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The Brain Can Recall and Reawaken Past Immune Responses

The brain not only helps to regulate immune responses, but also stores and retrieves "memories" of them.

Esther Landhuis *Contributing Writer*

Dogs that habitually hear a bell at chow time become classically conditioned to drool at the mere chime, as the physiologist Ivan Pavlov showed in the 1890s: Their brains learn to associate the bell with food and instruct the salivary glands to respond accordingly.

More than a century later, in a paper published today in *Cell*, the neuroimmunologist Asya Rolls has shown that a similar kind of conditioning extends to immune responses. Using state-of-the-art genetic tools in mice, her team at the Technion in Haifa, Israel, identified brain neurons that became active during experimentally induced inflammation in the abdomen. Later, the researchers showed that restimulating those neurons could trigger the same types of inflammation again.

"This is an outstanding body of work," said Kevin Tracey, a neurosurgeon and president of the Feinstein Institutes for Medical Research in Manhasset, New York. It "establishes that the classic concept of immunological memory can be represented in neurons." Others before Rolls have suggested that the brain could remember and retrieve immune responses, he said, but "she proved it."

Ruslan Medzhitov, an immunologist at the Yale School of Medicine in New Haven, Connecticut, considers the new research "very provocative." But unlike other groundbreaking studies that push boundaries and challenge conventional concepts, he said that this one also evokes "the 'Oh, it makes sense' type of reaction."

Decades of research and everyday experience offer striking examples of the interplay between mind and body. Around the time Pavlov was experimenting with drooling dogs, the American physician John Mackenzie watched one of his patients develop an itchy throat and struggle to breathe upon seeing an artificial rose — suggesting that the perception that pollen was present was enough to provoke her allergy symptoms. In the 1970s, scientists discovered a similar phenomenon while conducting taste-aversion experiments on rats: They repeatedly gave the animals an immunosuppressive drug along with the artificial sweetener saccharin; eventually, they found they could quell the animals' immune activity with saccharin alone. Many of us can recall times when the mere scent of a food that once made us sick could trigger nausea anew.

But the mechanism responsible for these psychosomatic reactions has always been shadowy. Such experiences "cannot be guided by immunological memory as we know it," said Rolls. Rather, it seems that these immune responses start in the brain, she said. "Somehow, there are these thoughts that initiate real physiological processes."

In recent years Rolls' lab has begun to get a handle on how thoughts and emotions could affect physical health. In 2018, she and her co-workers reported that stimulating neurons in the brain's pleasure centers in mice disabled a subset of immune cells that suppress the body's defenses; tumor growth slowed in those animals. In a study published in May, her team found that activating specific nerves in the colon prevented immune cells in the blood from entering the tissue — offering a mechanism for brain control over local inflammation.

Given that these groups of neurons regulated immune activity with such precision, Rolls couldn't imagine that the brain would control a system without knowing its status. "So we wanted to see how the brain represents the state of the immune system," she said.

Her team focused on the insular cortex, a structure deep within the brain that processes pain, emotions and the body's inner physical sensations. "It would make perfect sense that the immune system

would be part of this interoceptive information," Rolls said.

To find out if that was true, the researchers slipped a chemical into the drinking water of laboratory mice to give them a weeklong bout of colitis. The chemical disrupted the inner lining of the colon and triggered a rush of immune cells to the damage, which then harmfully spiraled out of control. A genetic modification in the mice enabled Rolls and her team to fluorescently label neurons active on the day the inflammation peaked, lighting up cells in the insula. They then used a second genetic tool to do something more powerful: They placed a molecular on/off switch onto the activated insula cells.

Then Rolls and her co-workers waited. Several weeks after the colitis subsided and the mice recovered, the researchers used their on/off switch to reactivate the neurons — and triggered a similar inflammatory response in the colon. They saw similar results in mice that had been induced to develop a different inflammatory disease, peritonitis, in the abdominal lining.

The immune responses sparked by neural stimulation "were reminiscent of the original" disease state, Rolls said. The similarities extended to the molecular level: In the mice with induced peritonitis, white blood cells carrying a specific receptor protein became more abundant in the abdominal lining during both the original inflammation and the inflammation evoked later.

The researchers also observed the opposite effect: When they instead inhibited the initial set of activated neurons, the animals' disease symptoms weren't as severe. This suggests that even during chemically induced inflammation, signals from the brain may be helping to determine its severity.

In a set of nerve-mapping experiments, the team determined that the insula neurons that kicked into action during the initial inflammation in fact "have a way to deliver a message all the way to the colon," Rolls said.

In Tracey's view, the new research shows "you can't separate the state of the neuron activity from the state of the immune system activity. It's a two-way street."

In 2002, Tracey and his colleagues broke ground in this area with their discovery that the brain can send anti-inflammatory signals to other parts of the body through the vagus nerve. This line of research has advanced to the point where bioelectronic devices are being developed and studied to control inflammation in rheumatoid arthritis, pulmonary hypertension and other diseases.

Unlike the vagal nerve system, however, the insula neurons in Rolls' mechanism sense the inflammation, remember that immune state and can reactivate it — a behavior that is more like Pavlovian conditioning than a negative feedback response, Medzhitov said. Tracey thinks of it this way: The vagus nerve is like a brake line in a car. Rolls' study shows "there is a driver," he said. "There is someone who decides whether to hit the brake or the gas pedal."

However, as Rolls and her colleagues noted in their paper, they cannot yet say whether the insula neurons' "memory" of the inflammation in some way describes the immune response itself, or if it's instead a record of the sensations from the inflamed body tissues — in effect, the memory of what it felt like to be sick with that inflammation. They also can't rule out that other parts of the brain could be involved in remembering the immune response too. What the study does show is that "this information is encoded even though it may not be consciously experienced," said Medzhitov.

The research could have far-reaching implications. Describing an anatomical pathway that links "your emotional state all the way to the inflammation in the colon," Medzhitov said, "that, to me, is probably the best demonstration available for psychosomatic control."

The new findings also upend the common top-down view of the brain. "Most people tend to think, 'We're so smart, we decide what

to do,' and then we make our body do it," Tracey said. "But that's not how the nervous system works." Instead, the brain receives and synthesizes information about changes in the body — an infection, a fever — and delivers a response.

Rolls' work shows that "the brain is inseparable from the immune system," said Tracey. "I think immunologists and neuroscientists both are going to be excited and surprised."

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Early Trials Underway to Test Mushrooms as COVID Treatment

Early trials are under way to test medicinal mushrooms and Chinese herbs to treat COVID-19 patients with mild to moderate symptoms.

Marcia Frellick

The US Food and Drug Administration (FDA) approved the MACH-19 trials (the acronym for Mushrooms and Chinese Herbs for COVID-19) after researchers applied for approval in April.

The first two phase 1 randomized, double-blind, placebo-controlled trials have begun at UCLA and the University of California San Diego to treat COVID-19 patients quarantining at home with mild to moderate symptoms. A third trial is investigating the use of medicinal mushrooms as an adjuvant to COVID-19 vaccines.

The researchers have also launched a fourth trial testing the mushrooms against placebo as an adjunct to a COVID booster shot. It looks at the effect in people who have comorbidities that would reduce their vaccine response. An article in *JAMA* last week described the trials.

The two mushroom varieties being tested — turkey tail and agarikon — are available as over-the-counter supplements, according to the report. They are a separate class from hallucinogenic or "magic" mushrooms being tested for other uses in medicine.

"They are not even as psychoactive as a cup of tea," Gordon Saxe, MD, PhD, MPH, principal investigator for the MACH-19 trials, told *Medscape Medical News*.

For each of the MACH-19 treatment trials, researchers plan to recruit 66 people who are quarantined at home with mild to moderate COVID-19 symptoms. Participants will be randomly assigned either to receive the mushroom combination, the Chinese herbs, or a placebo for 2 weeks, according to the *JAMA* paper.

D. Craig Hopp, PhD, deputy director of the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH), told *JAMA* in an interview that he was "mildly concerned" about using mushrooms to treat people with active SARS-CoV-2 infection.

"We know that a cytokine storm poses the greatest risk of COVID mortality, not the virus itself," Hopp said. "The danger is that an immune-stimulating agent like mushrooms might supercharge an individual's immune response, leading to a cytokine storm."

Stephen Wilson, PhD, an immunologist who consulted on the trials when he was chief operating officer of the La Jolla Institute for Immunology, says in the *JAMA* article that a cytokine storm is unlikely for these patients because the mushroom components "don't mimic inflammatory cytokines." Wilson is now chief innovations officer at Statera Biopharma.

"We think the mushrooms increase the number of immunologic opportunities to better see and respond to a specific threat. In the doses used, the mushrooms perturb the immune system in a good way but fall far short of driving hyper or sustained inflammation," Wilson said.

Dr Gordon Saxe said the FDA process was extensive and rigorous and FDA investigators also asked about potential cytokine storms before approving the trials. Cytokine storm is not an issue with a healthy response, Saxe pointed out. It's a response that's not

balanced or modulated.

"Mushrooms are immunomodulatory," he said. "In some ways they very specifically enhance immunity. In other ways they calm down overimmunity." Saxe noted that they did a sentinel study for the storm potential "and we didn't see any evidence for it."

"Not a Crazy Concept"

Saxe pointed out that one of the mushrooms in the combo they use — agarikon — was used to treat pulmonary infections 2300 years ago. "Hippocrates, the father of western medicine, used mushrooms," he said. "Penicillin comes from fungi. It's not a crazy concept. Most people who oppose this or are skeptics — to some extent, it's a lack of information."

Saxe explained that there are receptors on human cells that bind specific mushroom polysaccharides. "There's a hand-in-glove fit there," Saxe said, and that's one way mushrooms can modulate immune cell behavior, which could have an effect against SARS-CoV-2.

Daniel Kuritzkes, MD, chief of the Division of Infectious Diseases at *Brigham* and Women's Hospital in Boston, Massachusetts, who was not part of the study, told *Medscape Medical News* said he wasn't surprised the FDA approved moving forward with the trials.

"As long as you can demonstrate that there is a rationale for doing the trial and that you have some safety data or a plan to collect safety data, they are fairly liberal about doing early-phase studies. It would be a much different issue, I think, if they were proposing to do a study for actual licensing or approval of a drug," Kuritzkes said.

As yet unanswered, he noted, is which component of the mushrooms or herbs is having the effect. It will be a challenge, he said, to know from one batch of the compound to the next that you have the same amount of material and that it's going to have the same potency among lots.

Another challenge is how the mushrooms and herbs might interact with other therapies, Kuritzkes said.

He gave the example of St. John's Wort, which has been problematic in HIV treatment. "If someone is on certain HIV medicines and they also are taking St. John's Wort, they basically are causing the liver to eat up the HIV drug and they don't get adequate levels of the drug," he said.

Though there are many challenges ahead, Kuritzkes acknowledged, but added that "this is a great starting point." He, too, pointed out that many traditional medicines were discovered from plants.

"The most famous of these is quinine, which came from cinchona bark that was used to treat malaria." Kuritzkes said. Digitalis, often used to treat heart failure, comes from the fox glove plant, he added.

He said it's important to remember that "people shouldn't be seeking experimental therapies *in place of* proven therapies, they should be thinking of them *in addition to* proven therapies."

A co-author reports an investment in the dietary supplement company Mycomedica Life Sciences, for which he also serves as an unpaid scientific adviser. Another co-author is a medical consultant for Evergreen Herbs and Medical Supplies. Hopp, Saxe, and Wilson have disclosed no relevant financial relationships. Kuritzkes consults for Merck, Gilead, and GlaxoSmithKline.

Marcia Frellick is a freelance journalist based in Chicago. She has previously written for the Chicago Tribune, Science News, and Nurse.com, and was an editor at the Chicago Sun-Times, the Cincinnati Enquirer, and the St. Cloud (Minnesota) Times. Follow her on Twitter at @mfrellick

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Something Big Happened to the Planet a Million Years Ago

Why did glacial cycles intensify a million years ago? Researchers find clues on the bed of the Atlantic Ocean.

Something big happened to the planet about a million years ago. There was a major shift in the response of Earth's climate system to variations in our orbit around the Sun. The shift is called the Mid-Pleistocene Transition.

Before the MPT, cycles between glacial (colder) and interglacial (warmer) periods happened every 41,000 years.

After the MPT, glacial periods became more intense—intense enough to form ice sheets in the Northern Hemisphere that lasted 100,000 years. This gave Earth the regular ice-age cycles that have persisted into human time.

Scientists have long puzzled over what triggered this.

A likely reason would be a phenomenon called Milankovitch cycles—cyclic changes in Earth's orbit and orientation toward the Sun that affect the amount of energy that Earth absorbs.

This, scientists agree, has been the main natural driver of alternating warm and cold periods for millions of years.

However, research has shown that the Milankovitch cycles did not undergo any kind of big change a million years ago, so something else likely was at work.

Coinciding with the MPT, a large system of ocean currents that helps move heat around the globe experienced a severe weakening.

That system, which sends heat north through the Atlantic Ocean, is the Atlantic Meridional Overturning Circulation (AMOC).

Was this slowdown related to the shift in glacial periods? If so, how and why? These have been open questions.

A new paper published on November 8, 2021, in the journal *Proceedings of the National Academy of Sciences* proposes an answer.

The researchers analyzed cores of deep-sea sediments taken in the south and north Atlantic, where ancient deep waters passed by and left chemical clues.

"What we found is the North Atlantic, right before this crash, was acting very differently than the rest of the basin," said lead author Maayan Yehudai, who did the work as a PhD.

student at Columbia University's Lamont-Doherty Earth Observatory.

Prior to that oceanic circulation crash, ice sheets in the Northern Hemisphere began to stick to their bedrock more effectively.

This caused glaciers to grow thicker than they had before.

This in turn led to a greater global cooling than before, and disrupted the Atlantic heat conveyor belt.

This led to both stronger ice ages and the ice-age cycle shift, says Yehudai.

The research supports a long-debated hypothesis that the gradual removal of accumulated slippery continental soils during previous ice ages allowed ice sheets to cling more tightly to the older, harder crystalline bedrock underneath, and grew thicker and more stable.

The findings indicate that this growth and stabilization just before the weakening of the AMOC shaped the global climate.

"Our research addresses one of the biggest questions about the largest climate change we had since the onset of the ice ages," said Yehudai. "It was one of the most substantial climate transitions and we don't fully understand it.

Our discovery pins the origin of this change to the Northern Hemisphere and the ice sheets that evolved there as driving this shift towards the climate patterns we observe today.

This is a very important step toward understanding what caused it and where it came from.

It highlights the importance of the North Atlantic region and ocean circulation for present and future climate change."

Reference: "Evidence for a Northern Hemispheric trigger of the 100,000-y glacial cyclicity" by Maayan Yehudai, Joohee Kim, Leopoldo D. Pena, Maria Jaume-Seguí, Karla P. Knudson, Louise Bolge, Alberto Malinverno, Torsten Bickert and Steven L. Goldstein, 8 November 2021, Proceedings of the National Academy of Sciences.
DOI: 10.1073/pnas.2020260118

The research was led also by Yehudai's advisor, Lamont geochemist Steven Goldstein, along with Lamont graduate student Joohee Kim. Other collaborators included Karla Knudson, Louise Bolge and Alberto Malinverno of Lamont-Doherty; Leo Pena and Maria Jaume-Segui of the University of Barcelona; and Torsten Bickert of the University of Bremen. Yehudai is now at the Max Planck Institute for Chemistry.

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How agriculture gave rise to one of the world's most mysterious language families

Transeurasian languages arose in China 9000 years ago, new study claims

By Michael Price

A tiny grain of millet may have given birth to one of the most mysterious—and widespread—language families on Earth, according to the largest study yet of linguistic, archaeological, and genetic evidence from about a dozen countries across Asia. The Transeurasian languages, sometimes known as Altaic, include the languages of Siberia, Mongolia, Central Asia, and possibly Japan and the Korean Peninsula. The new study suggests the language family arose in northeastern China 9000 years ago, expanding with the spread of agriculture.

"It's convincing," says Peter Bellwood, an archaeologist at Australian National University who wasn't involved with the work. "Languages don't just go wandering off by themselves; they expand because the people who speak those languages spread." Farming, he adds, is a strong reason for such an expansion.

The origins of so-called Transeurasian languages—about 80 at the highest count—are hotly debated. Some linguists believe they sprang from the same source, but others say extensive borrowing between ancient languages explains why certain sounds, terms, and grammatical features are common among many tongues, from Turkish to Tungusic. Some researchers had suggested the family arose about 5000 years ago with nomadic shepherds in Central Asia. Martine Robbeets, an archaeolinguist at the Max Planck Institute for the Science of Human History, has long believed the Transeurasian languages belong to one family. To bring new evidence to the debate, she teamed up with linguists, archaeologists, and geneticists from China, Japan, Russia, and South Korea to build an extensive linguistic family tree for languages across Eurasia. They focused on what Robbeets calls "culture-free" vocabulary, including words for basic items such as "field," "pig," and "house." The team used similarities between such basic terms and known historic shifts in sound to reconstruct an ancestral language, Proto-Transeurasian. Their family tree, which went back approximately 9200 years, suggested a common origin for dozens of words related to the growing and harvesting of a grain known as broomcorn millet. "That tells us that the speakers of Proto-Transeurasian were … farmers probably concentrating on millet," Robbeets says.

Next, archaeologists examined data from 255 sites across Central and Eastern Asia dating from about 8500 to 2000 years ago. Previous research had found fully domesticated millet arose in China's Liao River Valley by at least 6000 years ago. The researchers tracked how similarities between nearby sites in pottery styles, burial styles, and the use of the same domesticated plants clustered together over time. They followed the spread of these "cultural packages" as they moved out of the Liao River Valley and diverged and meshed with other cultures over time. That spread roughly matched the march of the hypothesized Proto-Transeurasian language.

Finally, geneticists analyzed DNA from 23 individuals who lived between 300 and 9000 years ago in what are now Siberia, Mongolia, China, South Korea, Japan, and Taiwan. They used computer algorithms to predict how those individuals were related to one another and to 2000 modern people whose genomes have been uploaded to genetic databases. Taken together, the three strands of evidence suggest a shared common ancestor for modern-day speakers of Japonic, Koreanic, Tungusic, Mongolic, and Turkic languages: farmers living in the Liao River Valley approximately 9000 years ago, the researchers write today in *Nature*.

Over time, ancient farmers got better at growing millet, and their

population expanded, Robbeets says, sending their language out into the world. Eventually, their populations split and merged with other groups across Eurasia, developing distinct languages and cultures, but retaining a still-recognizable linguistic backbone.

Melinda Yang, a geneticist at the University of Richmond who studies the genetic history of ancient East Asian populations, says she'd like more information on how the researchers calculated the relatedness among ancient individuals whose DNA they sampled. Still, she is impressed by the sheer amount of data the team synthesized in the new paper, and says it seems to mostly agree with the existing data from linguistics, archaeology, and ancient DNA. She broadly agrees with "the large brushstrokes" laid out by the study. At the same time, she adds, the very scope of the paper means it will take time for researchers to wrap their heads around the findings. "It's not something you can read in an hour and fully understand."

https://wb.md/30k1v57

Unvaccinated People 20 Times More Likely to Die From COVID: Texas Study

Unvaccinated people were 13 times more likely to test positive for COVID-19 than people who were fully vaccinated

Carolyn Crist

During the month of September, Texans who weren't vaccinated against COVID-19 were 20 times more likely to die from COVID-19 and related complications than those who were fully vaccinated, according to a new study from the Texas Department of State Health Services. The data also showed that unvaccinated people were 13 times more likely to test positive for COVID-19 than people who were fully vaccinated.

"This analysis quantifies what we've known for months," Jennifer Shuford, MD, the state's chief epidemiologist, told *The Dallas Morning News* .

"The COVID-19 vaccines are doing an excellent job of protecting people from getting sick and from dying from COVID-19," she said. "Vaccination remains the best way to keep yourself and the people close to you safe from this deadly disease."

As part of the study, researchers analyzed electronic lab reports, death certificates, and state immunization records, with a particular focus on September when the contagious Delta variant surged across Texas. The research marks the state's first statistical analysis of COVID-19 vaccinations in Texas and the effects, the newspaper reported.

The protective effect of vaccination was most noticeable among younger groups. During September, the risk of COVID-19 death was 23 times higher in unvaccinated people in their 30s and 55 times higher for unvaccinated people in their 40s.

In addition, there were fewer than 10 COVID-19 deaths in September among fully vaccinated people between ages 18-29, as compared with 339 deaths among unvaccinated people in the same age group.

Then, looking at a longer time period — from Jan. 15 to Oct. 1 — the researchers found that unvaccinated people were 45 times more likely to contract COVID-19 than fully vaccinated people. The protective effect of vaccination against infection was strong across all adult age groups but greatest among ages 12-17.

"All authorized COVID-19 vaccines in the United States are highly effective at protecting people from getting sick or severely ill with COVID-19, including those infected with Delta and other known variants," the study authors wrote. "Real world data from Texas clearly shows these benefits."

About 15.6 million people in Texas have been fully vaccinated against COVID-19 in a state of about 29 million residents, according to state data. About 66% of the population has received at least one dose, while 58% is fully vaccinated

Sources:

Texas Department of State Health Services: "COVID-19 Cases and Deaths by Vaccination Status."
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Census.gov.

https://bit.ly/3Hhm56T

This 'Tree of Death' Is So Toxic, You Can't Even Stand Under It When It Rains

The manchineel tree (Hippomane mancinella), sometimes referred to as 'beach apple' or 'poison guava'

Signe Dean

In 1999, radiologist Nicola Strickland went on a holiday to the Caribbean island of Tobago, a tropical paradise complete with idyllic, deserted beaches.

On her first morning there, she went foraging for shells and corals in the white sand, but the holiday quickly took a turn for the worse.

Scattered amongst the coconuts and mangoes on the beach, Strickland and her friend found some sweet-smelling green fruit that looked much like small crabapples.

Both foolishly decided to take a bite. Within moments the pleasantly sweet flavor was overwhelmed by a peppery, burning feeling and an excruciating tightness in the throat that gradually got so bad, the women could barely swallow.

The fruit in question belonged to the manchineel tree (*Hippomane mancinella*), sometimes referred to as 'beach apple' or 'poison guava'. It's native to the tropical parts of southern North America, as well as Central America, the Caribbean, and parts of northern South America.

(Karuna Eberl/Shutterstock)

The plant bears another name in Spanish, *arbol de la muerte*, which literally means "tree of death". According to the Guinness World Records, the manchineel tree is in fact the most dangerous tree in the world.

As explained by the Florida Institute of Food and Agricultural Sciences, all parts of manchineel are extremely poisonous, and "interaction with and ingestion of any part of this tree may be lethal".

Manchineel belongs to the large and diverse *Euphorbia* genus, which also contains the decorative Christmas poinsettia. The tree produces a thick, milky sap, which oozes out of everything – the bark, the leaves, and even the fruit – and can cause severe, burn-like blisters if it comes into contact with skin.

Because phorbol is highly water-soluble, you don't even want to be standing under a manchineel when it's raining – the raindrops carrying the diluted sap can still severely burn your skin. **(arctic_whirlwind/Flickr)**

That's because the sap contains a range of toxins; it's thought that the most serious reactions come from phorbol, an organic compound that belongs to the diterpene family of esters.

Because of these horrifying properties, in some parts of the tree's natural range they are painted with a red cross, a red ring of paint, or even paired with explicit warning signs.

You'd think humans could just remove the trees, but they actually play a valuable role in their local ecosystems – as a large shrub, the manchineel grows into dense thickets that provide excellent windbreaking, and a protection against coastal erosion on Central American beaches.

There have been reports of severe cases of eye inflammation and even temporary blindness caused by the smoke of burning manchineel wood – not to mention the effects of inhaling the stuff.

However, Caribbean carpenters have been using manchineel

wood in furniture for centuries, after carefully cutting it and drying in the sun to neutralize the poisonous sap.

"The real death threat comes from eating its small round fruit," Ella Davies writes for the BBC. "Ingesting the fruit can prove fatal when severe vomiting and diarrhea dehydrate the body to the point of no return."

Fortunately, Strickland and her friend lived to tell the tale, because they only ate a tiny amount of death apple. In 2000, Strickland published a letter in *The British Medical Journal*, describing her symptoms in detail.

It took over eight hours for their pain to slowly subside, as they carefully sipped pina coladas and milk. The toxin went on to drain into the lymph nodes on their necks, providing further agony.

"Recounting our experience to the locals elicited frank horror and incredulity, such was the fruit's poisonous reputation," Strickland wrote. "We found our experience frightening."

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Discovery of first carbon-producing microbes presents biochemical mystery

How and why do deep sea groups of archaea and bacteria make elemental carbon?

By Frances Addison

Deep sea microbes that produce elemental carbon have been discovered by researchers from the US and Germany. While bacteria that degrade elemental carbon have been known for over a century, this is the first time organisms have been found to produce it.

Carbon is present in nature in a wide range of oxidation states. Elemental carbon, which has an oxidation state of zero, typically occurs in one of two forms: as highly ordered crystalline state formed under high temperature and pressure such as diamond, and as amorphous black carbon formed by incomplete combustion of biomaterials. There has previously been no evidence, however, that there are biochemical pathways that produce elemental carbon.

Now, researchers have identified two microbial groups – found near hydrothermal vents in the Gulf of California and deep-sea mud volcanoes in the Mediterranean Sea, respectively – that seem to biosynthesise black carbon. Consisting of anaerobic methane-producing archaea and sulfate-reducing bacteria, they produce a black material with characteristics similar to disordered graphite and amorphous carbon. When the team analysed the material by Raman spectroscopy, they found it to be elemental carbon.

The mysterious black substance found in deep sea microorganism colonies (scale bar 200µm) turned out to be elemental carbon, whereas the amber colour is due to bacterial cytochromes

But the exact mechanism and enzymatic activity involved in producing it remains unclear. The team suggests it may be through a thermodynamically favourable conversion of carbon dioxide and hydrogen into carbon and water.

Why the microorganisms produce elemental carbon also requires further research. Possible answers include that they use it as a scaffolding material during interactions with other organisms or as a means of transferring reductants between symbiotic microbes living within the same group. Alternatively, carbon materials' electric conductivity could mean that the organisms are using them to facilitate electron transfer processes.

References *K D Allen et al, Sci. Adv., 2021, **7**, eabg9739 (DOI: 10.1126/sciadv.abg9739)* ***https://bit.ly/321GLzV***

Non-Opioid Compound Developed That Provides Innovative Pain Relief

Researchers targeted a common sodium ion channel to reverse pain, with positive results that could lead to a non-addictive solution to treat pain.

Researchers at the University of Arizona Health Sciences are closer

to developing a safe and effective non-opioid pain reliever after a study showed that a new compound they created reduces the sensation of pain by regulating a biological channel linked to pain.

Most people experience pain at some point in their lives, and the National Institutes of Health estimates 100 million people in the U.S. suffer from chronic pain. Approximately 21-29% of patients prescribed opioids for chronic pain misuse them and 8-12% of people using an opioid for chronic pain develop an opioid use disorder, according to the National Institute on Drug Abuse. In 2019, nearly 50,000 people in the U.S. died from opioid-involved overdoses.

"Drug discovery for chronic pain is at the forefront of this research, and it's being amplified by the intersection of the COVID-19 pandemic and the opioid epidemic," said Rajesh Khanna, PhD, associate director of the UArizona Health Sciences Comprehensive Pain and Addiction Center and professor of pharmacology in the UArizona College of Medicine – Tucson. "Drug discovery is a very arduous process. Our lab looked at a fundamental mechanism of pain, came up with a way to differentiate it from those before us and found a compound that has the potential as a new non-opioid treatment for pain."

The paper, "Selective targeting of NaV1.7 via inhibition of the CRMP2-Ubc9 interaction reduces pain in rodents," was published today (November 10, 2021) in *Science Translational Medicine*.

The biological mechanism at the heart of the research is NaV1.7, a sodium ion channel that previously was linked to the sensation of pain through genetic studies of people with rare pain disorders.

Nerve cells, or neurons, use electrical currents to send signals to the brain and throughout the body, and sodium ion channels are vital to a cell's ability to generate those electrical currents. When a neuron is stimulated, the NaV1.7 channel opens and allows positively charged sodium ions to cross the cell membrane and enter the previously negatively charged cell. The change in charge across the cell membrane generates an electrical current, which increases the excitability of the neuron and sets in motion a cascade of events that leads to pain.

Because NaV1.7 is a human-validated target for pain, multiple attempts have tried to stop pain by using sodium ion channel inhibitors to block NaV1.7. None have been successful. Dr. Khanna and his team took a different approach – rather than block NaV1.7, they wanted to indirectly regulate it.

Using a compound they designed and dubbed 194, the team successfully regulated NaV1.7 activation in the laboratory using nerve cells from four different species, including humans. In animal models, 194 was effective in reversing pain in six different pain models in both sexes.

Researchers also found that 194 also may promote pain relief by activating the body's endogenous, or naturally occurring, opioid system. Once produced, endogenous opioids activate receptors that produce physiological changes such as pain relief. And 194 did so without causing motor performance issues, depressive behaviors or addiction.

Finally, Dr. Khanna and the team observed a synergistic effect when 194 was combined with morphine and gabapentin. This is a promising sign that 194 could also be used in a dose-reduction strategy for painkillers that have negative side effects, including opioids, while maintaining high levels of pain relief.

The science behind 194

Dr. Khanna's prior research identified a protein, collapsin response mediator protein 2 (CRMP2), and an enzyme, Ubc9, that both play a role in NaV1.7 activation. CRMP2 is a protein that binds to NaV1.7 and transports it to the cell membrane, where sodium ions are then transferred into the cell. Ubc9 is an enzyme that tags CRMP2 with another protein – a small ubiquitin-like modifier

protein – to specifically direct control of NaV1.7.

Building on this knowledge, Dr. Khanna and the team set out to determine if they could directly regulate the activity of NaV1.7 by blocking Ubc9 from interacting with CRMP2. Team members including May Khanna, PhD, associate professor of pharmacology and BIO5 Institute member, Vijay Gokhale, PhD, associate research professor in the BIO5 Institute, and Samantha Perez-Miller, PhD, researcher and scientist in the Department of Pharmacology, examined 50,000 existing small molecules to identify the ones with a structure similar to Ubc9.

They selected less than 50 of the closest matches, which were then tested in Dr. Khanna's laboratory to see if their presence would suppress the influx of sodium through NaV1.7. The findings were promising, so the team set their sights on developing a unique, more effective compound.

The result was 194, which UArizona patented and licensed to startup Regulonix LLC through Tech Launch Arizona, the UArizona office that commercializes inventions stemming from university research. Drs. Khanna and Gokhale founded Regulonix LLC in 2016 to address the growing opioid epidemic by developing new, non-addictive ways to treat pain and commercializing those innovations.

While 194 shows great promise for pain relief, Dr. Khanna and the team have been working with the National Institutes of Health's National Center for Advancing Translational Sciences to optimize the compound. In this case, an NCATS team is primarily focusing on improving 194's half-life – the time it takes for a drug to reduce by half in your body – and its drug-like properties.

It is an important step in optimizing the compound's potential as a pain-relieving drug and advancing to the next stage, where researchers will file for Food and Drug Administration approval to begin clinical trials.

Reference: "Selective targeting of NaV1.7 via inhibition of the CRMP2-Ubc9 interaction reduces pain in rodents" by Song Cai, Aubin Moutal, Jie Yu, Lindsey A. Chew, Jörg Isensee, Reena Chawla, Kimberly Gomez, Shizhen Luo, Yuan Zhou, Aude Chefdeville, Cynthia Madura, Samantha Perez-Miller, Shreya Sai Bellampalli, Angie Dorame, David D. Scott, Liberty François-Moutal, Zhiming Shan, Taylor Woodward, Vijay Gokhale, Andrea G. Hohmann, Todd W. Vanderah, Marcel Patek, May Khanna, Tim Hucho and Rajesh Khanna, 10 November 2021, Science Translational Medicine.
DOI: 10.1126/scitranslmed.abh1314

https://bit.ly/3kVruaz

Global Temperature Reconstruction Over Last 24,000 Years Show Today's Warming "Unprecedented"

The University of Arizona team created maps of global temperatures for each 200-year interval since the last ice age.

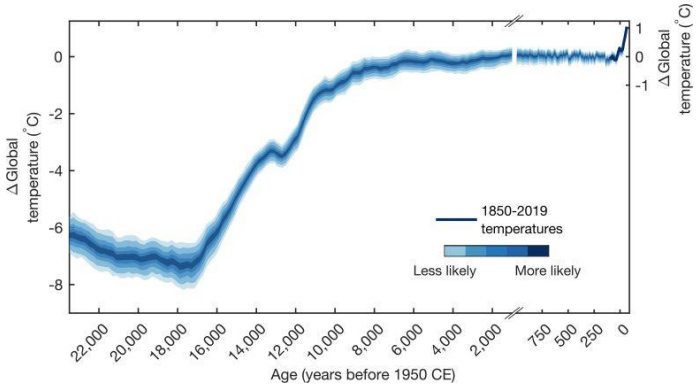
A University of Arizona-led effort to reconstruct Earth's climate since the last ice age, about 24,000 years ago, highlights the main drivers of climate change and how far out of bounds human activity has pushed the climate system. The study, published Wednesday (November 10, 2021) in *Nature*, has three main findings:

- It verifies that the main drivers of climate change since the last ice age are rising greenhouse gas concentrations and the retreat of the ice sheets.
- It suggests a general warming trend over the last 10,000 years, settling a decade-long debate the paleoclimatology community about whether this period trended warmer or cooler.
- The magnitude and rate warming over the last 150 years far surpasses the magnitude and rate of changes over the last 24,000 years.

"This reconstruction suggests that current temperatures are unprecedented in 24,000 years, and also suggests that the speed of human-caused global warming is faster than anything we've seen in that same time," said Jessica Tierney, a UArizona geosciences associate professor and co-author of the study.

Tierney, who heads the lab in which this research was conducted, is also known for her contributions to the Intergovernmental Panel on

Climate Change reports and climate briefings for the U.S. Congress. "The fact that we're today so far out of bounds of what we might consider normal is cause for alarm and should be surprising to everybody," said lead study author Matthew Osman, a geosciences postdoctoral researcher at UArizona.



Global average surface temperature since the last ice age 24,000 years ago. Time is stretched for the past 1000 years to visualize recent changes. **Credit: Matthew Osman**

An online search of "global temperature change since the last ice age" returns a graph of global temperature change over time that was created eight years ago. "Our team's reconstruction improves on that curve by adding a spatial dimension," Tierney said.

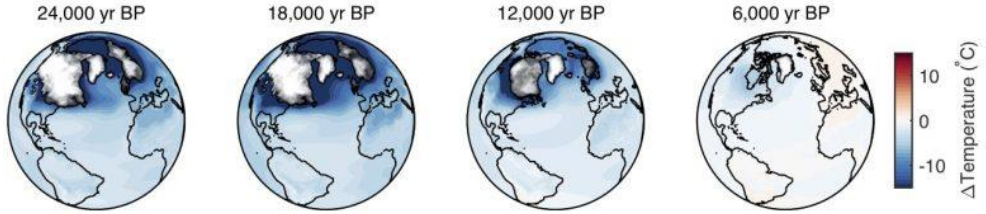
The team created maps of global temperature changes for every 200-year interval going back 24,000 years.

"These maps are really powerful," Osman said. "With them, it's possible for anyone to explore how temperatures have changed across Earth, on a very personal level. For me, being able to visualize the 24,000-year evolution of temperatures at the exact location I'm sitting today, or where I grew up, really helped ingrain a sense of just how severe climate change is today."

There are different methods for reconstructing past temperatures. The team combined two independent datasets – temperature data from marine sediments and computer simulations of climate – to create a more complete picture of the past.

The researchers looked at the chemical signatures of marine sediments to get information about past temperatures. Because temperature changes over time can affect the chemistry of a long-dead animal's shell, paleoclimatologists can use those measurements to estimate temperature in an area. It's not a perfect thermometer, but it's a starting point.

Computer-simulated climate models, on the other hand, provide temperature information based on scientists' best understanding of the physics of the climate system, which also isn't perfect.



These maps show global average surface temperature at different periods in Earth's history going back 24,000 years. The darker the shade of blue, the colder the temperature compared to today. **Credit: Matthew Osman**

The team decided to combine the methods to harness the strengths of each. This is called data assimilation and is also commonly used in weather forecasting.

"To forecast the weather, meteorologists start with a model that reflects current weather, then add in observations such as temperature, pressure, humidity, wind direction, and so on to create an updated forecast," Tierney said.

The team applied this same idea to past climate.

"With this method, we are able to leverage the relative merits of each of these unique datasets to generate observationally constrained, dynamically consistent, and spatially complete reconstructions of past climate change," Osman said.

Now, the team is working on using their method to investigate climate changes even further in the past. "We're excited to apply this approach to ancient climates that were warmer than today,"

Tierney said, “because these times are essentially windows into our future as greenhouse gas emissions rise.”

Reference: “Globally resolved surface temperatures since the Last Glacial Maximum” by Matthew B. Osman, Jessica E. Tierney, Jiang Zhu, Robert Tardif, Gregory J. Hakim, Jonathan King and Christopher J. Poulsen, 10 November 2021, Nature.

DOI: 10.1038/s41586-021-03984-4

The study also included co-authors Jonathan King from the UArizona geosciences department, Jiang Zhu from the Climate and Global Dynamics Laboratory at the National Center for Atmospheric Research, Robert Tardif and Gregory J. Hakim from the University of Washington, and Christopher J. Poulsen from the University of Michigan, Ann Arbor.

https://bit.ly/3osS5wr

Genetic Research Reveals New Clues for the Shared Origins of Irritable Bowel Syndrome and Mental Health Disorders

IBS symptoms may be caused by the same biological processes as conditions such as anxiety

An international study of more than 50,000 people with irritable bowel syndrome (IBS) has revealed that IBS symptoms may be caused by the same biological processes as conditions such as anxiety. The research highlights the close relationship between brain and gut health and paves the way for development of new treatments.

IBS is a common condition world-wide, affecting around 1 in 10 people and causing a wide range of symptoms including abdominal pain, bloating, and bowel dysfunction that can significantly affect people’s lives. Diagnosis is usually made after considering other possible conditions (such as Crohn’s disease or bowel cancer), with clinical tests coming back ‘normal’. The condition often runs in families and is also more common among people who are prone to anxiety. The causes of IBS are not well understood, but an international team of researchers has now identified several genes that provide clues into the origins of IBS.

“Although IBS occurs more frequently in those who are prone to anxiety, we don’t believe that one causes the other – our study shows these conditions have shared genetic origins.” — *Miles Parkes*

The research team, including more than 40 institutions and coordinated by scientists in UK and Spain, looked at genetic data from 40,548 people who suffer from IBS from the UK Biobank and 12,852 from the Bellygenes initiative (a world-wide study aiming to identify genes linked to IBS) and compared them to 433,201 people without IBS (controls), focusing on individuals of European ancestry. The findings were repeated with de-identified data from the genomics company 23andMe Inc., provided by customers who have consented to research, by comparing 205,252 people with IBS to 1,384,055 controls.

The results showed that overall, heritability of IBS (how much your genes influence the likelihood of developing a particular condition) is quite low, indicating the importance of environmental factors such as diet, stress and patterns of behavior that may also be shared in the family environment.

However, 6 genetic differences (influencing the genes NCAM1, CADM2, PHF2/FAM120A, DOCK9, CKAP2/TPTE2P3 and BAG6) were more common in people with IBS than in controls. As IBS symptoms affect the gut and bowel, it would be expected that genes associated with increased risk of IBS would be expressed there – but this is not what the researchers found. Instead, most of the altered genes appear to have more clear-cut roles in the brain and possibly the nerves which supply the gut, rather than the gut itself.

Researchers also looked for overlap between susceptibility to IBS and other physical and mental health conditions. They found that the same genetic make-up that puts people at increased risk of IBS also increases the risk for common mood and anxiety disorders such as anxiety, depression, and neuroticism, as well as insomnia.

However, the researchers stress that this doesn't mean that anxiety causes IBS symptoms or vice versa.

Study co-senior investigator and consultant gastroenterologist Professor Miles Parkes from the University of Cambridge explained: "IBS is a common problem, and its symptoms are real and debilitating. Although IBS occurs more frequently in those who are prone to anxiety, we don't believe that one causes the other – our study shows these conditions have shared genetic origins, with the affected genes possibly leading to physical changes in brain or nerve cells that in turn cause symptoms in the brain and symptoms in the gut."

The study also found that people with both IBS and anxiety were more likely to have been treated frequently with antibiotics during childhood. The study authors hypothesize that repeated use of antibiotics during childhood might increase the risk of IBS (and perhaps anxiety) by altering the 'normal' gut flora (healthy bacteria that normally live in the gut) which in turn influence nerve cell development and mood.

Current treatments for IBS vary widely and include dietary changes, prescription medications targeting the gut or brain, or behavioral interventions. Lead author Chris Eijsbouts from the University of Oxford suggests that discovering genes that contribute to IBS may aid in the development of new treatments in the long term. He said: "Even genetic changes that have only subtle effects on IBS can provide clues about pathways to target therapeutically. Unlike the individual genetic changes themselves, drugs targeting the pathways they tell us about may have a considerable impact on the condition, as we know from other disease areas."

Co-senior investigator Dr Luke Jostins from the University Oxford commented: "We anticipate that future research will build on our discoveries, both by investigating the target genes identified and exploring the shared genetic risk across conditions to improve understanding of the disordered brain-gut interactions which characterize IBS."

"IBS represents a remarkable challenge for genetic studies. These initial findings have been long awaited, and finally tell us this type of research is worth the struggle," added Ikerbasque Professor Mauro D'Amato from CIC bioGUNE, co-senior investigator and coordinator of the Bellygenes initiative.

Reference: "Genome-wide analysis of 53,400 people with irritable bowel syndrome highlights shared genetic pathways with mood and anxiety disorders" by Chris Eijsbouts, Tenghao Zheng, Nicholas A. Kennedy, Ferdinando Bonfiglio, Carl A. Anderson, Loukas Moutsianas, Joanne Holliday, Jingchunzi Shi, Suyash Shringarpure, 23andMe Research Team, Alexandru-Ioan Voda, The Bellygenes Initiative, Gianrico Farrugia, Andre Franke, Matthias Hübenthal, Gonçalo Abecasis, Matthew Zawistowski, Anne Heidi Skogholt, Eivind Ness-Jensen, Kristian Hveem, Tõnu Esko, Maris Teder-Laving, Alexandra Zhernakova, Michael Camilleri, Guy Boeckxstaens, Peter J. Whorwell, Robin Spiller, Gil McVean, Mauro D'Amato, Luke Jostins and Miles Parkes, 5 November 2021, Nature Genetics.

DOI: 10.1038/s41588-021-00950-8

This research received funding and support from National Institute for Health Research (NIHR) Biomedical Research Centres in Cambridge, Oxford, Nottingham and Manchester. Further funding and support was received from the Wellcome Trust, the Li Ka Shing Foundation and the Kennedy Trust for Rheumatology Research in the UK, and the Spanish Ministry of Economy and Competitiveness (Instituto Salud Carlos III), the Health Department of the Basque Government and the Swedish Research Council (Vetenskapsradet).

https://bit.ly/3HlJqV9

Ferris-wheel-size chunk of the moon is orbiting suspiciously close to Earth

The asteroid Kamo`oalewa passes within 9 million miles of Earth every April. It may have once been part of our moon.

By Brandon Specktor

A small asteroid orbiting close to Earth could be a fragment of the moon that snapped off during an ancient impact, according to new research published Nov. 11 in the journal Communications Earth & Environment. If confirmed, that would make the asteroid the first near-Earth object with a known lunar origin — and could help shed

light on the chaotic history of our planet and its pockmarked companion, the researchers said.

The asteroid in question is called Kamo`oalewa — a Hawaiian word that roughly means "the oscillating celestial fragment" — and was discovered in 2016 by astronomers using the PanSTARRS telescope in Hawaii.

Though the object is about 4 million times fainter than what humans can see with the naked eye, every April the rock's orbit brings it close enough to Earth that it becomes briefly visible to our most powerful telescopes. (In this case, "close enough" means about 9 million miles, or 14.4 million kilometers, from Earth — or nearly 40 times the distance between Earth and the moon).

Observations showed that the asteroid measures about the size of a ferris wheel, with a diameter of no more than 190 feet (58 meters).

Because of its near-Earth orbit, Kamo`oalewa fits into a category of celestial objects called quasi-satellites — essentially, objects that orbit the sun, but stay pretty close to Earth. Astronomers have detected plenty of quasi-satellites before, but they have a hard time studying them in detail, given the objects' typically small size and incredible dimness.

The origins of such tiny travelers are hard to pin down — but the authors of the new paper made an attempt to uncover Kamo`oalewa's secrets by studying the faint patterns of reflected light on its surface. Using the Large Binocular Telescope on a mountaintop in southern Arizona, the researchers watched Kamo`oalewa closely during its regular April visits for several years.

They found that the asteroid's light spectrum matched that of lunar samples from NASA's Apollo missions almost perfectly, suggesting the ferris-wheel-size boulder may be a loose piece of lunar debris.

Furthermore, the asteroid's orbit — which is incredibly similar to Earth's — is atypical of the rocks that make their way toward our planet from the outer solar system, the researchers added. It seems more likely that the rock has been near us for a long time.

"It is very unlikely that a garden-variety near-Earth asteroid would spontaneously move into a quasi-satellite orbit like Kamo`oalewa's," study co-author Renu Malhotra, a planetary sciences professor at the University of Arizona, said in a statement.

If Kamo`oalewa is a piece of the smashed-up lunar surface, it's unclear what exactly kicked it loose, or how it ended up in its current orbit; no near-Earth object with a lunar origin has ever been detected before, the researchers wrote. However, after analyzing the rock's orbit, the team found three other near-Earth asteroids with similar enough orbital patterns that they could be considered "companions" to Kamo`oalewa; all of the rocks may have been ejected into space during the same ancient lunar impact.

More research on these quasi-satellites is required to pin down their origins. Luckily, researchers have a few hundred more Aprils to check in with Kamo`oalewa. According to the study authors, the asteroid will remain in its current orbit for another 300 years or so before finally escaping into space.

See you next spring, space neighbor!

https://wb.md/3Hollqn

Real-World Metastatic Breast Cancer Treatments Fall Far Short of Pivotal Trial Outcomes

Comparison between patients treated in the real world compared with the results reported in clinical trials

Kathy D. Miller, MD

Hi, everyone. It's Dr Kathy Miller from Indiana University. I came across an article in *JAMA Oncology* this July that is both sobering and not terribly surprising. I want to make sure you have a chance to see it and think about it as well.

This study looked at a comparison between patients treated in the real world — as in, not part of a clinical trial — compared with the

results reported in clinical trials with the same baseline therapy. This is work from Dr Christopher Booth and his colleagues in Ontario, and they evaluated 795 patients treated with pertuzumab-based regimens for metastatic HER2-positive therapy and 506 patients treated with trastuzumab emtansine (T-DM1), also for metastatic HER2-positive disease.

In the pertuzumab group, median overall survival was 43 months, which was significantly shorter than in the pivotal trial. In the T-DM1 group, median overall survival was 15 months, also significantly shorter.

We should not assume that this means the clinical trial results were wrong, done incorrectly, or somehow fraudulent. The real world is different. Patients tend to be a little bit older and have more previous therapy. There was less fidelity to the rigors of organ function and all of the details that go into patients who are treated in clinical trials.

We've known about the difficulties with selection bias in clinical trials for a long time, and this analysis simply reminds us of the impact of that selection bias, intentional and unintentional, and how the results from those clinical trials compare when we move into the much broader population. It also means that analyses like these will continue to be important.

One of the things that the pandemic may allow us to do is think about doing clinical trials in more of a real-world setting with less rigid selection criteria, more flexibility, and focused on those key end points of overall survival. If we are able to do that, the results might not fall so far when they go from the rarefied air of clinical trials into the clinic patients whom we see every day. Take a look at this article in *JAMA Oncology*. It's a fascinating and sobering read.

Kathy D. Miller, MD, is associate director of clinical research and co-director of the breast cancer program at the Melvin and Bren Simon Cancer Center at Indiana University. Her career has combined both laboratory and clinical research in breast cancer.

https://wb.md/3caLHUR

Substantial Declines in Mortality for Most Cancers

Mortality from cancer has dropped substantially in the United States over the past five decades, according to a new analysis.

Pam Harrison

Researchers found that rates for all cancers combined declined by 27% overall between 1971 and 2019 and decreased significantly for 12 of the 15 top cancer sites analyzed.

The data revealed even greater mortality declines for certain cancers in particular years. For example, mortality from lung cancer was 44% lower in 2019 compared to its peak rate in 1993, whereas it was only 13% lower compared to morality rates in 1971.

"The cancer mortality rate has reduced considerably since 1971 overall and for most cancer sites because of improvements in prevention, early detection, and treatment," lead author Ahmedin Jemal, DVM, PhD, American Cancer Society, Kennesaw, Georgia, and colleagues write.

Advances in surgery, radiotherapy, chemotherapy, precision medicine, and combinations therapies over the past five decades have contributed to these significant declines in mortality, Jemal and colleagues explained. The researchers also credit the "expanded investment" in the National Cancer Institute's annual budget following the 1971 National Cancer Act, which increased the budget 25-fold from $227 million in 1971 to $6 billion in 2019.

The report, published online today in *JAMA Oncology*, analyzed mortality rates for all cancers as well as the top 15 sites using the National Center for Health Statistics.

The researchers found that, overall, deaths declined significantly for all cancers over the study period. Some of the biggest headway since 1971 occurred for stomach and cervical cancers — with 72% and 69% lower mortality rates, respectively — as well as colorectal cancer (56%), oral cavity and pharynx cancer (43%), and ovarian

cancer (41%). Mortality rates of female breast cancer and prostate cancer also dropped considerably — both by 39%.

"The decline in mortality for female breast, cervical, colorectal, and prostate cancer in part reflects increased detection (and removal) of premalignant lesions and early-stage cancers," Jemal and colleagues noted.

Data suggest that screening likely explains about half of the observed decline in mortality from colorectal cancer between 1975 and 2002. A 2019 study also found that the use of adjuvant chemotherapy was responsible for 63% of the decline in mortality from female breast cancer between 2000 and 2012.

In addition, the authors note, "the decline in lung, oral cavity and bladder cancers largely reflects reductions in smoking because of enhanced public awareness of the health consequences, implementation of increased cigarette excise taxes, and comprehensive smoke-free laws."

However, mortality did increase in a few categories. For instance, the mortality rate from pancreatic cancer increased by 3% between 1971 and 2019, and by 8% for both esophageal and brain cancers. Mortality rates from cancer were also greater for 29% of the United States counties included in the analysis, mostly those in the south.

The increase in mortality from pancreatic cancer likely reflects the growing rates of obesity in the US, along with no real advances in pancreatic cancer prevention, early detection, or treatment, the authors suggested. In addition, lack of progress in regions of the south may be related to unequal access to improvements in treatment compared with other parts of the country.

"Improving equity through investment in the social determinants of health and implementation research is critical to furthering the national cancer-control agenda," the authors conclude.

The authors have disclosed no relevant financial relationships.

JAMA Oncology. Published online November 11, 2021. Research Letter

https://bit.ly/3kwcakq

Diet Implicated in Autism-Microbiome Link

The unbalanced gut flora present in some people with autism is not a driver of the condition but rather a consequence of eating behaviors characteristic of the condition, a new study claims.

Ruth Williams

The gut microbiome has been suggested to influence a variety of human health conditions, including autism spectrum disorder. This has led to proposals that altering the microbiome—whether by diet, probiotics, or fecal transfer—might alleviate symptoms. A study published in *Cell* today (November 11), however, turns this idea on its head. Rather than gut microbes influencing autism spectrum disorder (ASD) behavior, the paper argues, it is the eating behavior of people with ASD that drives the make-up of their gut microbiomes. While the findings raise doubt about the potential of microbiome-manipulating treatments for ASD, not everyone is ready to throw the bacteria out with the bathwater.

Kevin Mitchell, a developmental neurobiologist and geneticist at Trinity College Dublin who was not involved in the study, says he has long had doubts about the contribution of gut microbes to ASD, so when he read the *Cell* study, he punched the air “because it basically confirms my expectations of what was going on.” Namely, that the microbiome has far less influence on ASD symptoms than the extensive literature would have one believe.

Although some patients with ASD have gastrointestinal issues and unbalanced gut microbes, or dysbiosis, the evidence that this contributes to ASD symptoms is unconvincing, says study coauthor Chloe Yap, a clinician scientist in the lab of neurogeneticist Jake Gratten at the Mater Research Institute, University of Queensland. For example, animal studies showing that the transference of certain microbes into mice can alleviate ASD-like behaviours are hard to interpret, says Yap, because “rodents don’t get autism.”

"There are things we can measure [in animals] that people claim relate to autism in some way," says Mitchell, "but the evidence base for that is very thin." As for studies and trials in humans, in Yap's view, they have generally been "small and underpowered and . . . the results are actually pretty inconsistent."

To clarify the issue, Yap, Gratten, and their colleagues went back to basics in a sense, asking if there is any link between gut microbial profiles and various clinical measures in ASD. The team used state-of-the-art DNA sequencing to catalogue the presence, proportions, and diversity of microbial species in stool samples from 247 children, 99 with and 148 without an autism diagnosis. They also "had access to really very deep data that many other studies haven't had access to," says Gratten, "including clinical data, data on diet, and also genetic data, and that meant we could really build up a very comprehensive view around factors that might influence the microbiome."

Armed with this data, says Yap, they were able to ask, "for a given trait, to what extent is the microbiome as a whole associated with that trait?" The overall profiles of the participants' microbiomes turned out to be strongly linked with traits such as age, diet, and stool consistency, says Yap, but the association with an ASD diagnosis itself was tenuous.

Looking specifically at microbiome diversity, the team found a strong positive correlation with a varied diet. Importantly, this link existed regardless of ASD diagnosis, although ASD-diagnosed kids were more likely to have a restricted and poor-quality diet than those without a diagnosis. The team also found that this diet seemed to be driven by certain traits associated with ASD including restricted, repetitive behaviors and sensory sensitivity.

This "makes sense," says Yap, "because if you have things that you like doing over and over again, then maybe that also relates to food, and you like eating the same thing over and over again." Similarly, for sensory sensitivity, she says, a child "might not like the sound of [a certain food] when they crunch it, or the feel of it in their mouth."

Altogether, the authors say, the findings support a model whereby ASD-associated repetitive behavior and sensory sensitivity lead to limited diet diversity and a consequently limited bacterial diversity in the gut.

"It's the reduced dietary diversity which is driving changes in the microbiome and not the other way around," says Gratten.

Jane Foster of McMaster University in Ontario, who studies, among other things, gut-brain interactions in neurodevelopment and was not part of the research team, takes a different view. "Their suggestion that low diet diversity might drive low microbiome diversity is completely valid, but that doesn't [mean] that the microbiome doesn't influence brain development in those kids," she argues. Indeed, the authors acknowledge that they cannot rule out the possibility that the microbiome, influenced by diet, might in turn affect behavior.

Foster adds that, "the design, the analytics, the approach [of the study] is top notch," and says she agrees with its central finding. However, the authors' conclusion was "a little more skeptical than the position I would have taken," she says.

Because some potentially positive outcomes have been observed in trials, Foster says, the possibility of microbial manipulation therapies needn't be given up entirely. Instead, what's necessary, she says, is a better understanding of which kids, if any, are most likely to benefit from a microbiome intervention.

Ultimately, Foster says, the authors "have provided the framework for additional investigators to go beyond their observations," and their model "is a suggestion to be tested."

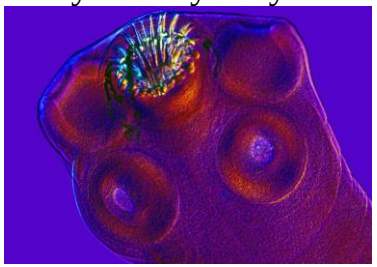
https://bit.ly/3oltiKI

Tapeworms found in man's brain years after he ate feces-tainted food

Neurocysticercosis and a most disturbing way to get tapeworms in your brain.

Beth Mole - 11/12/2021, 7:07 AM

On a night that seemed like any other, a perfectly healthy 38-year-old man in Massachusetts fell from his bed amid a violent seizure at 4 am. The commotion woke his wife, who found her husband on the floor, shaking and "speaking gibberish." He was rushed to Massachusetts General Hospital.



Enlarge / ***Head of pork tapeworm.*** Getty | Michael J Klein

There, doctors witnessed the man have a two-minute-long tonic-clonic (grand mal) seizure, in which he lost consciousness and his muscles aggressively contracted. Doctors began the painstaking process of trying to piece together what was wrong by performing a battery of tests and interviewing his family.

By nearly every account, the man was in very good health. He had no history of seizures or of any cardiovascular, respiratory, gastrointestinal, genitourinary, or neurologic disorders. His toxicology screens were clear. He took no medications, prescribed or over-the-counter. He didn't smoke and rarely drank. There was no evidence that anything had happened to him recently that would provoke a seizure; the man had spent the previous day with his children, then he had dinner with his brother, who reported nothing out of the ordinary. The only initial hint of the diagnosis to come was that the man had immigrated to Boston from a rural area of Guatemala about 20 years earlier.

But when doctors performed a CT (computed tomography) scan of his head, they quickly narrowed the possibilities. The scan revealed three calcified lesions in his brain, and doctors homed in on the diagnosis of neurocysticercosis. In other words, larval cysts from a pork tapeworm had migrated to his head years ago and nestled into various parts of his brain. The doctors documented their work on the man's illness in a case study published on Thursday, November 11, in The New England Journal of Medicine.

Gut to brain

Learning about the path to neurocysticercosis is not for the weak of stomach; it's a cruddy calamity as nauseating as it is dangerous. The pork tapeworms, *Taenia solium*, typically tuck into human intestines, where they can grow to a shocking length of two to eight meters. The worm's victims, meanwhile, expel parasitic eggs in their feces. If that egg-laden excrement makes its way into an environment with pigs, the pigs can carry out the worm's life cycle by ingesting the eggs.

In the pig's stomach, gastric acid prompts the eggs to lose their protective coating and hatch into larval cysts, called oncospheres. These can penetrate the intestinal wall and take a ride through the pig's body via the circulatory system. They eventually burrow into the pig's muscles and lie in wait as cysticerci—which are typically not a bother for the pig.

But if a human ends up eating undercooked pork containing those larval cysts, the life cycle continues. In a human gastrointestinal tract, the worm emerges from its cystic form and sinks its hooks and four suckers into the human's upper intestines. There, it can happily slurp away for years, growing its ribbon-like body meters long and shedding more eggs. And the life cycle begins again.

Things go sideways, however, when a human—not a pig—ends up eating the worm's eggs. This can happen in a nauseating scenario in which someone infected with a tapeworm happens to have bad hygiene and also prepares food. In other words, a poopy-handed tapeworm victim contaminates a meal. In this case, the eggs hatch

in the human's stomach, as they do in pigs. The larval cysts can end up in a human's muscles (cysticercosis), but they can also migrate to the eyes and brain (neurocysticercosis). This is a dead end for the worm and can develop into a big problem for the human.

Worms on the brain

In a human brain, the cyst goes through four stages. At first, it quietly lies in wait as a viable worm, provoking little to no immune responses—and thus no symptoms. This stage can last many years. But over time, the cyst degenerates and leaks fluid that alerts the immune system that a parasite is present, prompting a strong response. The cyst degenerates further and forms a nodule in the brain. Finally, the nodule becomes a calcified granuloma. Seizures have been associated with the inflammatory responses linked to the late-stage calcification.

Neurocysticercosis is the most common parasitic infection of the human brain and can cause headaches, confusion, balance problems, seizures, and even death. The disease is also the most common cause of acquired epilepsy. It's endemic in areas of Asia and Central America.

Given all of the medical information on the 38-year-old patient and his history of living in rural Guatemala, the doctors determined that neurocysticercosis was the most likely cause of his abrupt seizure and brain lesions.

After he was initially brought to the hospital, he was given multiple doses of an antiseizure medication, intubated, and transferred to the neurosciences intensive care unit. When he was stabilized and extubated, doctors began a treatment of two antiparasitic drugs and an anti-inflammatory drug, and they continued use of antiseizure medication. He was released from the hospital five days later with no remaining neurological symptoms or seizures.

Doctors followed up with him over the course of three years. Months after treatment, additional brain scans found that the swelling around the largest lesion in his right frontal lobe had gone down. He also remained seizure-free, though he was still taking his antiseizure medication. Because the calcified lesions will stay with him, it's unclear if or when he can stop taking the medication.

https://bit.ly/3qwaKds

In an Astonishing Feat, a New Drug Reversed Paralysis in Mice With Spinal Cord Injury

New form of drug promotes regeneration of cells and reversed paralysis in mice with spinal injuries, allowing them to walk again within weeks of treatment

Issam Ahmed, AFP

US scientists have developed a new form of drug that promotes the regeneration of cells and reversed paralysis in mice with spinal injuries, allowing them to walk again within four weeks of treatment.

The research was published in the journal *Science* on Thursday, and the team of Northwestern University scientists behind it hope to approach the Food and Drug Administration (FDA) as early as next year to propose human trials.

"The aim of our research was to develop a translatable therapy that could be brought to the clinic to prevent individuals from becoming paralyzed after major trauma or disease," Northwestern's Samuel Stupp, who led the study, told AFP.

Curing paralysis is a longstanding goal of medicine, and other cutting-edge research in the field includes experimental treatments using stem cells to make new neurons (nerve cells), gene therapy that tells the body to produce certain proteins to aid nerve repair, or injecting proteins.

Stupp's team, on the other hand, used nanofibers to mimic the architecture of the extracellular matrix – a naturally occurring network of molecules surrounding tissue that is responsible for supporting cells.

Each fiber is about 10,000 times narrower than a human hair, and they are made up of hundreds of thousands of bioactive molecules called peptides that transmit signals to promote nerve regeneration.

The therapy was injected as a gel into tissue surrounding the spinal cords of lab mice 24 hours after an incision was made in their spines.

The team decided to wait a day because humans who receive devastating spinal injuries from car accidents, gunshots and so on also experience delays in getting treatment. Four weeks later, mice who received the treatment regained their ability to walk almost as well as before the injury. Those left untreated did not.

The mice were then put down to examine the impacts of the therapy on the cellular level, and the team found dramatic improvements to the spinal cords. The severed extensions of neurons called axons regenerated, and scar tissue that can act as a physical barrier to regeneration was significantly diminished.

What's more, an insulating layer of axons called myelin that is important in transmitting electric signals had reformed, blood vessels that deliver nutrients to injured cells had formed, and more motor neurons survived.

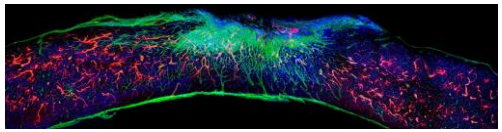
'Dancing' molecules

A key discovery by the team was that creating a certain mutation in the molecules intensified their collective motion and heightened their efficacy. This is because receptors in neurons are naturally in constant motion, Stupp explained, and increasing the motion of the therapeutic molecules within the nanofibers helps connect them more effectively with their moving targets.

The researchers in fact tested two versions of the treatment – one with the mutation and one without – and found that mice that received the modified version regained more function.

The gel developed by the scientists is the first of its kind, but could usher in a new generation of medicines known as "supramolecular drugs," because the therapy is an assembly of many molecules rather than a single molecule, said Stupp.

According to the team, it is safe because the materials biodegrade within a matter of weeks and become nutrients for cells.



Above: Regenerating blood vessels (red) grow through spinal cord cells (blue) cellular support (green) tissues, 12 weeks after injury. **(Samuel I. Stupp Laboratory/Northwestern University)**

Stupp said he hopes to rapidly move direct to human studies next without the need for further animal testing, such as on primates.

This is because the nervous system is highly similar across mammal species and "there is nothing out there to help spinal cord injury patients, and this is a huge human problem," he said.

According to official statistics, nearly 300,000 people are living with a spinal cord injury in the United States alone. Their lifespan is shorter than people without spinal injury, and has not improved since the 1980s.

"The challenge will be how the FDA will look at these therapies because they're completely new," predicted Stupp.

https://bit.ly/3oqZHQa

Biomarker Discovered That Predicts Type 2 Diabetes Many Years Before Diagnosis

A large study led by Lund University in Sweden has identified a protein in the blood that could predict type 2 diabetes up to nineteen years before the onset of the disease. The study is published in Nature Communications.

Type 2 diabetes is a growing global epidemic, with 6% of the world population suffering from the disease. However, the risk of developing type 2 diabetes can be greatly reduced by weight control, eating well and exercising before the actual manifestation of the disease. Early detection of type 2 diabetes risk before symptoms

could help minimize health complications related to diabetes.

"We found that higher levels of the protein follistatin circulating in the blood predict type 2 diabetes up to nineteen years before the onset of the disease, regardless of other known risk factors, such as age, body mass index (BMI), fasting blood glucose levels, diet or physical activity," says Dr. Yang De Marinis, associate professor at Lund University and lead author of the study.

This discovery is based on studies that followed 5,318 people over the course of 4 to 19 years in two different locations in Sweden and Finland.

Follistatin is a protein that is mainly secreted from the liver and involved in the regulation of metabolism. The study investigated what happens to the body when follistatin in the blood circulation becomes too high. Using clinical data from the German Tübingen Diabetes Family Study and cell biology investigation, the researchers found that follistatin promotes fat breakdown from the adipose tissue, resulting in increased lipid accumulation in the liver. This in turn increases the risk of nonalcoholic fatty liver disease and type 2 diabetes.

To find out what regulates blood follistatin levels, the researchers performed genome-wide association study (GWAS) on 5,124 people from Sweden, the UK and Italy, and revealed that follistatin levels are genetically regulated by glucokinase regulatory protein (GCKR), which impact on several metabolic traits.

"This study shows that follistatin has the potential to become an important biomarker to predict future type 2 diabetes, and it also brings us one step closer to the understanding of the mechanisms behind the disease," says Yang De Marinis.

The next step is to put the results into clinical use. An AI-based diagnostic tool using follistatin as a biomarker for type 2 diabetes is being developed through the biotech startup Lundoch Diagnostics, where Yang De Marinis is CEO. This will commercialize the tool under patent applications in global markets. The tool aims to provide a simple blood test, where results from a protein biomarker panel can be imputed in an AI-driven algorithm, and ultimately give patients a risk score to assess their risk of future type 2 diabetes.

"This discovery holds the opportunity of instituting measures to prevent type 2 diabetes from becoming established. Our research will continue towards this goal," concludes Yang De Marinis.

Reference: "Elevated circulating follistatin associates with an increased risk of type 2 diabetes" by Chuanyan Wu, Yan Borné, Rui Gao, Maykel López Rodriguez, William C. Roell, Jonathan M. Wilson, Ajit Regmi, Cheng Luan, Dina Mansour Aly, Andreas Peter, Jürgen Machann, Harald Staiger, Andreas Fritsche, Andreas L. Birkenfeld, Rongya Tao, Robert Wagner, Mickaël Canouil, Mun-Gwan Hong, Jochen M. Schwenk, Emma Ahlqvist, Minna U. Kaikkonen, Peter Nilsson, Angela C. Shore, Faisel Khan, Andrea Natali, Olle Melander, Marju Orho-Melander, Jan Nilsson, Hans-Ulrich Häring, Erik Renström, Claes B. Wollheim, Gunnar Engström, Jianping Weng, Ewan R. Pearson, Paul W. Franks, Morris F. White, Kevin L. Duffin, Allan Arthur Vaag, Markku Laakso, Norbert Stefan, Leif Groop and Yang De Marinis, 10 November 2021, Nature Communications.
DOI: 10.1038/s41467-021-26536-w

https://wb.md/3nbGm66

Multivitamins, but Not Cocoa, Tied to Slowed Brain Aging

Taking a daily multivitamin for 3 years is associated with a 60% slowing of cognitive aging, with the effects especially pronounced in patients with cardiovascular (CVD) disease, new research suggests.

Pauline Anderson

Taking a daily multivitamin for 3 years is associated with a 60% slowing of cognitive aging, with the effects especially pronounced in patients with cardiovascular (CVD) disease, new research suggests.

In addition to testing the effect of a daily multivitamin on cognition the COSMOS-Mind study also examined the effect of cocoa flavanols, but showed no beneficial effect.

The findings "may have important public health implications, particularly for brain health, given the accessibility of multivitamins and minerals, and their low cost and safety," said study investigator Laura D. Baker, PhD, professor, Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina. The findings were presented at the 14th Clinical Trials on Alzheimer's Disease (CTAD) conference.

Placebo-Controlled Study

The study is a substudy of a large parent trial that compared the effects of cocoa extract (500 mg/day cocoa flavanols) and a standard multivitamin-mineral (MVM) to placebo on cardiovascular and cancer outcomes in more than 21,000 older participants.

COSMOS-Mind included 2262 adults aged 65 and over without dementia who underwent cognitive testing at baseline and annually for 3 years. The mean age at baseline was 73 years, and 40.4% were men. Most participants (88.7%) were non-Hispanic white and almost half (49.2%) had some post-college education.

All study groups were balanced with respect to demographics, CVD history, diabetes, depression, smoking status, alcohol intake, chocolate intake and prior multivitamin use. Baseline cognitive scores were also similar between study groups. Researchers had complete data on 77% of study participants.

The primary endpoint was the effect of cocoa extract (CE) vs placebo on Global Cognitive Function composite score. The secondary outcome was the effect of MVM vs placebo on global cognitive function.

Additional outcomes included the impact of supplements on executive function and memory and the treatment effects for prespecified subgroups, including subjects with a history of CVD.

Using a graph of change over time, Baker showed there was no effect of cocoa on global cognitive function (effect: 0.03; 95% CI, -0.02 to 0.08; *P* = .28). "We see the to-be-expected practice effects, but there's no separation between the active and placebo groups," she said.

It was a different story for MVM. Here, there was the same practice effect, but the graph showed the lines separated for global cognitive function composite score (effect: 0.07; 95% CI, 0.02 - 0.12; *P* = .007).

"We see a positive effect of multivitamins for the active group relative to placebo, peaking at 2 years and then remaining stable over time," said Baker.

There were similar findings with MVM for the memory composite score, and the executive function composite score. "We have significance in all three, where the two lines do separate over and above the practice effects," said Baker**.**

New Evidence

Investigators found a baseline history of CVD, including transient ischemic attack, congestive heart failure, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and stent, but not myocardial infarction or stroke as these were excluded in the parent trial because they affected the response to multivitamins.

As expected, those with CVD had lower cognitive scores at baseline. "But after an initial bump due to practice effect, at year 1, the cardiovascular disease history folks continue to benefit from multivitamins, whereas those who got placebo multivitamins continue to decline over time," said Baker.

Based on information from a baseline scatter plot of cognitive function scores by age, the study's modeling estimated the multivitamin treatment effect had a positive benefit of .028 standard deviations (SD) per year.

"Daily multivitamin-mineral supplementation appears to slow cognitive aging by 60% or by 1.8 years," Baker added.

To date, the effect of MVM supplementation on cognition has been

tested in only one large randomized clinical trial — the Physicians Health Study II. That study did not show an effect, but included only older male physicians — and cognitive testing began 2.5 years after randomization, said Baker.

"Our study provides new evidence that daily multivitamin supplementation may benefit cognitive function in older women and men, and the multivitamin effects may be more pronounced in participants with cardiovascular disease."

For effects of multivitamins on Alzheimer's disease prevalence and progression, "stay tuned," Baker concluded.

Following the presentation, session co-chair Suzanne Schindler, MD, PhD, instructor, Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, said she and her colleagues "always check vitamin B12 levels" in patients with memory and cognitive difficulties and wondered if study subjects with a low level or deficiency of vitamin B12 benefited from the intervention.

"We are asking ourselves that as well," said Baker.

"Some of this is a work in progress," Baker added. "We still need to look at that more in-depth to understand whether it might be a mechanism for improvement. I think the results are still out on that topic."

The study received support from the NIH/NIA. Pfizer Consumer Healthcare (now GSK Consumer Healthcare) provided study pills and packaging. Baker has disclosed no relevant financial relationships.

14th Clinical Trials on Alzheimer's Disease (CTAD) conference: Oral Communications (OC) #4. Presented November 10, 2021.

https://bit.ly/3Fismxo

Unexpected Discovery: Vascular Defects Appear to Underlie the Progression of Parkinson's Disease

Researchers have identified what appears to be a significant vascular defect in patients with moderately severe Parkinson's disease

In an unexpected discovery, Georgetown University Medical Center researchers have identified what appears to be a significant vascular defect in patients with moderately severe Parkinson's disease. The finding could help explain an earlier outcome of the same study, in which the drug nilotinib was able to halt motor and non-motor (cognition and quality of life) decline in the long term.

The researchers say their finding, detailed in a study published today (November 12, 2021) in *Neurology Genetics*, suggests that blood vessel walls called the blood brain barrier, which normally act as a crucial filter to protect the brain against toxins as well as allow passage of nutrients to nourish it, doesn't work correctly in some Parkinson's patients: it prohibits toxins from leaving the brain and inhibits nutrients such as glucose from entering. Perhaps even more damaging, the dysfunctional barrier allows inflammatory cells and molecules from the body to enter and damage the brain.

The research, the first longitudinal study to use such advanced genomics, now provides investigators with a new target for therapeutic intervention in Parkinson's disease, says the study's senior author, Charbel Moussa, MBBS, PhD, director of the Medical Center's Translational Neurotherapeutics Program.

The new discovery comes from the second part of a Phase II clinical trial that featured next generation whole genome sequencing of the cerebrospinal fluid of 75 Parkinson's patients, before and after treatment with a repurposed leukemia drug, nilotinib, or placebo.

This study lasted 27 months; the initial trial was double-blinded and patients were randomized to either placebo, or 150mgs or 300mgs nilotinib for 12 months. The patients had severe Parkinson's disease; all treated with optimal standard of care and many (30%) had also used the most sophisticated treatments possible, such as deep brain stimulation. The second part of the study employed an adaptive design and all participants had a 3-month drug washout

period before re-randomization to either 150mgs or 300mgs for an additional 12 months. After 27 months, nilotinib was found to be safe, and patients who received nilotinib showed a dose-dependent increase of dopamine, the chemical lost as a result of neuronal destruction.

"It appeared nilotinib halted motor and non-motor decline in the patients taking the 300mgs higher dose," says Moussa. The clinical outcomes of this study was published in Movement Disorders in March 2021.

The current part of the study just published, examined the cerebrospinal fluid of patients via epigenomics, which is a systematic analysis of the global state of gene expression, in correlation with continuing clinical outcomes. The new analysis helps explain the clinical findings.

Nilotinib inactivated a protein (DDR1) that was destroying the ability of the blood brain barrier to function properly. When DDR1 was inhibited, normal transport of molecules in and out of the brain filter resumed, and inflammation declined to the point that dopamine, the neurotransmitter depleted by the disease process, was being produced again.

Moussa and his team have long been working on the effects that nilotinib (Tasigna) may have on neurodegeneration, including Alzheimer's and Parkinson's diseases. The drug was approved in 2007 for chronic myelogenous leukemia (CML), but Moussa reasoned that its mechanism of action may help the brain destroy toxins that develop in the brains of patients with neurodegenerative disorders.

"Not only does nilotinib flip on the brain's garbage disposal system to eliminate bad toxic proteins, but it appears to also repair the blood brain barrier to allow this toxic waste to leave the brain and to allow nutrients in," Moussa explains. "Parkinson's disease is generally believed to involve mitochondrial or energy deficits that can be caused by environmental toxins or by toxic protein accumulation; it has never been identified as a vascular disease."

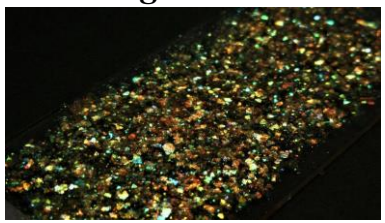
"To our knowledge, this is the first study to show that the body's blood brain barrier potentially offers a target for the treatment for Parkinson's disease," Moussa says. "Much work remains to be done, but just knowing that a patient's brain vascular system is playing a significant role in the progression of the disease is a very promising discovery."

Reference: "CSF MicroRNAs Reveal Impairment of Angiogenesis and Autophagy in Parkinson Disease" by Alan J. Fowler, Jaeil Ahn, Michaeline Hebron, Timothy Chiu, Reem Ayoub, Sanjana Mulki, Habtom Ressom, Yasar Torres-Yaghi, Barbara Wilmarth, Fernando L. Pagan and Charbel Moussa, 12 November 2021, Neurology Genetics.
DOI: 10.1212/NXG.0000000000000633
In addition to Moussa, authors on the report include Alan J Fowler, MS; Jaeil Ahn, PhD; Michaeline Hebron, MS; Timothy Chiu; Reem Ayoub; Sanjana Mulki, MS; Habtom Ressom, PhD; Yasar Torres-Yaghi, MD; Barbara Wilmarth, NP; and Fernando L Pagan, MD.

https://bit.ly/3ceV4TE

Sustainable, Biodegradable, Vegan Glitter That's Just As Sparkly – From Your Fruit Bowl

Sustainable, non-toxic, vegan, and biodegradable glitter from cellulose that's just as sparkly as the original



The photograph is a close-up of the glass slide that has been covered with gold flakes with high lighting contrast and observed at a larger angle. **Credit: Benjamin Drouguet**

Glitter is the bane of every parent and primary school teacher. But beyond its general annoyance factor, it's also made of toxic and unsustainable materials, and contributes to plastic pollution.

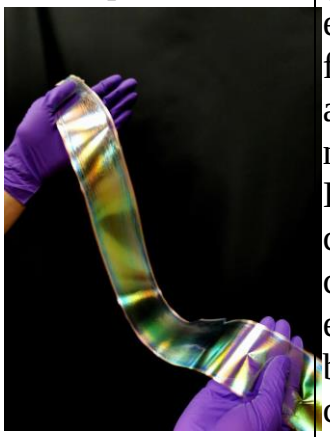
Now, researchers from the University of Cambridge have found a way to make sustainable, non-toxic, vegan, and biodegradable glitter from cellulose – the main building block of cell walls in plants, fruits, and vegetables – and that's just as sparkly as the

original.

The glitter is made from cellulose nanocrystals, which can bend light in such a way to create vivid colors through a process called structural color. The same phenomenon produces some of the brightest colors in nature – such as those of butterfly wings and peacock feathers – and results in hues that do not fade, even after a century.

Using self-assembly techniques that allow the cellulose to produce intensely-colored films, the researchers say their materials could be used to replace the plastic glitter particles and tiny mineral effect pigments which are widely used in cosmetics. In Europe, the cosmetics industry uses about 5,500 tonnes of microplastics every year.

The films of cellulose nanocrystals prepared by the team can be made at scale using roll-to-roll processes like those used to make paper from wood pulp, and this is the first time these materials have been fabricated at industrial scale. The results are reported in the journal *Nature Materials*.



The photograph shows a film of cellulose nanocrystal that has been successfully peeled from its substrate, over a black background. **Credit: Benjamin Drouguet**

"Conventional pigments, like your everyday glitter, are not produced sustainably," said Professor Silvia Vignolini from Cambridge's Yusuf Hamied Department of Chemistry, the paper's senior author. "They get into the soil, the ocean and contribute to an overall level of pollution. Consumers are starting to realize that while glitters are fun, they also have real environmental harms."

For many years, Vignolini's research group has been extracting cellulose from wood pulp and transforming it into shiny, colorful materials, which could be used to replace toxic pigments used in numerous consumer products, such as paints and cosmetics.

"The challenge has been how to control conditions so that we can manage all the physical-chemical interactions simultaneously, from the nanoscale up to several meters, so that we can produce these materials at scale," said first author Benjamin Droguet, also from the Department of Chemistry.

By carefully optimizing the cellulose solution and the coating parameters, the research team was able to fully control the self-assembly process, so that the material could be made on a roll-to-roll machine. Their process is compatible with existing industrial-scale machines. Using commercially available cellulose materials transformed into suitable liquid suspension in just few steps, the team showed continuous deposition and drying of the cellulose-containing suspension on a commercial roll-to-roll machine.

After producing the large-scale cellulose films, the researchers ground them into particles of the size used for making glitters or effect pigments. The resulting particles are biodegradable, plastic-free and non-toxic. The demonstration of the fabrication process on a commercial equipment is an important step towards making the new material available outside the lab.

In addition, the process is far less energy-intensive than conventional methods. When they do not use synthetic polymers, companies often use mica and titanium dioxide combined into an effect pigment. However, titanium dioxide has recently been banned in the EU for food application due to its potential carcinogenic effects, while the extraction of mica often takes place in developing countries that may rely on exploitative practices, including child labor.

"Traditionally, effect pigment minerals have to be heated at temperatures as high as 800°C to form pigment particles. When you consider the quantity of mineral effect pigments that is produced

worldwide, you realise that their use is harmful to the planet," said Droguet.

"We believe this product could revolutionize the cosmetics industry by providing a fully sustainable, biodegradable, and vegan pigment and glitter," said Vignolini.

Although further optimization of the process is still needed, the researchers are hoping to form a spin-out company to make their pigments and glitters commercially available in the coming years.

But will their glitter be as annoying as conventional glitter to anyone who's ever done a craft project with small children?

"It will be just as annoying – but it won't harm the planet and is safe for your little ones," said Vignolini.

Reference: "Large-scale fabrication of structurally coloured cellulose nanocrystal films and effect pigments" by Benjamin E. Droguet, Hsin-Ling Liang, Bruno Frka-Petesic, Richard M. Parker, Michael F. L. De Volder, Jeremy J. Baumberg and Silvia Vignolini, 11 November 2021, Nature Materials. DOI: 10.1038/s41563-021-01135-8

The research was funded in part by the European Research Council and the Engineering and Physical Sciences Research Council (EPSRC).

https://bit.ly/3qCUasv

Major Global Study Reveals Risk of Early Breast Cancer Spreading to Other Parts of the Body

Younger women found to face higher risk.

The risk of early breast cancer spreading to another part of the body ranges from 6% to 22%, according to the first results of a large and detailed global study of metastatic breast cancer presented at the Advanced Breast Cancer Sixth International Consensus Conference (ABC 6).

The study also shows that certain women face a higher risk than others, including women diagnosed with breast cancer at a younger age, those diagnosed with larger tumors at initial diagnosis, and those with specific types of breast cancer, for example those called luminal B.

Around 2.3 million people are diagnosed with breast cancer each year around the world, but this is the first study of its kind to investigate how many of these patients go on to develop advanced breast cancer (ABC). Researchers say the new study sheds light on the extent of ABC, who is most at risk and what treatments are needed.

The research was presented by Dr Eileen Morgan from the International Agency for Research on Cancer (IARC). She said: "Breast cancer is the most common form of cancer in the world. Most women are diagnosed when their cancer is confined to the breast or has only spread to nearby tissue. But in some women, the cancer will grow and spread to other parts of the body or come back in a different part of the body several years after the end of their initial treatment. At this point the cancer becomes much harder to treat and the risk of dying is higher. However, we don't really know how many people develop metastatic breast cancer because cancer registries have not been routinely collecting this data."

The new findings are part of a meta-analysis of the available literature. This means the researchers gathered together the data from as many different studies as they could find on breast cancer and whether it spreads to other parts of the body. By combining lots of data together, researchers can get the most reliable information on the overall risk of metastasis and how it varies for different groups of patients.

This analysis included tens of thousands women who between them took part in more than 400 studies from North and South America, Europe, Africa, Asia, and Oceania. This ongoing meta-analysis will allow the researchers to look at many factors and how they influence the risk of metastasis, but they began by studying women's age when they were diagnosed with breast cancer, and the different types and stages of breast cancer. They also looked at whether rates of metastasis have changed over time.

The analysis shows that the overall risk of metastasis for most

breast cancer patients is between 6% and 22%. This is a range that reflects the level of risk for half of the women in the analysis, with only a quarter of women having a higher risk and a quarter of women having a lower risk (known as the interquartile range). Researchers say the range is broad because the risk varies a great deal depending on different risk factors. For example, women first diagnosed below the age of 35 years, have a 12.7% to 38% risk of their breast cancer coming back and spreading to other parts of the body, while women aged 50 years or older have a risk of 3.7% to 28.6%. Dr Morgan said: "This may be because younger women have a more aggressive form of breast cancer or because they are being diagnosed at a later stage."

Among the different types of breast cancer, women diagnosed with luminal B cancer (hormone-receptor positive and tends to grow faster) had a 4.2% to 35.5% risk of metastasis compared to 2.3% to 11.8% risk in women diagnosed with luminal A cancer (hormone-receptor positive and tends to grow slower).

The study suggests that rates of distant recurrence, meaning breast cancer coming back after initial diagnosis and spreading to other organs, have decreased over time from women first diagnosed in the 1970s and '80s to more recent diagnoses, but some of this may be due to the time lag between a first diagnosis of breast cancer and the appearance of metastases.

The researchers will continue to work with the data they have gathered to try and quantify how many women are living with advanced breast cancer around the world, to look for other factors that may alter the risk, and to monitor how the risk is changing over time.

Dr. Shani Paluch-Shimon, a member of the Scientific Committee for ABC 6, Director of the Breast Unit at Hadassah University Hospital, Israel, who was not involved with the research said: "There has been a knowledge gap about how many people are living with advanced breast cancer around the world. This study is a step towards filling that gap. The researchers have already been able to give the first reliable estimate of how many breast cancer patients go on to develop advanced disease in contemporary cohorts and identify some of the groups, such as younger women, who face a higher risk. The second part of this study will define how cancer registries can collect adequate data about relapses so that we may know how many patients with metastatic cancer there are in each country.

"This information is, of course, important for patients who want to understand their prognosis. But it's also vital at a public health level for those of us working to treat and prevent advanced breast cancer to help us understand the scale of the disease around the world. It will help us identify at-risk groups across different populations and demonstrate how disease course is changing with contemporary treatments. It will also help us understand what resources are needed and where, to ensure we can collect and analyze quality data in real-time as this is key for resource allocation and planning future studies."

https://bit.ly/3DmuVhu

Team of Experts Approve Do-It-Yourself Artificial Pancreas for People With Type 1 Diabetes

More than 40 healthcare professionals and legal experts have issued the first guidance of its kind to support people with type 1 diabetes using Do-it-Yourself (DIY) technology-driven systems to manage their condition.

The paper was co-led by King's College London and Guy's and St Thomas' NHS Foundation Trust. It sets out recommendations that allow health-care professionals to support DIY artificial pancreas systems as a safe and effective treatment option for type 1 diabetes.

The work is published today (November 13, 2021) in *The Lancet Diabetes & Endocrinology* and endorsed by nine professional

diabetes organizations including the International Diabetes Federation. Patients say using the technology has been a "revolution and a revelation" that has had positive impacts on their wider health.

Study co-lead Dr. Sufyan Hussain, a consultant diabetologist and honorary senior lecturer from King's College London, who has lived with type 1 diabetes for over 30 years says: "The medical and legal position of do-it-yourself and citizen science approaches have been subject to a lot of debate and uncertainty. This paper not only clarifies the position for do-it-yourself artificial pancreas systems in diabetes as a safe and effective treatment but sets a precedent for achieving an international professional consensus for other treatments based on user-driven do-it-yourself technologies and innovations."

Traditional monitoring of type 1 diabetes involves taking blood samples from the fingertips several times a day and calculating precise injections of insulin to maintain blood sugar levels. This can be a time-consuming and stressful method, but according to the paper's authors, more than 10,000 people worldwide are choosing a different approach, and the number is growing.

The DIY systems, also known as open-source Automated Insulin Delivery (AID) systems, automatically adjust insulin dosing in response to continuous sensor glucose, insulin pump data, and additional information using community-generated algorithms. It means that the algorithm can calculate the dosage and administer the dose automatically through conventional insulin pumps.

The authors note that such systems aim to reduce both hypo- and hyperglycemia, but can also improve glycaemic and long-term health outcomes, reducing diabetes distress and burden, and improving sleep quality.

A limited number of commercial versions of these systems have recently been approved by regulators, but they can be expensive and are accessible only in certain countries. In June 2021, then NHS England Chief Executive Sir Simon Stevens announced up to 1,000 patients will benefit from a pilot of the innovative closed loop technology with approved commercially available systems. However, these systems are not accessible by most globally and work with limited devices that do not allow customization, which is necessary for some people living with type 1 diabetes. Instead, DIY systems are a product of citizen science that have been co-created by people living with diabetes. These systems are not regulated. However, today's landmark paper provides professional validation and clear recommendations for their use.

At least 20% of DIY system users are children or adolescents, although use in pregnancy and the elderly is also widely noted. For many families and users, use of an AID system improved quality of life for caregivers, allowing carers to remotely monitor their condition.

However, like other insulin-based treatments, these systems are not without risk, authors warn. Historically, people living with diabetes had to do their own research on how to build and set up these systems. The paper recommends clinicians work with individuals living with diabetes or their caregivers to ensure safe and effective use of these systems and detail guidance on how to achieve this.

Dominic Nutt, 54 from South West London, was diagnosed with diabetes aged 15. He has a personalized algorithm that controls his glucose monitor and insulin pump automatically. He manages the process through a smartphone, putting in when he eats carbohydrates or exercises, as this affects his blood sugar.

He says: "I'm not a techie at all, but since I was diagnosed, I've always been excited to try the latest developments as soon as they're available. A friend put me in touch with someone who could help me to personalize the algorithm to my diabetes and my insulin pump. I then worked with Dr Hussain who helped me to

make it work for my diabetes and the technology I was already using.

"It's been a revolution and a revelation. The swings in my blood sugar have gone. I used to have severe hypos needing emergency care about once every six months – my kids got used to having to talk to the paramedics. Now that never happens, my blood sugar is under control, which has wider health benefits as well, plus I'm feeling fitter and stronger, and I don't have to eat as much sugar to control my blood sugar.

"The emotional weight that has been lifted is huge. I still have to think about my diabetes sometimes, but it's not the daily grind it used to be. It's exciting that now there's more of an opportunity for others with diabetes to get the kind of personalized advice that I've had."

Hilary Nathan, JDRF UK Policy and Communications Director said: "JDRF UK welcomes this international consensus which is profoundly important to people who use Do-It-Yourself technology systems to manage their type 1 diabetes.

"This international guidance has wider implications: citizen-led science has been shown to up-end the traditional treatment pathway which is traditionally research trials, followed by regulatory approval, followed by clinical guidance and then patient uptake. Dr Hussain's work provides a new blueprint in developing an international consensus for healthcare guidance in the field of citizen and user development of health treatment technology."

Reference: "Open-source automated insulin delivery: international consensus statement and practical guidance for health-care professionals" by Katarina Braune, MD; Rayhan A Lal, MD; Lenka Petruželková, MD; Gary Scheiner, CDCES; Per Winterdijk, MD; Signe Schmidt, MD; Linda Raimond, DSN; Prof Korey K Hood, PhD; Prof Michael C Riddell, PhD; Prof Timothy C Skinner, PhD; Prof Klemens Raile, MD and Sufyan Hussain, PhD on behalf of theOPEN International Healthcare Professional Network and OPEN Legal Advisory Group, 13 November 2021, The Lancet Diabetes & Endocrinology. DOI: 10.1016/S2213-8587(21)00267-9

https://wb.md/2YKepbY

CRAVE: No Spike in Atrial Arrhythmias Among Coffee Drinkers

A novel trial using real-time monitoring found that drinking coffee did not increase atrial arrhythmias but was associated with more premature ventricular contractions.

Patrice Wendling

There was no increase in premature atrial contractions (PACs) or supraventricular tachycardia (SVT) with coffee consumption, and, in fact, there was less SVT in per protocol analyses.

Coffee consumption was also linked to a "clinically meaningful increase in physical activity as well as a clinically meaningful reduction in sleep," co-principal investigator Gregory M. Marcus, MD, University of California, San Francisco, reported at the American Heart Association (AHA) Scientific Sessions 2021.

Although some professional society guidelines warn against caffeine consumption to avoid arrhythmias, he noted that the data have been mixed and that growing evidence suggests coffee consumption may actually lower the risk for arrhythmias, diabetes, and even mortality. The exact relationship has been hard to prove, however, as most coffee studies are observational and rely on self-report.

The Coffee and Real-time Atrial and Ventricular Ectopy (CRAVE) trial took advantage of digital health tools to examine the effect of caffeine consumption on cardiac ectopy burden in 100 healthy volunteers using an N-of-1 design. The primary outcomes were daily PAC and premature ventricular contraction (PVC) counts.

Participants consumed as much coffee as they wanted for 1 day and avoided all caffeine the next, alternating the assignment in 2-day blocks over 2 weeks. They used a smartphone app to receive daily coffee assignments and reminders and wore a continuous recording electrocardiography monitor (*ZioPatch*, iRhythm Technologies); a

continuous glucose monitor (Dexcom); and Fitbit *Flex 2*, which recorded step counts and sleep duration.

At baseline, 21% of participants drank 6 to 7 cups of coffee per month, 29% drank 1 cup per day, 21% drank 2 to 3 cups per day, and 3% drank 4 to 5 cups per day. The U.S. Food and Drug Administration has cited 400 mg per day, or about 4 or 5 cups of coffee, as generally safe for healthy adults.

To assess adherence, participants were asked to press the button on the ZioPatch for every coffee drink and were queried daily regarding actual coffee consumption the previous day. Date-stamped receipts for coffee purchases were reimbursed, and smartphone geolocation was used to track coffee shop visits. The great majority of times, participants followed their assignment by all measures, Marcus said.

ITT and Per Protocol Analyses

ZioPatch data collected over a median of 13.3 days showed a daily median of 12.8 PACs, 7.5 PVCs, 1 nonsustained SVT, and 1 nonsustained ventricular tachycardia.

In intention-to-treat (ITT) analyses, there was no evidence of a relationship between coffee consumption and daily PAC counts (RR, 1.09; 95% CI, 0.98 - 1.20; $P = .10$).

In contrast, participants had an average of 54% more PVCs on days randomized to coffee by ITT (RR, 1.54; 95% CI, 1.19 - 2.00; $P = .001$) and, per protocol, those consuming more than 2 cups of coffee per day had a doubling of PVCs (RR, 2.20; 95% CI, 1.24 - 3.92; $P = .007$).

No relationship was observed with coffee consumption and SVT episodes in ITT analyses (RR, 0.84; 95% CI, 0.69 - 1.03; $P = .10$) but, per protocol, every additional coffee drink consumed in real time was associated with a 12% lower risk for an SVT episode (RR, 0.88; 95% CI, 0.79 - 0.99; $P = .028$).

No significant relationships were observed with VT episodes, which were admittedly rare, Marcus said.

In ITT analyses that adjusted for day of the week, participants took an average of 1058 more steps on days they drank coffee (95% CI, 441 - 1675 steps; $P = .001$) but slept 36 fewer minutes (95% CI, 22 - 50 minutes; $P < .001$).

Per protocol, every additional coffee drink was associated with 587 more steps per day (95% CI, 355 - 820 steps; $P < .001$) and 18 fewer minutes of sleep (95% CI, 13 - 23 minutes; $P < .001$).

No significant differences in glucose levels were observed. Genetic analyses revealed 2 significant interactions: fast coffee metabolizers had a heightened risk for PVCs and slow metabolizers experienced more sleep deprivation, Marcus said.

Typical Patients?

Dedicated discussant Sana Al-Khatib, MD, MHS, Duke University Medical Center, Durham, North Carolina, said CRAVE is a "well-conducted and informative trial" that very nicely and effectively used a digital health platform.

She pointed out, however, that the trial enrolled healthy volunteers who not only owned a smartphone but were able to interact with the study team using it. They also had an average age of 38 years, median body mass index of 24 kg/m^2, and no prior arrhythmias or cardiovascular issues. "These are not representative of the average patient that we see in clinical practice."

"The other thing to keep in mind is that the primary outcome that they looked at, while relevant, is not adequate in my view to help us derive definitive conclusions about how coffee consumption affects clinically meaningful arrhythmias," Al-Khatib said. "Yes, PACs trigger atrial fibrillation, but they don't do so in every patient. And PVCs have been shown to be associated with increased mortality as well as worsened cardiovascular outcomes, but that's mostly in patients with structural heart disease."

She praised the investigators for including genetic data in their

analysis. "Whether the results related to physical activity and sleep translate into any major effect on clinical outcomes deserves a study."

The overall findings need to be replicated by other groups, in other populations, and examining hard outcomes over longer follow-up, concluded Al-Khatib.

Speaking to *theheart.org | Medscape Cardiology*, Marcus countered that the participants were "pretty run of the mill" coffee drinkers of all ages and that the study highlights the complexity of coffee consumption as well as providing unique data inferring causality regarding increasing physical activity.

"Because coffee is so commonly consumed, highlighting the actual effects is important and the hope is that understanding those true causal effects and minimizing confounding will help tailor recommendations regarding coffee consumption," he said. "For those concerned about atrial fibrillation, for example, these data suggest that avoiding coffee does not necessarily make sense to reduce the risk of atrial fibrillation. For those with ventricular arrhythmias, abstinence or minimizing coffee may be a worthwhile experiment."

Kalyanam Shivkumar, MD, PhD, director of the Cardiac Arrhythmia Center at the University of California, Los Angeles, told *theheart.org | Medscape Cardiology* that CRAVE is an important and much-needed study that provides reassuring and objective data for a common clinical question.

"It fits in with the emerging consensus that, in itself, coffee is not problematic," he said. "And it provides a nice framework for what we'll be seeing in the future — more studies that use these types of long ECG recordings and interlinking that data with biological readouts."

Although it is too early to draw any conclusions regarding the genetic analyses, "future studies could use this is as a baseline to further explore what happens between fast and slow metabolizers. This is a very useful stepping stone to putting data in context for an individual patient."

Unless coffee consumption is excessive, such as over 5 cups per day in young people, all of the evidence points to coffee and caffeine being safe, Chip Lavie, MD, a frequent coffee researcher and medical director of cardiac rehabilitation and prevention at John Ochsner Heart and Vascular Institute, New Orleans, Louisiana, told *theheart.org | Medscape Cardiology*.

"The benefits of coffee on physical activity/sleep seem to outweigh the risks as this current study suggests," he said. "This study also supports the safety with regards to atrial arrhythmias, and suggests that those with symptomatic PVCs could try reducing coffee to see if they feel better. In total, however, the benefits of one or several cups of coffee per day on cardiovascular disease outweigh the risks."

The study was funded by the University of California, San Francisco. Marcus reports research with the National Institutes of Health, the Patient-Centered Outcomes Research Institute, Tobacco-Related Disease Research Program, Medtronic, Eight Sleep, and Baylis; consulting for InCarda Therapeutics and Johnson & Johnson; and equity in InCarda Therapeutics as cofounder.

American Heart Association (AHA) Scientific Sessions 2021. Presented November 14, 2021. LBS.03. Abstract

https://bit.ly/3cfEbIp

After decades of work, an effective cytomegalovirus vaccine is on the horizon

Monoclonal antibodies reveal key vaccine structure

Georgina To'a Salazar

Cytomegalovirus infection before birth is a leading cause of sickness affecting children's development.

There are no approved vaccines to prevent this infection, which happens when a pregnant person is exposed to cytomegalovirus (CMV) and the virus passes through the placenta to the fetus. To

better evaluate vaccine candidates for clinical trials, we need an "immune correlate of protection," a sign that helps us predict whether a vaccine will protect against CMV infection and disease. Such a sign was discovered through a study conducted under the leadership of Sallie R. Permar, a physician-scientist at the Duke University School of Medicine.

CMV infection in healthy children and adults is common and usually asymptomatic or has mild, flu or cold-like symptoms. CMV awareness is fairly poor. In 2011, the US Congress even passed a resolution naming June National CMV Awareness Month. This recognition aims to increase awareness of CMV exposure risks. Young children are a common source of CMV. So, there may be a greater risk of congenital CMV infection for people who have frequent contact with young children. This awareness helps reduce the spread of CMV and makes early treatment possible for those severely affected.

The primary objective of this study was to define the immune responses elicited by a CMV vaccine tested in two clinical trials, one with postpartum people and another with healthy adolescents. In this vaccine, a subunit of CMV, called glycoprotein B (gB), is combined with a novel adjuvant, MF59, a proprietary oil-in-water emulsion. Vaccinees were given either the gB/MF59 vaccine or placebo, then followed to assess any side effects experienced. Infants born to participants in one study were checked for CMV infection. Researchers sought to identify an association between those immune responses and the risk of CMV infection that could damage a fetal nervous system if the infection occurred during pregnancy. One aspect of the study that makes it unique is that it investigates the response of the most efficacious CMV vaccine tested at that time.

One hypothesis of this research was that antibodies in the blood of vaccinees should be correlated with vaccine efficacy. One challenge was that many antibodies generated in response to the vaccine being tested don't inhibit viral infection of cells, which is usually expected of antibodies that protect against a virus. Evidence has suggested non-neutralizing antibodies contribute to protection in other ways, but studies presenting that evidence lacked real statistical power. A key result of the study was the discovery that an antibody binding CMV gB on the surface of infected cells, but not free gB that's not associated with a cell, is associated with protection against CMV infection. This suggests that antibody binding to cell-associated gB *is* an immune correlate of vaccine efficacy.

Results of the study are expected to advance the development of a CMV vaccine that could protect developing infants. A CMV vaccine would also spare transplant recipients the need for expensive, limited antiviral treatments, improving patient survival and procedure success rates.

An obvious next step would be further studies to investigate immune responses and immune correlates of other CMV vaccine antigens. Another step would be to investigate correlates of protection against secondary infection and re-activation since this study focused on primary infection. Studies to confirm that the antibody response described in this paper could serve as an endpoint for vaccine development and evaluation is a third obvious next step.

CMV infection is almost universal and generally mild. But it can have devastating effects when infection occurs during pregnancy. CMV vaccines are hard to develop in part because of participants must be followed for years to determine vaccine efficacy. Studies defining immune correlates of protection, such as this one, facilitate the evaluation of vaccine efficacy and thus accelerate vaccine development.

To scientists, this study is important because it includes results of

phase 2 clinical trials of a CMV vaccine; work at the forefront of a research effort that has been a focus of researchers across the world for decades. Also, the study results are expected to have a positive impact because they support understanding of human interaction with CMV. The CMV DNA genome of 236 kilobases (kb), encodes dozens of proteins, making it one of the largest and most complex viruses known to infect humans. By contrast, the sizes of the RNA genomes of influenza A, SARS-CoV-2, and HIV-1 are about 14 kb, 30 kb, and 10 kb. The size and complexity of CMV support many functions that allow CMV to sustain its lifelong, mostly-asymptomatic infection of humans. They also contribute to difficulty preventing and treating the infection in those who are vulnerable to serious effects.

This paper builds on previous research that shows the development of CMV vaccines can be helped by the identification of immune correlates of protection, signs in the immune response of vaccinees that show they're protected. It also builds on research describing the structure of the CMV virus and its interaction with the human immune response.