UC Health physician specializing in diseases of the nose and sinuses. "The only element of COVID-19 that was associated with depressed mood and anxiety was the severity of patients' loss of smell and taste. This is an unexpected and shocking result."

Sedaghat conducted a prospective, cross-sectional telephone questionnaire study which examined characteristics and symptoms of 114 patients who were diagnosed with COVID-19 over a six-week period at Kantonsspital Aarau in Aarau, Switzerland. Severity of the loss of smell or taste, nasal obstruction, excessive mucus production, fever, cough and shortness of breath during COVID-19 were assessed. The findings of the study are available online in *The Laryngoscope*.

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First author of the study is Marlene M. Speth, MD, and other co-authors include Thirza Singer-Cornelius, MD; Michael Oberle, PhD; Isabelle Gengler, MD; and Steffi Brockmeier, MD.

At the time of enrollment in the study, when participants were experiencing COVID-19, 47.4% of participants reported at least several days of depressed mood per week while 21.1% reported depressed mood nearly every day. In terms of severity, 44.7% of participants reported expressing mild anxiety while 10.5% reported severe anxiety.

"The unexpected finding that the potentially least worrisome symptoms of COVID-19 may be causing the greatest degree of psychological distress could potentially tell us something about the disease," says Sedaghat. "We think our findings suggest the possibility that psychological distress in the form of depressed mood or anxiety may reflect the penetration of SARS-CoV-2, the virus that causes COVID-19, into the central nervous system."

Sedaghat says researchers have long thought that the olfactory tract may be the primary way that coronaviruses enter the central nervous system. There was evidence of this with SARS, or severe acute respiratory syndrome, a viral illness that first emerged in China in November 2002 and spread through international travel to 29 countries. Studies using mouse models of that virus have shown that the olfactory tract, or the pathway for communication of odors from the nose to the brain, was a gateway into the central nervous system and infection of the brain.

"These symptoms of psychological distress, such as depressed mood and anxiety are central nervous system symptoms if they are associated only with how diminished is your sense of smell," says Sedaghat. "This may indicate that the virus is infecting olfactory neurons, decreasing the sense of smell, and then using the olfactory tract to enter the central nervous symptom."

Infrequent but severe central nervous system symptoms of COVID-19 such as seizures or altered mental status have been described, but depressed mood and anxiety may be the considerably more common but milder central nervous symptom of COVID-19, explains Sedaghat.

"There may be more central nervous system penetration of the virus than we think based on the prevalence of olfaction-associated depressed mood and anxiety and this really opens up doors for future investigations to look at how the virus may interact with the central nervous system," says Sedaghat.

For the cross-sectional telephone questionnaire study: The two-item Patient Health Question (PHQ-2) and the two-item Generalized Anxiety Disorder questionnaire (GAD-2) were used to measure depressed mood and anxiety level, respectively during COVID-19 and for participants' baseline pre-COVID-19 state.

Funding for the study came from Kantonsspital Aarau, Aarau, Switzerland.

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Heart Abnormalities Found in COVID-19 Patients Mean Scans Are Vital, Scientists Say

Over half of coronavirus patients who received a heart scan in hospitals demonstrated "abnormalities" in their heart function

Thomas Colson, Business Insider

More than half of coronavirus patients who received a heart scan in hospitals demonstrated "abnormalities" in their heart function, according to a major new study. It adds to growing evidence that COVID-19 causes unusually excessive blood-clotting, which can damage organs throughout the body.

The new research based on data from 69 countries, published in the *European Heart Journal* and commissioned by the British Heart Foundation, found that 55 percent of 1,261 patients scanned had abnormally functioning hearts.

Around one in seven patients who were scanned showed "severe abnormalities" which were likely to have a significant impact on their chances of survival and recovery.

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A majority – 901 patients – of those with abnormally functioning hearts had not demonstrated heart problems before, leading the authors of the report to conclude that the coronavirus is responsible for causing heart problems.

The study, carried out by researchers at the British Heart Foundation Centre of Research Excellence at the University of Edinburgh, emphasised that the study was limited only to people who doctors had cause to believe had heart abnormalities in the first place.

The new findings are significant because they add to a growing field of evidence that suggest coronavirus damages not only the heart but also other major organs, which seems to stem from blood-clotting.

A growing body of evidence has charted unusual blood-clotting in COVID-19 patients, leading to strokes, heart failure, pulmonary embolisms, and 'COVID toes'. The finding offered a possible explanation as to why there has been a higher rate of death from COVID-19 among people with underlying heart conditions.

The heart has to work harder in coronavirus patients because the virus causes inflammation and fluid build-up in the lungs, *The Guardian* reported. That can cause the heart either to fail or for its tissue to become damaged, while in some cases the virus can infect the muscle tissue directly.

Marc Dweck, a consultant cardiologist at the University of Edinburgh who helped lead the research said, "COVID-19 is a complex, multisystem disease which can have profound effects on many parts of the body, including the heart. Many doctors have been hesitant to order echocardiograms for patients with COVID-19 because it's an added procedure which involves close contact with patients. Our work shows that these scans are important – they improved the treatment for a third of patients who received them."

"Damage to the heart is known to occur in severe flu, but we were surprised to see so many patients with damage to their heart with COVID-19 and so many patients with severe dysfunction. We now need to understand the exact mechanism of this damage, whether it is reversible and what the long-term consequences of COVID-19 infection are on the heart."

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Fertility rate: 'Jaw-dropping' global crash in children being born

The world is ill-prepared for the global crash in children being born which is set to have a "jaw-dropping" impact on societies, say researchers.

By James Gallagher Health and science correspondent

Falling fertility rates mean nearly every country could have shrinking populations by the end of the century. And 23 nations - including Spain and Japan - are expected to see their populations halve by 2100. Countries will also age dramatically, with as many people turning 80 as there are being born.

What is going on?

The fertility rate - the average number of children a woman gives birth to - is falling. If the number falls below approximately 2.1, then the size of the population starts to fall. In 1950, women were having an average of 4.7 children in their lifetime.

Researchers at the University of Washington's Institute for Health Metrics and Evaluation showed the global fertility rate nearly halved to 2.4 in 2017 - and their study, published in the Lancet, projects it will fall below 1.7 by 2100. As a result, the researchers expect the number of people on the planet to peak at 9.7 billion around 2064, before falling down to 8.8 billion by the end of the century.

"That's a pretty big thing; most of the world is transitioning into natural population decline," researcher Prof Christopher Murray

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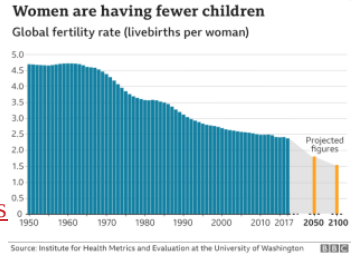
told the BBC. "I think it's incredibly hard to think this through and recognise how big a thing this is; it's extraordinary, we'll have to reorganise societies."

Why are fertility rates falling?

It has nothing to do with sperm counts or the usual things that come to mind when discussing fertility.

Instead it is being driven by more women in education and work, as well as greater access to contraception, leading to women choosing to have fewer children.

In many ways, falling fertility rates are a success story.



Which countries will be most affected?

Japan's population is projected to fall from a peak of 128 million in 2017 to less than 53 million by the end of the century.

Italy is expected to see an equally dramatic population crash from 61 million to 28 million over the same timeframe. They are two of 23 countries - which also include Spain, Portugal, Thailand and South Korea - expected to see their population more than halve.

"That is jaw-dropping," Prof Christopher Murray told me.

China, currently the most populous nation in the world, is expected to peak at 1.4 billion in four years' time before nearly halving to 732 million by 2100. India will take its place. The UK is predicted to peak at 75 million in 2063, and fall to 71 million by 2100.

However, this will be a truly global issue, with 183 out of 195 countries having a fertility rate below the replacement level.

Why is this a problem?

You might think this is great for the environment. A smaller population would reduce carbon emissions as well as deforestation for farmland. "That would be true except for the inverted age structure (more old people than young people) and all the uniformly negative consequences of an inverted age structure," says Prof Murray.

he study projects:

- ***The number of under-fives will fall from 681 million in 2017 to 401 million in 2100.***
- ***The number of over 80-year-olds will soar from 141 million in 2017 to 866 million in 2100.***

Prof Murray adds: "It will create enormous social change. It makes me worried because I have an eight-year-old daughter and I wonder what the world will be like."

Who pays tax in a massively aged world? Who pays for healthcare for the elderly? Who looks after the elderly? Will people still be able to retire from work?

"We need a soft landing," argues Prof Murray.

Are there any solutions?

Countries, including the UK, have used migration to boost their population and compensate for falling fertility rates. However, this stops being the answer once nearly every country's population is shrinking.

"We will go from the period where it's a choice to open borders, or not, to frank competition for migrants, as there won't be enough," argues Prof Murray.

Some countries have tried policies such as enhanced maternity and paternity leave, free childcare, financial incentives and extra employment rights, but there is no clear answer. Sweden has dragged its fertility rate up from 1.7 to 1.9, but other countries that have put significant effort into tackling the "baby bust" have struggled. Singapore still has a fertility rate of around 1.3.

Prof Murray says: "I find people laugh it off; they can't imagine it could be true, they think women will just decide to have more kids.

"If you can't [find a solution] then eventually the species disappears, but that's a few centuries away."

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The researchers warn against undoing the progress on women's education and access to contraception.

Prof Stein Emil Vollset said: "Responding to population decline is likely to become an overriding policy concern in many nations, but must not compromise efforts to enhance women's reproductive health or progress on women's rights."

What about Africa?

The population of sub-Saharan Africa is expected to treble in size to more than three billion people by 2100.

And the study says Nigeria will become the world's second biggest country, with a population of 791 million.

Prof Murray says: "We will have many more people of African descent in many more countries as we go through this.

"Global recognition of the challenges around racism are going to be all the more critical if there are large numbers of people of African descent in many countries."

Why is 2.1 the fertility rate threshold?

You might think the number should be 2.0 - two parents have two children, so the population stays the same size.

But even with the best healthcare, not all children survive to adulthood. Also, babies are ever so slightly more likely to be male. It means the replacement figure is 2.1 in developed countries.

Nations with higher childhood mortality also need a higher fertility rate.

What do the experts say?

Prof Ibrahim Abubakar, University College London (UCL), said: "If these predictions are even half accurate, migration will become a necessity for all nations and not an option.

"To be successful we need a fundamental rethink of global politics.

"The distribution of working-age populations will be crucial to whether humanity prospers or withers."

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'Invasion' of ancient Egypt may have actually been immigrant uprising

Ancient Egypt's first "foreign" takeover may actually have been an inside job.

By Colin Barras

About 3600 years ago, the pharaohs briefly lost control of northern Egypt to the Hyksos, rulers who looked and behaved like people from an area stretching from present-day Syria in the north to Israel in the south. The traditional explanation is that the Hyksos were an invading force. But a fresh analysis of skeletons from the ancient Hyksos capital suggests an alternative: The Hyksos were Egyptian-born members of an immigrant community that rose up and grabbed power.

Ancient Egyptian wall art shows the Hyksos wore brightly colored clothes, whereas Egyptians often opted for white. **FALKENSTEINFOTO/Alamy Stock Photo**

The pharaohs ruled Egypt from about 3100 B.C.E. to 30 B.C.E., but they weren't always in complete command of their territory. One period of vulnerability began around 1800 B.C.E., with a succession of ineffectual pharaohs who struggled to maintain order. The Hyksos took advantage of the power vacuum by seizing control of northern Egypt, according to ancient texts, leaving the pharaohs in charge of only a tiny strip of land to the south.

Archaeologists know the Hyksos were unlike typical Egyptians: They had names like those of people from the neighboring region of southwest Asia. Ancient artwork depicts them wearing long,

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multicolored clothes, unlike normal Egyptian white attire. But exactly who they were has been unclear.

The pharaohs later claimed the Hyksos were foreign invaders who took northern Egypt by force and brought disorder and chaos. But some historians say this was simply ancient Egyptian propaganda.

In the 1940s, researchers identified the ancient Hyksos capital city, Avaris, at a site in the Nile delta about 120 kilometers northeast of Cairo. In the new study, archaeologist Chris Stantis at Bournemouth University and her colleagues analyzed teeth taken from skeletons buried at Avaris to get a clearer picture of who the Hyksos really were.

As teeth form in childhood, tiny quantities of strontium metal in food are incorporated into the enamel. By comparing the balance of strontium isotopes in enamel with those in the region's soil, researchers can judge where an individual grew up.

When Stantis and her colleagues examined teeth from 36 skeletons buried at Avaris during the 350 years before the Hyksos seized power, they discovered that 24 of the individuals—both male and female—were foreign-born. They couldn't tell where the foreigners hailed from, but the researchers say their findings show Egypt had welcomed immigrants for hundreds of years before the Hyksos rose to power. Data from the teeth of a further 35 people buried at Avaris during the Hyksos period show a similar pattern of immigration continued after they rose to power.

As such, Stantis suggests the Hyksos rulers were not necessarily foreign-born invaders, but might instead have emerged from a centuries-old immigrant community living in Avaris, her team reports today in *PLOS ONE*.

Historian and archaeologist Anna-Latifa Mourad at Macquarie University thinks this conclusion makes sense. Archaeologists have found little evidence for the fighting and destruction that should have occurred at Avaris if the city had been captured by foreign invaders.

Egyptologist Orly Goldwasser at the Hebrew University of Jerusalem thinks most of the immigrants probably traveled to Egypt in peace. They may even have invented the alphabet once they arrived, according to her research.

Their rise to power is probably explained by the failings of the pharaohs to control the area, says Egyptologist John Darnell at Yale University.

The Hyksos ruled for 100 years, and then the pharaohs recaptured their territory. Researchers have speculated that the pharaonic forces banished the Hyksos rulers to southwest Asia—and that the punishment may have helped inspire Exodus, the biblical story in which the Israelites left Egypt and, eventually, reached the promised land in southwest Asia.

Ultimately, even though the Hyksos may only have ruled for about 100 years, they appear to have left their mark on world culture.

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NASA's first lunar habitat may be an RV-like rover built by Toyota

"NASA's budget is stretched pretty thin."

Last year Vice President Mike Pence directed NASA to return humans to the Moon by 2024. NASA has since been working hard toward this goal, creating the Artemis Program and issuing contracts for three different teams to begin developing lunar landers. But in his speech, Pence went beyond just setting a date for the landing. He also said the space agency should "establish a permanent base there, and develop the technologies to take American astronauts to Mars and beyond. That's the next giant leap."

Now, we're starting to get some details on what that may look like. On Friday a NASA engineer named Mark Kirasich, who is acting

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director of NASA's Advanced Exploration Systems, spoke at a meeting of the Solar System Exploration Research Virtual Institute (see video). During his presentation, Kirasich laid out NASA's plans for lunar surface activities.

Assuming NASA makes the goal of landing humans on the Moon by 2024—which is theoretically possible but would require a lot of budgetary, political, and technical factors to fall the space agency's way—a "Lunar Terrain Vehicle" would follow in 2025. This would be delivered via the "Commercial Lunar Payload Services" program, in which NASA has a pool of private companies to choose from for lunar delivery services.

This rover would be a relatively simple, unpressurized vehicle similar to what astronauts had at their disposal during the final three Apollo missions to the Moon. "This is the very first of the surface elements that we're going to build," Kirasich said. Following an acquisition strategy meeting this week, he said NASA will move to formally establish a program office for the rover at the Johnson Space Center in Houston.

The next step would involve development of a pressurized rover. "This thing is the coolest element I've ever seen for people," Kirasich said. "It's like an RV for the Moon. We are going to try and develop this jointly with JAXA, as a Japanese contribution to our plan."

Last week NASA formalized this agreement by signing a "Joint Exploration Declaration of Intent" that includes Japanese contributions to the Lunar Gateway, in orbit and surface exploration. This potentially means that Japan's space agency, JAXA, will lead development of a critical piece of the Artemis Program architecture, a rover that doubles as a habitat for up to two people for 14 days. Kirasich did not provide a date for when this larger rover might launch.

The Japanese partnership is notable because NASA spent more than half a decade in the 2000s working on the Lunar Electric Rover, which was one element planned to facilitate lunar astronaut stays for as long as 180 days. This was part of the Constellation Program, which was canceled in 2010 after it was found to be behind schedule and over budget. Asked whether it was justifiable for NASA to delegate this work to JAXA and its commercial partner Toyota, Kirasich said it was necessary.

"Our job depends on federal funding, so we have to listen to our constituents who fund us," he said. "It's very important to our leadership at the moment to involve JAXA in a major surface element. Number two, the Japanese, and their auto industry, have a very strong interest in rover type things. So there was an idea to, even though we have done a lot of work, to let the Japanese lead development of a pressurized rover. So right now that's the direction we're heading in."

A senior lunar scientist who participated in the meeting, Notre Dame's Clive Neal, said the announcement that Japan would now lead development of a pressurized habitat on the Moon came as a surprise. "Under Constellation NASA had a sophisticated rover put together," Neal told Ars. "It's pretty sad if it's never going to get to the Moon."

However, Neal added that he understands NASA and its administrator, Jim Bridenstine, need to broaden the appeal of the Artemis Program and bring in additional partners. Not only does that make it easier for Congress to support Artemis, as well as future presidential administrations, it helps defray the high costs of a lunar return. "NASA's budget is stretched pretty thin, and this helps them afford to do it," he said.

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Penn researchers find three distinct immune responses for sicker COVID-19 patients

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New immune profiles could help predict disease and guide treatments, suggests two Penn studies

PHILADELPHIA -- Researchers from the Penn Institute of Immunology discovered three distinct immune responses to the SARS-CoV2 infection that could help predict the trajectory of disease in severe COVID-19 patients and may ultimately inform how to best treat them.

The findings were published in *Science*.

"For patients who are hospitalized with COVID-19, there isn't just one way for the immune system to respond. There's a lot of heterogeneity, which we've distilled down into what we're calling three "immunotypes," said senior author E. John Wherry, PhD, chair of the department of Systems Pharmacology and Translational Therapeutics and director of the Penn Institute of Immunology in the Perelman School of Medicine at the University of Pennsylvania. "We're hopeful we may actually be able to predict, or at least infer, the different immune patterns a patient has based on clinical data. This would allow us to start thinking about enrolling patients to different types of clinical trials investigating treatments."

The coronavirus triggers different immune responses and symptoms in critically ill patients, but how those two correspond has remained poorly understood, making treatment decisions more difficult.

While recent studies reveal details on the immune's response to the virus, most have been single-case reports or focused on a small group of individuals. This is the first study, to the author's knowledge, to offer up a comprehensive immune profile of a large number of hospitalized patients.

The researchers applied deep immune profiling to capture individual responses of 163 patients during the course of their infections. The study included 90 hospitalized patients treated at the Hospital of the University of Pennsylvania, 29 non-hospitalized patients, and 44 healthy donors with no COVID-19 infection. The immune responses varied among the group, but there were patterns that hold clinical promise.

The first immunotype had robust CD4+ T cell activity, with modest activation of CD8+ T cells and peripheral blood lymphocytes. CD4+ and CD8+ act as the main inflammatory immune cells that work to clear viruses. The second immunotype was characterized mainly by a subset of CD8+ T cells known as EM and EMRA and a modest activation of CD8+ T cells, memory B cells, and peripheral blood lymphocytes. The third immunotype showed little to no evidence of an immune response to the infection.

Next, researchers combined the profiling with clinical data to understand the relationships between immune responses and disease. The first immunotype was tied to more severe disease that included inflammation, organ failure, and acute kidney disease. The second correlated not with disease severity but instead pre-existing immunosuppression and mortality. The third type, which had no immune activation, was not associated with specific symptoms or clinical features, though they varied.

The immunotypes developed by Wherry and team represent adaptive immune responses. A second study from researchers at Penn, published in Science Immunology, uncovered new details about the innate, or initial, response to SARS-CoV2.

"T and B cell activity are informed by innate immune responses," said senior author Michael R. Betts, PhD, a professor of Microbiology and program leader in the Penn Institute of Immunology, who is also a co-author on the first study. "We believe what's happening with the innate response of the immune system might be what's leading to these three immune phenotypes Dr. Wherry's lab identified."

Profiling the blood samples of 42 infected patients (with moderate and severe disease) and 12 healthy donors, the researchers found a similar heterogeneity in immune adaptive responses: robust

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activation of CD4+ and CD8+ T cells, B cells, along with peripheral blood cells, like neutrophils, monocytes, and "natural killer," or NK, cells.

While the innate responses were also heterogenous, the researchers observed a decrease of CD15 and CD16 molecules on neutrophils and CD16 on NK cells, immature granulocytes, and monocytes, in patients with more severe disease. These two molecules are known players in the immune's response to viral infections that also represent a potential target for immunotherapy. How they are driving and exacerbating the adaptive responses in the three immunotypes is an important question the labs are working to better understand.

COVID-19 studies have been moving at an unprecedented speed as researchers band together to find answers. Among its many efforts, Penn formed lab and clinical research teams from diverse backgrounds to strengthen its focus on the immune system, along with the COVID Processing Unit to manage specimens to profile.

"Understanding the power of the immune system to regulate responses to disease is one of the major advances in medicine in the last decade, and Penn has been at the center leading that discovery. We are now applying the broad expertise and experience of our more than 200-person immunology community toward the research and treatment of COVID-19," said Jonathan A. Epstein, MD, executive vice dean, chief scientific officer, and a professor of Cardiovascular Research at Penn. "The deep immuno-profiling work the investigators applied here is likely to be useful not only now, for this disease, but into the future for many others."

The studies were supported by the Penn Institute for Immunology Glick COVID-19 research award; the National Institute of Health (HL137006, HL137915, UM1- AI144288, P30-CA016520, AI105343, AI115712, AI117950, AI108545, AI082630, CA210944, CA230157); Mentored Clinical Scientist Career Development Award from the National Institute of Allergy and Infectious Diseases (K08 AI136660); Athersys, Inc, Biomarck Inc, and the Marcus Foundation for Research; the Parker Institute for Cancer Immunotherapy; the Allen Institute for Immunology.

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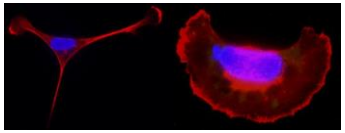
Study: Dangerous parasite controls host cell to spread around body

Toxoplasma essentially hijacks these cells, using them as vehicles to get to various organ systems, including the brain

Researchers at Indiana University School of Medicine have discovered new information about how a dangerous parasite takes control of a patient's cells as it spreads throughout their body, an important finding that could help in the development of new drugs to treat this infection.



***This image shows two different Toxoplasma host cells changing their shape to migrate.* IU School of Medicine**

"The parasite essentially hijacks these cells, using them as vehicles to get to various organ systems, including the brain," said Leonardo Augusto, PhD, a postdoctoral fellow in the Department of Pharmacology and Toxicology and lead author on the National Institutes of Health-funded study, which was recently published in *mBio*. "It's like the parasite is taking the wheel of its host cell and using it to spread around the body."

Toxoplasma gondii infects up to one-third of the world's population. People typically become infected with it through exposure to cat feces, which is where it goes through its reproductive phases, or consumption of contaminated food and water. The parasite causes life-threatening issues in some patients because of its ability to disseminate to the brain. In the brain and other tissues, the parasite persists as a latent cyst, waiting to reactivate if immunity should wane, such as what happens in HIV/AIDS patients.

"One of the key problems in battling an infection like Toxoplasma is controlling its spread to other parts of the body," Augusto said.

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"Upon ingestion of the parasite, it makes its way into immune cells and causes them to move--a behavior called hypermigratory activity. How these parasites cause their infected cells to start migrating is largely unknown."

The team's new research is shedding light on this important clinical question, discovering that the parasite trips an alarm system in its host cell that leads to the activation of a protein called IRE1. IRE1 helps the cell cope with stress, which can involve getting it to move to a different location. In cells infected with Toxoplasma, IRE1 connects to the cytoskeleton, a network of structural proteins that gives the cell its shape and coordinates movement. By engaging this network through IRE1, Toxoplasma takes the wheel and causes hypermigration.

"When we infected host cells that were depleted of IRE1, they could no longer move," Augusto said. "These cells were greatly impaired at disseminating Toxoplasma to the brains of infected mice."

These findings reveal a new mechanism underlying host-pathogen interactions, demonstrating how host cells are co-opted to spread a persistent infection. A better understanding of this pathogen dissemination is helpful in the development of new drugs to curtail the spread of a Toxoplasma gondii infection throughout the body.

The work is part of a longstanding collaboration between Bill Sullivan, PhD, Showalter professor in the Department of Pharmacology and Toxicology, and Ronald Wek, PhD, Showalter professor in the Department of Biochemistry and Molecular Biology.

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Traditional Chinese medicine could help treat COVID-19

Chinese doctors took this approach with SARS in 2003, and are hoping it could work again

Vivian Su

Over the last couple of months, COVID-19 (SARS-CoV-2) has spread from China to the rest of the world at an unprecedented rate. In China, over 85% of COVID-19 patients have undergone Traditional Chinese Medicine (TCM) treatment, which utilizes herbal products and mind and body practices to promote health. While it is difficult to imagine how these mysterious mixtures of herbs may be capable of fighting powerful pathogens, we must remember that plants have unique chemical properties, just like pills and vaccines, that allow them to do so.

In 2015, Tu Youyou received the 2015 Nobel Prize in Medicine for discovering the compound artemisinin, a component of anti-malarial drugs. Instead of being created synthetically in a lab, artemisinin was isolated from the plant *Artemisia annua*, or sweet wormwood, an herb already widely used in TCM. This remarkable discovery showed that there were scientific explanations for how these mystifying TCM remedies healed the body, and that they had true clinical significance.

Because TCM had already been used to combat the SARS-CoV outbreak in 2002 and SARS-CoV and SARS-CoV-2 are very similar, researchers at the Institute of Chinese Medical Sciences and the University of Macau assessed the overall effectiveness of TCM in treating SARS-CoV symptoms by conducting a literature review. By doing so, they hoped to gain a better understanding of how the specific chemical compounds present in TCM herbal formulas can be used to combat the current COVID-19 pandemic.

The researchers started by analyzing clinical research that had been done previously during the SARS-CoV outbreak. Chest X-rays were taken periodically for both a control group receiving only Western treatment and experimental groups receiving both Western

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and TCM treatments. The X-rays for both of the experimental groups showed that the patients' lungs were clearing up faster than those in the control group. Ingredients in various TCM herbal formulas were also found to have effects on coronaviruses.

For example, the active compound glycyrrhizin in licorice root was found to potentially inhibit replication of the SARS virus, as well as ginseng and eucalyptus extracts. Rhubarb and lychee extracts inhibited activity of an enzyme vital to viral reproduction. *Shuang Huang Lian*, an herbal formula prepared from multiple flowers, reduces inflammation by inhibiting cytokines, or signaling proteins that help regulate immune responses.

As of now, the Chinese government has wholeheartedly embraced TCM as an effective treatment for COVID-19. There are currently more than 300 ongoing clinical trials examining the effects of TCM herbal treatments on patients. However, more rigorous scientific research and clinical trials are definitely needed to determine the efficacy of TCM in treating COVID-19.

The current COVID-19 pandemic and the research on TCM has reminded us that no matter how technologically advanced we become, we are still products of nature. When vaccines aren't available or our technology fails us, we should not hesitate to turn over every rock to treat this disease.

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Analysis Finds List Prices for COVID-19 Tests Range from $20 to $850 At Large Hospitals Nationwide

In many cases, the prices exceed what Medicare pays for COVID testing

A new KFF analysis of what large hospitals nationwide charge for out-of-network COVID-19 tests show a wide range of publicly posted prices — from $20 to $850 for a single test. In many cases, the prices exceed what Medicare pays for COVID testing, which is either $51 or $100 depending on the test.

Federal law now requires private insurers, Medicare and Medicaid to cover COVID-19 tests without any cost to the patient and provides funding to support free testing for some people without health insurance, though it does not guarantee access to no-cost tests for the uninsured. Those laws ensure that most people will not have to pay out of pocket for COVID tests, though limits to the federal requirements mean that some people with and without health insurance could receive bills for COVID-19 tests.

The analysis finds:

- ***The median price for a COVID-19 was $127, and about half of hospitals price their tests between $100 and $199. About one in five price their tests at more than $200.***
- ***Some hospitals list a discounted rate for self-pay individuals, which range from $36 to $180. Other hospitals indicate that uninsured or self-pay individuals could receive free or discounted care through their financial assistance programs.***
- ***Prices also vary for COVID-19 antibody tests, which are not used to diagnose active infections, from $35 to $300 at hospitals that list their prices.***

The analysis set out to examine publicly posted prices at the two largest hospitals in each state and the District of Columbia. Although federal law requires hospitals to make COVID-19 prices publicly available on their websites, prices could only be found for 78 of the 102 hospitals examined. The prices reflect what they would charge for out-of-network services. Data on the negotiated rates for in-network services is not available.

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Elusive Metal-Eating Bacteria Predicted Over a Century Ago Discovered in Lab Accident

First bacteria found to use manganese as their source of fuel

Tessa Koumoundouros

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When microbiologist Jared Leadbeater returned to his office for the first time in months after a work trip, he found something strange. A cream-coloured manganese carbonate ($MnCO_3$) compound, coating glassware he'd left soaking in his sink, had turned dark. Something had stolen some of its electrons.

"I thought, 'What is that?'" said Leadbeater, a researcher at the California Institute of Technology (Caltech). The dark substance was a form of manganese oxide - a product that forms when manganese ions lose electrons and undergo a reaction called oxidation.

But something had to be initiating the reaction - an electron thief.

"I started to wonder if long-sought-after microbes might be responsible," Leadbeater explained, "so we systematically performed tests to figure that out."

To check if this was really happening due to a biological process, Leadbeater and his team coated more jars with $MnCO_3$ and sterilised some them using scorching steam ($MnCO_3$ is known to be stable in these conditions).

The manganese compound on those didn't darken (even a year later), but the flasks that hadn't been sterilised did. Therefore, the electron thief had to be something that could be destroyed by hot steam.

So, the researchers cultured what was on the jars. RNA analysis revealed 70 species of bacteria, but with further tests the team managed to rule some out, until just two possible culprits remained.

They were Nitrospirae bacteria which is usually crescent-shaped, and the rod-shaped betaproteobacterium. Relatives of both these bacteria species are known to live in groundwater.

"We isolated [the betaproteobacterium] from disrupted oxides as single colonies... but this species does not oxidise $MnCO_3$ alone. Either the Nitropirae is solely responsible for Mn(II) oxidation or the activity is consortial," the team writes in a new study.

The electron theft may have been a team effort, the team realised. But what was the motive? The researchers had their suspicions.

They used manganese labelled with carbon 13 in some of their cultures and, sure enough, the bacteria incorporated these carbon isotopes into their bodies.

This confirmed the suspect bacteria were autotrophic - are able to produce their own food using a source of energy.

The bacteria were using the energy from the manganese electrons to change CO_2 into usable carbon, like plants use sunlight to turn CO_2 and water into sugars and oxygen during photosynthesis.

This process is called chemosynthesis, and while known to occur using other metals, it's the first time we've seen cells make use of manganese in this way.

"These are the first bacteria found to use manganese as their source of fuel," explained Leadbetter, although such microbes were predicted to exist over a century ago.

Manganese is an essential nutrient for us as well. Our bodies use it for things like processing fats and proteins and bone formation, and we get it from foods such as nuts and teas and leafy greens.

While it's one of the most common elements on our planet's surface, a lot about manganese and its cycle on Earth remains a mystery - including its strange tendency to clog water pipes.

"There is a whole set of environmental engineering literature on drinking-water-distribution systems getting clogged by manganese oxides," said Leadbetter.

"But how and for what reason such material is generated there has remained an enigma. Clearly, many scientists have considered that bacteria using manganese for energy might be responsible, but evidence supporting this idea was not available until now."

Manganese oxide also mysteriously appears as nodules across much of the seafloor, and manganese is involved in many interconnected cycles of elements including carbon, nitrogen, iron, and oxygen.

So, the existence of manganese electron-stealing thieves, like these newly discovered bacteria, could explain a lot.

The researchers say the bacteria's cell doubling times and rates of oxidation would create manganese oxides in amounts equivalent to global reserves in just two years.

Close relatives of these species seem to be present in many places, so their potential to cycle this metal across Earth could be vast.

"This discovery fills a major intellectual gap in our understanding of Earth's elemental cycles, and adds to the diverse ways in which manganese, an abstruse but common transition metal, has shaped the evolution of life on our planet," said Caltech geobiologist Woodward Fischer, who was not involved with the study.

This research was published in *Nature*.

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Immunity to COVID-19 may not last. This threatens a vaccine and herd immunity

How is the world going to go back to the days when we could grab a coffee, see a movie, or attend a concert or footy game with anyone?

Nigel McMillan*

Opinion suggests there are two options: an effective vaccine, or herd immunity via at least 60-80% of people becoming infected. Either one of these options requires that people become immune to SARS-CoV-2, the coronavirus that causes COVID-19.

An important new study released online this week could have a large bearing on how our future looks in 2021 and beyond.

It suggests our immunity to SARS-CoV-2 does not last very long at all — as little as two months for some people. If this is the case, it means a potential vaccine might require regular boosters, and herd immunity might not be viable at all.

Immunity dwindles quickly

Antibodies are an important part of our immune system that mainly work by physically binding to virus particles and stopping them infecting cells. They can attach to infected cells to induce cell death in some cases.

We also have T cells, another part of the immune system that is much better at recognising and killing virus-infected cells. But for COVID-19, antibodies are important in the lungs because T cells aren't good at getting to airways where the virus first invades.

The newly released research, from Katie Doores and her team at Kings College London, looked at how long the antibody response lasted in people who had COVID-19. It has been submitted to a journal but hasn't been peer-reviewed, so it must be treated with some caution.

Of the 65 patients studied, 63 produced antibody responses. The important measurements in the study relate to how good the response is. This is measured in the lab by putting patients' blood serum together with infectious SARS-CoV-2 virus and seeing whether the virus can infect cells in a lab dish. This is called a "neutralisation assay", and here the results were good.

Around 60% of people produced a very potent neutralisation response that stopped virus growing in the lab cells.

Finally, the researchers measured how long the antibody response lasted. This is the most important data. Unfortunately, antibodies levels began falling after day 20 and only 17% of patients retained a potent level at day 57. Some patients completely lost their antibodies after two months.

This suggests our immune response to SARS-CoV-2 may be lost much faster than we might have hoped, and people might thereafter be susceptible to reinfection with the virus.

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One vaccine might not be enough

It therefore follows that COVID-19 vaccines may not be as effective as we hope. The fact antibody levels reduce over time is normal, but this typically happens much more slowly. Antibody responses against the mumps, measles and chickenpox viruses last for more than 50 years. A tetanus vaccination wanes more quickly but still lasts 5-10 years before a booster is needed.

So why is this happening? It comes down to the nature of the SARS-CoV-2 coronavirus itself. The four normal strains of coronaviruses that cause common colds in humans also fail to prompt a long-lasting immune response, with most people losing antibodies completely after 6-12 months. Coronaviruses in general seems to be particularly good at not being well recognised by our immune system. Indeed, a feature of common cold coronaviruses is that people get reinfected by them all the time.

SARS, another coronavirus which caused a pandemic in 2003, seems to produce a slightly longer antibody response, lasting up to three years. It's still a long way short of a lifetime, but it perhaps helps explain why the virus disappeared in 2003.

Herd immunity might be in trouble

So herd immunity may not be the solution some think. This is because if immunity is short-lived, we will be in an ongoing cycle of endless reinfection. For herd immunity to be effective we need a high percentage (perhaps more than 60%) of people to be immune at any one time to disrupt chains of transmission. This can't happen if a lot of reinfection is occurring. The hope is vaccines will give much stronger and longer lasting immune responses to the virus than getting and recovering from COVID-19 itself. Indeed, the first vaccine candidates from Pfizer and Moderna, reported in early July, show very strong immune responses.

However, these studies only reported out to 14 and 57 days, respectively, after vaccinations were completed. They don't tell us whether there is a long-lived response that we would need for a vaccine to be truly protective. Phase 3 trials designed to measure this are due to report in December 2020, so watch this space.

While we wait, we should reflect on the fact that although the results of the Kings College study are in one sense disappointing news, this knowledge adds to the truly remarkable scientific progress we have made in understanding a virus that only emerged in December 2019.

*Program Director, Infectious Diseases and Immunology, Menzies Health Institute, Griffith University

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Cave's Clues Show It's More Than Just Oldest Outhouse in the Americas

Preserved dung in Oregon's Paisley Caves is helping to fill in some mysteries about some of the earliest people on our continent.

By Asher Elbein

Over 14,000 years ago, near a stone fire pit in the cool, dry depths of a cavern in the Pacific Northwest, a group of humans heard a call that nobody can deny: the call of nature.

This wasn't unusual — everybody poops — but unlike the vast majority of deposited droppings, these were preserved in the arid climate of what are today called the Paisley Caves of Oregon. On Wednesday, a paper published in Science Advances confirmed that the droppings are among the oldest known evidence of human presence in North America, which could help settle an argument about when people first arrived in the Americas, as well as crucial clues to how they lived.

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Starting in the 1930s, some archaeologists studying the peopling of the Americas believed that the Clovis culture — a group represented in the archaeological record by distinctive spearheads — were the first humans to arrive in the Americas, around 13,000 years ago. But newer evidence has challenged this idea.

"For the past decade, it's been quite well accepted that pre-Clovis populations were present in America," said Lisa-Marie Shillito, an archaeologist at the University of Newcastle in England and lead author on the study. "Paisley Cave is one of the key case studies for pre-Clovis populations, because it's one of the only sites where we have archaeological material like stone tools in direct association with material that can be dated."

The most famous signs of human occupation at Paisley Caves are preserved dung called coprolites. In 2007, an ongoing excavation of the caves led by Dennis Jenkins of the University of Oregon, a co-author of the new study, found a new set of coprolites at the lowest levels of the dig, and radiocarbon dated them to around 14,000 years old.

According to Vaughn Bryant Jr, a specialist in coprolites at Texas A&M who was not involved in the study, the first round of DNA analysis suggested that the coprolites had been deposited by humans. But some archaeologists argued that the specimens had been left by animals and were accidentally contaminated by later humans.

Contamination is always a possibility with DNA analysis, said Ian Bull, a chemist at the University of Bristol in England and a co-author on the paper. But in 2017, Dr. Shillito's team analyzed the droppings using a technique that looked for organic compounds called lipids. Unlike DNA, the process of identifying lipids doesn't amplify them: the fecal biomarkers are very difficult to accidentally contaminate. The presence of both human DNA and human fecal markers makes it all but certain that the dung belonged to 14,000-year-old squatters.

"This is a really good example of how you can get synergy between multiple lines of analysis," Dr. Bull said. "You see some studies out there that'll just hang everything on one type of analysis, and we absolutely don't believe in that."

But the Paisley Caves aren't just America's oldest-known outhouse. Coprolites can also offer a glimpse into how people lived.

"They're really great not just for looking to see whether people are present, but as nice little packages of information about diet and health," Dr. Shillito said.

The dung found at Paisley Cave suggests a varied diet, not just of large game like mammoths that early Americans are stereotyped as eating. It contains partially digested seed coatings, rodent bones and the outer casings of insects, as well as organic compounds from plants.

Dr. Shillito said that in coprolites, "what you largely find is that maybe they were hunting large animals sometimes, but on a day-to-day basis their diets were a lot more varied and diverse."

The coprolites in Paisley Cave also aren't concentrated in latrines or central rubbish pits, which became common in Europe and Asia around 12,000 years ago, as roving bands began living in more permanent settlements, and thus had to begin managing their waste.

Instead, Dr. Shillito said, the droppings in the cave generally seem to have been left where they lay. While that might seem strange to us, Dr. Shillito said, it makes sense for nomadic people who likely used the cave sporadically.

The team's research is part of a larger project studying the entire assemblage of coprolites laid down in Paisley Caves over thousands of years, in hopes of mapping how diets changed alongside shifts in the climate and environment. Moreover, these fecal remains —

along with others from Texas, New Mexico, and Utah — suggest how quickly the first Americans settled the continent.

As more pre-Clovis sites are found, Dr. Shillito said, so do opportunities for research. "We'll get a more detailed idea of exactly how people were moving around across the continent, and what they were doing in the environment, rather than just thinking about when they got there."

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Beyond antibodies, the immune response to coronavirus is complicated

T-cell-based immunity may offer longer protection, but initial results are confusing.

John Timmer

Ultimately, the only way for societies to return to some semblance of normal in the wake of the current pandemic is to reach a state called herd immunity. This is where a large-enough percentage of the population has acquired immunity to SARS-CoV-2—either through infection or a vaccine—that most people exposed to the virus are already immune to it. This will mean that the infection rate will slow and eventually fizzle out, protecting society as a whole.

Given that this is our ultimate goal, we need to understand how the immune system responds to this virus. Most of what we know is based on a combination of what we know about other coronaviruses that infect humans and the antibody response to SARS-CoV-2. But now, data is coming in on the response of T-cells, and it indicates that their response is more complex: longer-lasting, broadly based, and including an overlap with the response to prior coronavirus infections. What this means for the prospect of long-lasting protection remains unclear.

What we know now

SARS-CoV-2 is one of seven coronaviruses known to infect humans. Some of these, like SARS and MERS, have only made the jump to humans recently. While more lethal than SARS-CoV-2, we are fortunate that they spread among humans less efficiently. These viruses seem to provoke a long-lasting immune response following infections. That's a sharp contrast to the four coronaviruses that circulate widely with humans, causing cold-like symptoms. These viruses induce an immunity that seems to last less than a year.

We don't know much about the immune response to SARS-CoV-2 yet. By tracking the production of antibodies, it's clear that many of those infected do have a robust immune response, but "many" is far from "all"—there's a lot of variability in the level of response. That variability is associated with a large difference in the severity of COVID-19 among patients. One area of concern is that the antibody response to SARS-CoV-2 appears to decline rapidly.

The antibody response, however, is only one part of the immune system's defense against a pathogen. Antibodies typically recognize the proteins that reside on the surface of a virus, since those are the ones that the cells that make antibodies are exposed to. But a second group of cells, called T-cells, have a different way of recognizing pathogens. T-cells rely on a system used by all cells, which takes small pieces of the proteins they are making and presents them on the cell surface. Because of how the system works, it has the potential to recognize more of the proteins made by a virus—not just the ones on its surface.

(Some immune cells that swallow pathogens also put protein fragments on their surface in the same way.)

Once there, any T-cells that recognize these small pieces of protein as foreign can mount a variety of responses, from activating their fellow immune cells to killing the cell that is making foreign proteins. Studying the T-cell response is much more challenging, since it's based on cells, rather than antibodies, which are proteins.

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But such study can be equally critical to understanding long-term immunity.

Studying the Ts

To study the T-cell response, a group of researchers based in Singapore focused on proteins that are either internal to the virus or used only in the cells it infects and thus aren't a major focus of the antibody response. To check the response to these proteins, the researchers made a set of 15-amino-acid-long protein fragments that, collectively, span the entire length of the protein. They then collected blood cells from people who had recovered from COVID-19, those who recovered from the original SARS, and those who have never been exposed to either virus.

These fragments were pooled and mixed with blood cells to determine whether any T-cells within them reacted to them. By narrowing down the pools, the researchers were able to identify the specific fragment—and thus the specific region of the protein it came from—that T-cells were responding to. The response was registered by checking the level of an immune-signaling molecule produced by T-cells.

One of the potentially reassuring findings was that people who had been exposed to the original SARS virus 17 years earlier still had T-cells that responded to fragments of the virus. This was true even though the antibody response to this virus had generally faded after several years. Less surprisingly, the people who had recently had COVID-19 also had T-cells that responded to fragments of the virus's proteins.

But there was a striking feature of the SARS and COVID-19 fragments that the T-cells responded to: many of them were identical. While SARS-CoV-1 and -2 are distinct viruses with different evolutionary histories, many of their proteins remain extremely similar. (That's probably because they continue to perform similar functions, and thus there's evolutionary pressure against changes.) As a result, several of the fragments that were made based on the SARS-CoV-2 proteins happened to be identical in the equivalent protein of SARS-CoV-1. So a T-cell that recognized one of these fragments could recognize both viruses—even though it came from a patient who had been exposed to only one.

Surprise!

That sets the stage for the most surprising result of the study. Participants who had never been exposed to either SARS virus also had some T-cells that recognized pieces of SARS-CoV-2 proteins. This wasn't true for every participant in the unexposed group; only about half of them had these reactive T-cells. But again, it was mostly based on cells that reacted to pieces of protein that were identical between SARS-CoV-2 and viruses that cause the common cold.

Mostly, but not all. There were two exceptions to this—two fragments of protein that didn't look like the cold virus but provoked a response from T-cells of unexposed participants—and the researchers struggle to explain them. Their only suggestion is that some other pathogen happens at random to have a small section of protein that looks like this. There were also differences among the groups regarding which of the three proteins their T-cells recognize, but the significance of these differences are not clear.

What's it all mean?

So, does this mean the common cold can potentially protect some of us from COVID-19? There's no way to know based on these results. Prior exposure to cold-causing coronaviruses seems to induce a response to different proteins than exposure to SARS-CoV-2. And there's no indication that antibodies to the common cold viruses cross-react to SARS-CoV-2. Would a T-cell-based response on its own be enough to ward off the virus? We don't know.

At the same time, the fact that this response is only present in a subset of the people who have never been exposed could potentially account for some of the differences in the severity of COVID-19 symptoms. There's obviously a lot more work to be done here.

The importance of T-cell-based immunity is also critical to understanding the issue of the apparently highly variable antibody response as well as the indications that it may fade out rapidly once the SARS-CoV-2 infection is cleared. This study indicates that T-cell responses are consistent and strong in this small population. The parallel work on SARS patients indicates that this response also lasts much longer than the antibody-based immune response. So, if it's sufficient to provide protection from reinfection, then we might be able to worry less about the erratic antibody response. Again, we don't know yet.

This could also have implications for the development of vaccines, which tend to focus on the production of neutralizing antibodies.

All of which implies that there's an urgent need to better understand the T-cell response to SARS-CoV-2, which is unfortunate, given how challenging studying T-cells is.

Nature, 2020. DOI: 10.1038/s41586-020-2550-z (About DOIs).

https://nyti.ms/2ZLbQ76

A Covid-19 Lesson: Some Seriously Ill Patients Can Be Treated at Home

To ease pressure on hospitals, Northwell Health brought medical workers, oxygen tanks and intravenous equipment into patients' homes. Now Florida is taking cues.

By Roni Caryn Rabin

Joan Murray had been home with Covid-19 for about a week when she ran into trouble. She had a fever of 103 degrees and chills that sent shivers up and down her spine. Her oxygen levels were dropping, and the tightness in her chest felt "as if somebody had bound up my lungs with string."

But the 77-year-old, a retired registered nurse who lives alone in Westbury, N.Y., was adamant that she wanted to fight the illness at home. "As a nurse, maybe I knew too much," she said. "The last place I wanted to be was the hospital."

So the hospital came to her.

Northwell Health, which has cared for thousands of coronavirus patients in its network of facilities in New York State, sent a nurse manager to Ms. Murray's home in May. Covered head to toe in protective gear — gown, gloves, mask, shield and disposable bootees — she spent nearly eight hours doing an assessment.

Ms. Murray was dehydrated and in need of supplemental oxygen. Within hours, she was hooked up to an intravenous line, set up in her bedroom to replenish her fluids. A phlebotomist in an N95 mask came to draw blood, an oxygen machine was delivered to her home, and Ms. Murray was prescribed a powerful blood thinner to prevent clots.

Over the course of the next week, nurses dropped by every day, and a Northwell critical care physician and lung specialist, Dr. Gita Lisker, called daily to talk with Ms. Murray.

"I was always waiting for her call — I would tell her all my troubles, and she would reassure me," Ms. Murray said. "I was like a child at that point, and she was my security blanket."

So-called wraparound home care services were created, on the fly, by Northwell Health to deal with the surge in coronavirus cases that New York experienced this spring. Now this model may help relieve health systems in the Sun Belt and other parts of the United States, where rising numbers of cases are putting extraordinary pressure on hospitals, filling intensive care units and sending providers scrambling to hire extra nurses and secure medical supplies.

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Northwell doctors are already discussing the program with physicians in Miami, where several hospitals have reached capacity. Florida has more than 300,000 Covid-19 cases, and more than 10,000 new cases were identified on Thursday.

The concept of hospital-at-home programs is not new, but they had been used primarily to treat patients with flare-ups of chronic conditions like heart failure.

In response to the coronavirus epidemic, Medicare relaxed the requirements for such care. Now patients are considered homebound if a medical practitioner advises them not to leave the home because of a diagnosis of confirmed or suspected Covid-19 or a condition that makes them more susceptible to contracting the virus.

In those situations, if a doctor says skilled services are needed, a home health agency can provide them under the Medicare Home Health benefit, officials said.

Since the start of the pandemic, some hospitals have switched to at-home services to open up hospital beds for Covid-19 patients or to provide follow-up care after Covid-19 patients are discharged from the hospital.

Northwell's outreach is different because it focuses on acutely ill Covid-19 patients in the community. A team of Northwell specialists uses telehealth to advise doctors and patients in the community with mild or moderate illness.

When necessary, a comprehensive health service sends nurses and equipment into the homes of patients with severe symptoms or underlying medical conditions who might need hospitalization without such close monitoring. Pulmonologists use telemedicine to follow these patients.

During New York's crisis, "80 to 90 percent of the patients who had the virus never went to the hospital," said Dr. Thomas McGinn, Northwell's senior vice president and deputy physician-in-chief, who helped create the program.

Many Covid-19 patients did not need to be hospitalized, while others — including some who would have been admitted — simply refused to go, he said: "Hospitals were becoming this place that scared everybody."

With a shortage of diagnostic tests, many sick patients were afraid that if they didn't already have the virus, they'd catch it at the hospital. And they were put off by the knowledge that they'd be cut off from friends and family, because visitors had been barred from health facilities to prevent further spreading of the virus.

At first, physicians were nervous about managing patients at home, Dr. McGinn and Dr. Lisker said. Since then, experts have learned a lot and have developed evidence-based protocols that rely on educating patients on how to monitor their temperature fluctuations, track their blood oxygen levels using pulse oximeters and report changes to their health care providers.

Pulmonologists, experienced in caring for very sick patients with lung disease, consulted with patients over the phone, Dr. Lisker said.

"I can have a phone conversation with a patient, and after the first two sentences, I can tell if they're going to have respiratory problems," she said. "We're trained to listen."

Any patient in respiratory distress would be hospitalized, she added. But most patients were able to ride out their illnesses at home.

Between April 27 and June 1, Northwell enrolled 182 patients in its home care program. They ranged in age from 24 to 100, and many had underlying chronic conditions like diabetes or obesity, which have been linked to worse outcomes in Covid-19 cases.

Several, like Ms. Murray, were older and lived alone. But they had been carefully screened by their regular doctors; only two eventually needed hospitalization, Dr. Lisker said.

The program also provides care for Covid-19 patients who have been discharged from the hospital but have lingering symptoms that require care. Other hospital systems, like Mount Sinai Health System in New York, have also created post-discharge programs that provide care across several specialties to Covid-19 patients and evaluate the long-term effects of the disease.

Ms. Murray, who has recovered from her illness, said that it was "fortuitous" that the hospital team had intervened when it did, because her condition was deteriorating. "I don't know what I would have done otherwise," she said.

Now Northwell is expanding the program, in preparation for potential uptick in cases in New York. "If there is resurgence in New York, on a dime we can get this up and running in huge numbers, and other cities can do this, too," Dr. Lisker said. "It's a win for the patient and a win for the health system."

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Experimental Vaccine Induces Anti-SARS-CoV-2 Immune Responses in All Participants

Vaccine candidate was generally well tolerated and prompted neutralizing antibody activity in all participants

Dr. Lisa Jackson, of Kaiser Permanente Washington Health Research Institute in Seattle and colleagues conducted a first-in-human Phase 1 clinical trial in healthy adults to evaluate the safety and immunogenicity of an investigational anti-SARS-CoV-2 vaccine called mRNA-1273. According to their report published in the *New England Journal of Medicine*, the vaccine candidate was generally well tolerated and prompted neutralizing antibody activity in all participants. The trial is supported by the NIH/National Institute of Allergy and Infectious Diseases (NIAID).

The mRNA-1273 vaccine candidate, manufactured by Moderna, Inc. of Cambridge, Massachusetts, is designed to induce neutralizing antibodies directed at a portion of SARS-CoV-2's spike protein, which the virus uses to bind to and enter human cells.

In the preliminary report, Dr. Jackson and co-authors detailed the findings from the first 45 participants (18 to 55 years old) enrolled at the study sites in Seattle and at Emory University in Atlanta.

Three groups of 15 participants received two intramuscular injections in March and April 2020 of either 25, 100 or 250 micrograms (mcg) of the mRNA-1273 vaccine.

All the participants received one injection; 42 received both scheduled injections.

Regarding safety, no serious adverse events were reported.

More than half of the participants reported fatigue, headache, chills, myalgia or pain at the injection site.

Systemic adverse events were more common following the second vaccination and in those who received the highest vaccine dose.

Data on side effects and immune responses at various vaccine dosages informed the doses used or planned for use in the Phase 2 and 3 clinical trials of the investigational vaccine.

The interim analysis includes results of tests measuring levels of vaccine-induced neutralizing activity through day 43 after the second injection.

"Two doses of vaccine prompted high levels of neutralizing antibody activity that were above the average values seen in convalescent sera obtained from persons with confirmed COVID-19 disease," the authors said.

"A Phase 2 clinical trial of mRNA-1273 began enrollment in May 2020. Plans are underway to launch a Phase 3 efficacy trial in July 2020."

Lisa A. Jackson *et al*. An mRNA Vaccine against SARS-CoV-2 – Preliminary Report. *New England Journal of Medicine*, published online July 14, 2020; doi: 10.1056/NEJMoa2022483

This article is based on text provided by the NIH/National Institute of Allergy and Infectious Diseases (NIAID).

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K-State study first to show SARS-CoV-2 is not transmitted by mosquitoes

A new study by Kansas State University researchers is the first to confirm that SARS-CoV-2 cannot be transmitted to people by mosquitoes.

Manhattan, Kansas -- Stephen Higgs, associate vice president for research and director of the university's Biosecurity Research Institute, or BRI, together with colleagues from the BRI and the College of Veterinary Medicine had the findings published July 17 by *Scientific Reports*.

The article, "SARS-CoV-2 failure to infect or replicate in mosquitoes: an extreme challenge," details the study's findings, which provide the first experimental investigation on the capacity of SARS-CoV-2, the virus that causes COVID-19 disease, to infect and be transmitted by mosquitoes.

"While the World Health Organization has definitively stated that mosquitoes cannot transmit the virus, our study is the first to provide conclusive data supporting the theory," said Higgs, Peine professor of biosecurity and university distinguished professor of diagnostic medicine and pathobiology.

The study, which was done at the BRI, a biosecurity level-3 facility, ultimately found that the virus is unable to replicate in three common and widely distributed species of mosquitoes -- Aedes aegypti, Aedes albopictus and Culex quinquefasciatus -- and therefore cannot be transmitted to humans.

"I am proud of the work we are doing at K-State to learn as much as we can about this and other dangerous pathogens," said Higgs. "This work was possible because of the unique capabilities of the BRI and the dedicated BRI and institutional staff."

Colleagues involved with the study include Yan-Jang Huang, research assistant professor of diagnostic medicine and pathobiology; Dana Vanlandingham, professor of diagnostic medicine and pathobiology; Ashley Bilyeu and Haelea Sharp, research assistants in diagnostic medicine and pathobiology; and Susan Hettenbach, research assistant at the BRI.

Researchers at the BRI have completed four additional studies on COVID-19 since March and this is the first peer-reviewed publication based on SARS-CoV-2 experiments wholly conducted at K-State.

Research at the Biosecurity Research Institute has been ongoing with other animal pathogens that can be transmitted from animals to people, including Rift Valley fever and Japanese encephalitis, as well as diseases that could devastate America's food supply, such as African swine fever and classical swine fever. The research was in part supported by the National Bio and Agro-Defense Facility Transition Fund provided by the state of Kansas.

"We have remarkable talent and capabilities working within our research and training facility at the BRI," said Peter Dorhout, K-State vice president for research. "The BRI is one of the critical anchor facilities in the North Campus Corridor, which serves as our growing research and development space for private sector and government agency partnerships with K-State."

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Study of Over 1 Million People Finds Intriguing Link Between Iron Levels And Lifespan

A massive new study has found evidence that blood iron levels could play a role in influencing how long you live.

David Nield

It's always important to take longevity studies with a big grain of salt, but the new research is impressive in its breadth, covering genetic information from well over 1 million people across three public databases. It also focused on three key measures of ageing:

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lifespan, years lived free of disease (referred to as healthspan), and making it to an extremely old age (AKA longevity).

Throughout the analysis, 10 key regions of the genome were shown to be related to these measures of long life, as were gene sets linked to how the body metabolises iron.

Put simply, having too much iron in the blood appeared to be linked to an increased risk of dying earlier.

"We are very excited by these findings as they strongly suggest that high levels of iron in the blood reduces our healthy years of life, and keeping these levels in check could prevent age-related damage," says data analyst Paul Timmers, from the University of Edinburgh in the UK.

"We speculate that our findings on iron metabolism might also start to explain why very high levels of iron-rich red meat in the diet has been linked to age-related conditions such as heart disease."

While correlation doesn't necessarily mean causation, the researchers used a statistical technique called Mendelian randomisation to reduce bias and attempt to infer causation in the data.

As the researchers note, genetics are thought to have around a 10 percent influence on lifespan and healthspan, and that can make it difficult to pick out the genes involved from all the other factors involved (like your smoking or drinking habits). With that in mind, one of the advantages of this new study is its sheer size and scope.

Five of the genetic markers the researchers found had not previously been highlighted as significant at the genome-wide level. Some, including APOE and FOXO3, have been singled out in the past as being important to the ageing process and human health.

"It is clear from the association of age-related diseases and the well-known ageing loci APOE and FOXO3 that we are capturing the human ageing process to some extent," write the researchers in their published paper.

While we're still in the early stages for investigating this association with iron metabolism, further down the line we could see the development of drugs designed to lower the levels of iron in the blood - which could potentially add extra years to our lives.

Besides genetics, blood iron is mostly controlled by diet and has already been linked to a number of age-related diseases, including Parkinson's and liver disease. It also affects our body's ability to fight off infection as we get older.

We can add this latest study to the growing evidence that 'iron overload', or not being able to break it down properly, can have an influence on how long we're likely to live, as well as how healthy we're likely to be in our later years.

"Our ultimate aim is to discover how ageing is regulated and find ways to increase health during ageing," says Joris Deelen who studies the biology of ageing at the Max Planck Institute for Biology of Ageing in Germany.

"The 10 regions of the genome we have discovered that are linked to lifespan, healthspan, and longevity are all exciting candidates for further studies."

The research has been published in *Nature Communications*.

 Name _____ Student number _____