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First-Ever Flu Vaccine Derived From Tobacco Plants Just Smashed Clinical Trials

A new flu vaccine grown in plants has been put to the test in two large-scale clinical trials, a first for vaccine research.

Clare Watson

The vaccine contained virus-like particles which resembled circulating flu strains, extracted from native Australian tobacco relatives that were genetically instructed to produce the viral proteins.

The two trials combined involved nearly 23,000 people and the results suggest that the plant-derived vaccine is not only safe, but comparable to current commercial flu vaccines.

"To the best of our knowledge, these studies and the clinical development programme that preceded them are the largest demonstration to date of the potential for a plant-based platform to produce a human vaccine that can be safe, immunogenic, and effective," the research team wrote.

Every year, the vaccines that protect us against influenza have to be reformulated for the next flu season, which is a huge undertaking.

The influenza virus is a chameleon of sorts, constantly changing the protein molecules it displays on its outer surface, and this has researchers feverishly looking for ways to improve our current vaccine technology.

Most influenza vaccines are currently made using virus particles grown in and harvested from chicken eggs or lab-grown cells, which takes months even after scientists work out which flu strains (and surface proteins) they need to target.

Plants, which can be engineered to produce select proteins and cultivated at scale, could be an alternative, helping to boost our capacity to produce seasonal flu vaccines.

The technique might also help to overcome complications encountered in the way current flu vaccines are manufactured that sometimes renders vaccines less effective.

In this system, the researchers used an Australian relative of the tobacco plant, *Nicotiana benthamiana*, engineered to produce just the outer shell of influenza viruses. These virus-like particles are then extracted and purified under strict conditions to make a flu vaccine.

The researchers tested their plant-derived vaccine in two clinical trials, funded by the Canadian biotech company which developed the technique, and no major safety concerns were reported.

Phase III trials testing safety and efficacy like this are usually one of the last hurdles vaccines need to clear before they can be approved for widespread use.

But keep in mind that even if a flu vaccine is approved as safe and effective, any manufacturer needs to be able to produce millions of doses every year, which could be a challenge for vaccine-producing plants.

The first trial involved more than 10,100 adults from Asia, Europe and North America, aged 18 to 64 years, and it was designed to show that the vaccine could prevent 70 percent of people in the trial from developing flu-like or other respiratory illnesses in one flu season.

Although this high benchmark was not reached in the trial, the vaccine did protect about a third of people from flu strains circulating in the 2017-2018 Northern Hemisphere winter that were a match for the viral particles in this vaccine.

That result might sound low, but the efficacy of commercial flu vaccines often varies year to year depending on how well a vaccine matches the different flu strains circulating that winter.

The researchers concluded, based on data collected during 2017-2018, that their plant-derived vaccine provided a "broadly similar"

level of protection as commercial vaccines used in that particularly long flu season, which is a fair result.

The second study recruited another 12,700 people aged 65 years and over. This is quite important because elderly people's immune systems tend to wane with age, making them more vulnerable to contracting infections.

"Like other influenza vaccines, antibody responses to the [plant-derived] vaccine also diminished with age," the researchers said.

The plant-derived vaccine stimulated less of an antibody response in older people, a somewhat expected result, but it did activate a substantial increase in immune cells ready to respond to flu-like infections.

Promisingly, the protection the vaccine granted people from flu-like illnesses in the 2018-2019 flu season was still on par with a commercially available flu vaccine used that season.

"The field of plant-derived vaccines has grown a lot in the past 28 years, since it was first shown [in 1992] that viral proteins could be expressed in plants," John Tregoning, an infectious disease researcher from Imperial College London, said in a commentary about the latest trial results. "This is the first time a plant vaccine has been tested in a [human] clinical trial," Tregoning added. "It is a milestone for this technology and sows the seeds for other plant-based vaccines and therapeutics."

If all goes well, this research might one day give us another way to manufacture seasonal flu vaccines that could also be scaled up in the event of another flu pandemic.

In their paper, the researchers claim that their plant-based system can produce the first doses of a newly designed flu vaccine within two months of identifying an emerging influenza strain.

But there is likely still a long road ahead navigating regulatory approvals for this vaccine, so watch this space.

The research was published in *The Lancet*.

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People who eat chili pepper may live longer?

Individuals who consume chili pepper may live longer and may have a significantly reduced risk of dying from cardiovascular disease or cancer

DALLAS - Individuals who consume chili pepper may live longer and may have a significantly reduced risk of dying from cardiovascular disease or cancer, according to preliminary research to be presented at the American Heart Association's Scientific Sessions 2020. The meeting will be held virtually, Friday, November 13-Tuesday, November 17, 2020, and is a premier global exchange of the latest scientific advancements, research and evidence-based clinical practice updates in cardiovascular science for health care worldwide.

Previous studies have found eating chili pepper has an anti-inflammatory, antioxidant, anticancer and blood-glucose regulating effect due to capsaicin, which gives chili pepper its characteristic mild to intense spice when eaten. To analyze the effects of chili pepper on all-cause and cardiovascular disease mortality, researchers screened 4,729 studies from five leading global health databases (Ovid, Cochrane, Medline, Embase and Scopus). Their final analysis includes four large studies that included health outcomes for participants with data on chili pepper consumption.

The health and dietary records of more than 570,000 individuals in the United States, Italy, China and Iran were used to compare the outcomes of those who consumed chili pepper to those who rarely or never ate chili pepper. Compared to individuals who rarely or never ate chili pepper, the analysis found that people who ate chili pepper had:

- ***a 26% relative reduction in cardiovascular mortality;***
- ***a 23% relative reduction in cancer mortality; and***
- ***a 25% relative reduction in all-cause mortality.***

"We were surprised to find that in these previously published studies, regular consumption of chili pepper was associated with an overall risk-reduction of all cause, CVD and cancer mortality. It highlights that dietary factors may play an important role in overall health," said senior author Bo Xu, M.D., cardiologist at the Cleveland Clinic's Heart, Vascular & Thoracic Institute in Cleveland, Ohio. "The exact reasons and mechanisms that might explain our findings, though, are currently unknown. Therefore, it is impossible to conclusively say that eating more chili pepper can prolong life and reduce deaths, especially from cardiovascular factors or cancer. More research, especially evidence from randomized controlled studies, is needed to confirm these preliminary findings."

Dr. Xu said that there are several limitations to this type of study. The four studies reviewed included limited specific health data on individuals or other factors that may have influenced the findings. Researcher also noted that the amount and type of chili pepper consumed was variable among the studies, making it difficult to draw conclusions about exactly how much, how often and which type of chili pepper consumption may be associated with health benefits. The researchers are continuing to analyze their data and hope to publish the full paper soon.

Co-authors are Manpreet Kaur, M.D.; Beni R. Verma, M.D.; Leon Zhou, M.D.; Simrat Kaur, M.D.; Yasser Sammour, M.D.; and Harssan Mehmood, M.D. Author disclosures are in the abstract.

https://bbc.in/3lv5LUS

Covid vaccine: First 'milestone' vaccine offers 90% protection

The first effective coronavirus vaccine can prevent more than 90% of people from getting Covid-19, a preliminary analysis shows.

By James Gallagher Health and science correspondent

The developers - Pfizer and BioNTech - described it as a "great day for science and humanity". Their vaccine has been tested on 43,500 people in six countries and no safety concerns have been raised. The companies plan to apply for emergency approval to use the vaccine by the end of the month.

No vaccine has gone from the drawing board to being proven highly effective in such a short period of time. There are still huge challenges ahead, but the announcement has been warmly welcomed with scientists describing themselves smiling "ear to ear" and some suggesting life could be back to normal by spring.

"I am probably the first guy to say that, but I will say that with some confidence," said Sir John Bell, regius professor of medicine at Oxford University.

How effective could it be?

A vaccine - alongside better treatments - is seen as the best way of getting out of the restrictions that have been imposed on all our lives. The data shows that two doses, three weeks apart, are needed. The trials - in US, Germany, Brazil, Argentina, South Africa and Turkey - show 90% protection is achieved seven days after the second dose. However, the data presented is not the final analysis as it is based on only the first 94 volunteers to develop Covid so the precise effectiveness of the vaccine may change when the full results are analysed.

Dr Albert Bourla, the chairman of Pfizer, said: "We are a significant step closer to providing people around the world with a much-needed breakthrough to help bring an end to this global health crisis." Prof Ugur Sahin, one of the founders of BioNTech, described the results as a "milestone".

When will the vaccine be available?

A limited number of people may get the vaccine this year.

Pfizer and BioNTech say they will have enough safety data by the third week of November to take their vaccine to regulators. Until it

has been approved it will not be possible for countries to begin their vaccination campaigns.

The two companies say they will be able to supply 50 million doses by the end of this year and around 1.3 billion by the end of 2021. Each person needs two doses. The UK should get 10 million doses by the end of the year, with a further 30 million doses already ordered.

Who would get it?

Not everyone will get the vaccine straight away and countries are each deciding who should be prioritised. Hospital staff and care home workers will be near the top of every list because of the vulnerable people they work with, as will the elderly who are most at risk of severe disease.

The UK is likely to prioritise older resident in care homes and the people that work there. But it says a final decision has not been made, saying it will depend on how well the vaccine works in different age-groups and how the virus is spreading. People under 50 and with no medical problems are likely to be last in the queue.

Are there any potential problems?

There are still many unanswered questions as this is only interim data. We do not know if the vaccine stops you spreading the virus or just from developing symptoms. Or if it works equally well in high-risk elderly people. The biggest question - how long does immunity last - will take months or potentially years to answer.

There are also massive manufacturing and logistical challenges in immunising huge numbers of people, as the vaccine has to be kept in ultra-cold storage at below minus 80C.

The vaccine appears safe from the large trials so far but nothing, including paracetamol, is 100% safe.

How does it work?

There are around a dozen vaccines in the final stages of testing - known as a phase 3 trial - but this is the first to show any results. It uses a completely experimental approach - that involves injecting part of the virus's genetic code - in order to train the immune system. Previous trials have shown the vaccine trains the body to make both antibodies - and another part of the immune system called T-cells to fight the coronavirus.

What has the reaction been?

The UK's chief medical advisor Prof Chris Whitty said the results showed the "power of science" and was a "reason for optimism" for 2021.

The US president-elect Joe Biden said it was "excellent news". "It is also important to understand that the end of the battle against Covid-19 is still months away," he added.

The UK Prime Minister's official spokesman said the results were "promising" and that "the NHS stands ready to begin a vaccination programme for those most at risk once a Covid-19 vaccine is available".

Prof Peter Horby, from the University of Oxford, said: "This news made me smile from ear to ear. "It is a relief... there is a long long way to go before vaccines will start to make a real difference, but this feels to me like a watershed moment."

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Cleveland Clinic researchers identify melatonin as possible COVID-19 treatment

New findings published in PLOS Biology use "big data" approach

Cleveland - Results from a new Cleveland Clinic-led study suggest that melatonin, a hormone that regulates the sleep-wake cycle and is commonly used as an over-the-counter sleep aid, may be a viable treatment option for COVID-19.

As COVID-19 continues to spread throughout the world, particularly with cases rising during what some have termed the "fall surge," repurposing drugs already approved by the U.S. Food

and Drug Administration for new therapeutic purposes continues to be the most efficient and cost-effective approach to treat or prevent the disease. According to the findings published today in *PLOS Biology*, a novel artificial intelligence platform developed by Lerner Research Institute researchers to identify possible drugs for COVID-19 repurposing has revealed melatonin as a promising candidate.

Analysis of patient data from Cleveland Clinic's COVID-19 registry also revealed that melatonin usage was associated with a nearly 30 percent reduced likelihood of testing positive for SARS-CoV-2 (the virus that causes COVID-19) after adjusting for age, race, smoking history and various disease comorbidities.

Notably, the reduced likelihood of testing positive for the virus increased from 30 to 52 percent for African Americans when adjusted for the same variables.

"It is very important to note these findings do not suggest people should start to take melatonin without consulting their physician," said Feixiong Cheng, Ph.D., assistant staff in Cleveland Clinic's Genomic Medicine Institute and lead author on the study.

"Large-scale observational studies and randomized controlled trials are critical to validate the clinical benefit of melatonin for patients with COVID-19, but we are excited about the associations put forth in this study and the opportunity to further explore them."

Here, the researchers harnessed network medicine methodologies and large-scale electronic health records from Cleveland Clinic patients to identify clinical manifestations and pathologies common between COVID-19 and other diseases. Specifically, they measured the proximity between host genes/proteins and those well-associated with 64 other diseases across several disease categories (malignant cancer and autoimmune, cardiovascular, metabolic, neurological and pulmonary diseases), where closer proximity indicates a higher likelihood of pathological associations between the diseases.

They found, for example, that proteins associated with respiratory distress syndrome and sepsis, two main causes of death in patients with severe COVID-19, were highly connected with multiple SARS-CoV-2 proteins. "This signals to us, then," explained Dr. Cheng, "that a drug already approved to treat these respiratory conditions may have some utility in also treating COVID-19 by acting on those shared biological targets."

Overall, they determined that autoimmune (e.g., inflammatory bowel disease), pulmonary (e.g., chronic obstructive pulmonary disease and pulmonary fibrosis) and neurological (e.g., depression and attention-deficit hyperactivity disorder) diseases showed significant network proximity to SARS-CoV-2 genes/proteins and identified 34 drugs as repurposing candidates, melatonin chief among them.

"Recent studies suggest that COVID-19 is a systematic disease impacting multiple cell types, tissues and organs, so knowledge of the complex interplays between the virus and other diseases is key to understanding COVID-19-related complications and identifying repurposable drugs," said Dr. Cheng. "Our study provides a powerful, integrative network medicine strategy to predict disease manifestations associated with COVID-19 and facilitate the search for an effective treatment."

Yadi Zhou, Ph.D., a data scientist, and Yuan Hou, Ph.D., a postdoctoral fellow, both members of the Cheng lab, are co-first authors of this study, which was supported in part by the National Institute on Aging and the National Heart, Lung, and Blood Institute, both parts of the National Institutes of Health.

Serpil Erzurum, M.D., chair of Cleveland Clinic's Lerner Research Institute; Lara Jehi, M.D., chief research information officer at Cleveland Clinic and leader of the Cleveland Clinic COVID-19 Registry; Reena Mehra, M.D,. director of sleep disorders research, Neurologic Institute at Cleveland Clinic; and Charis Eng, M.D., Ph.D., chair of the Genomic Medicine Institute, are co-authors of this study.

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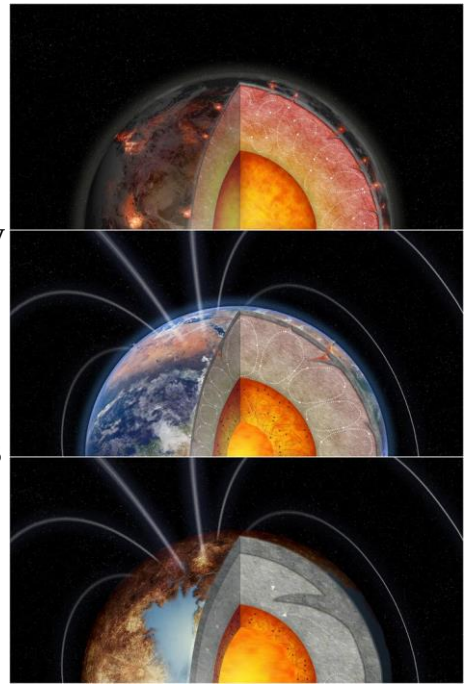
Radioactive elements may be crucial to the habitability of rocky planets

Earth-size planets can have varying amounts of radioactive elements, which generate internal heat that drives a planet's geological activity and magnetism



The amount of long-lived radioactive elements incorporated into a rocky planet as it forms may be a crucial factor in determining its future habitability, according to a new study by an interdisciplinary team of scientists at UC Santa Cruz.

That's because internal heating from the radioactive decay of the heavy elements thorium and uranium drives plate tectonics and may be necessary for the planet to generate a magnetic field. Earth's magnetic field protects the planet from solar winds and cosmic rays.

These illustrations show three versions of a rocky planet with different amounts of internal heating from radioactive elements. The middle planet is Earth-like, with plate tectonics and an internal dynamo generating a magnetic field. The top planet, with more radiogenic heating, has extreme volcanism but no dynamo or magnetic field. The bottom planet, with less radiogenic heating, is geologically 'dead,' with no volcanism. **Credit: Illustrations by Melissa Weiss**

Convection in Earth's molten metallic core creates an internal dynamo (the "geodynamo") that generates the planet's magnetic field. Earth's supply of radioactive elements provides more than enough internal heating to generate a persistent geodynamo, according to Francis Nimmo, professor of Earth and planetary sciences at UC Santa Cruz and first author of a paper on the new findings, published November 10 in *Astrophysical Journal Letters*.

"What we realized was that different planets accumulate different amounts of these radioactive elements that ultimately power geological activity and the magnetic field," Nimmo explained. "So we took a model of the Earth and dialed the amount of internal radiogenic heat production up and down to see what happens."

What they found is that if the radiogenic heating is more than the Earth's, the planet can't permanently sustain a dynamo, as Earth has done. That happens because most of the thorium and uranium end up in the mantle, and too much heat in the mantle acts as an insulator, preventing the molten core from losing heat fast enough to generate the convective motions that produce the magnetic field.

With more radiogenic internal heating, the planet also has much more volcanic activity, which could produce frequent mass extinction events. On the other hand, too little radioactive heat results in no volcanism and a geologically "dead" planet.

"Just by changing this one variable, you sweep through these different scenarios, from geologically dead to Earth-like to extremely volcanic without a dynamo," Nimmo said, adding that these findings warrant more detailed studies.

"Now that we see the important implications of varying the amount of radiogenic heating, the simplified model that we used should be checked by more detailed calculations," he said.

A planetary dynamo has been tied to habitability in several ways, according to Natalie Batalha, a professor of astronomy and astrophysics whose Astrobiology Initiative at UC Santa Cruz sparked the interdisciplinary collaboration that led to this paper.

"It has long been speculated that internal heating drives plate tectonics, which creates carbon cycling and geological activity like volcanism, which produces an atmosphere," Batalha explained.

"And the ability to retain an atmosphere is related to the magnetic field, which is also driven by internal heating."

Coauthor Joel Primack, a professor emeritus of physics, explained that stellar winds, which are fast-moving flows of material ejected from stars, can steadily erode a planet's atmosphere if it has no magnetic field.

"The lack of a magnetic field is apparently part of the reason, along with its lower gravity, why Mars has a very thin atmosphere," he said. "It used to have a thicker atmosphere, and for a while it had surface water. Without the protection of a magnetic field, much more radiation gets through and the surface of the planet also becomes less habitable."

Primack noted that the heavy elements crucial to radiogenic heating are created during mergers of neutron stars, which are extremely rare events. The creation of these so-called r-process elements during neutron-star mergers has been a focus of research by coauthor Enrico Ramirez-Ruiz, professor of astronomy and astrophysics. "We would expect considerable variability in the amounts of these elements incorporated into stars and planets, because it depends on how close the matter that formed them was to where these rare events occurred in the galaxy," Primack said.

Astronomers can use spectroscopy to measure the abundance of different elements in stars, and the compositions of planets are expected to be similar to those of the stars they orbit. The rare earth element europium, which is readily observed in stellar spectra, is created by the same process that makes the two longest-lived radioactive elements, thorium and uranium, so europium can be used as a tracer to study the variability of those elements in our galaxy's stars and planets.

Astronomers have obtained europium measurements for many stars in our galactic neighborhood. Nimmo was able use those measurements to establish a natural range of inputs to his models of radiogenic heating. The sun's composition is in the middle of that range. According to Primack, many stars have half as much europium compared to magnesium as the sun, and many stars have up to two times more than the sun.

The importance and variability of radiogenic heating opens up many new questions for astrobiologists, Batalha said.

"It's a complex story, because both extremes have implications for habitability. You need enough radiogenic heating to sustain plate tectonics but not so much that you shut down the magnetic dynamo," she said. "Ultimately, we're looking for the most likely abodes of life. The abundance of uranium and thorium appear to be key factors, possibly even another dimension for defining a Goldilocks planet."

Using europium measurements of their stars to identify planetary systems with different amounts of radiogenic elements, astronomers can start looking for differences between the planets in those systems, Nimmo said, especially once the James Webb Space Telescope is deployed. "The James Webb Space Telescope will be a powerful tool for the characterization of exoplanet atmospheres," he said.

In addition to Nimmo, Primack, and Ramirez-Ruiz, the coauthors of the paper include Sandra Faber, professor emerita of astronomy and astrophysics, and postdoctoral scholar Mohammadtaher Safarzadeh.

https://bit.ly/36AmQq7

Rapid test can ID unknown causes of infections throughout the body

All-in-one 'metagenomic' test advances efforts to eliminate lengthy diagnosis

UC San Francisco scientists have developed a single clinical laboratory test capable of zeroing in on the microbial miscreant afflicting patients hospitalized with serious infections in as little as six hours -- irrespective of what body fluid is sampled, the type or

species of infectious agent, or whether physicians start out with any clue as to what the culprit may be.

The test will be a lifesaver, speeding appropriate drug treatment for the seriously ill, and should transform the way infectious diseases are diagnosed, said the authors of the study, published November 9, 2020 in *Nature Medicine*.

"The advance here is that we can detect any infection from any body fluid, without special handling or processing for each distinct body fluid," said study corresponding author Charles Chiu, MD, PhD, a professor in the UCSF Department of Laboratory Medicine and director of the UCSF-Abbott Viral Diagnostics and Discovery Center. "It's a simple procedure."

Conventional diagnostic tests are designed to detect only one or sometimes a small panel of potential pathogens. In contrast, the new protocol employs powerful "next-generation" DNA-sequencing technology to account for all DNA in a sample, which may be from any species -- human, bacterial, viral, parasitic, or fungal. Clinicians do not need to have a suspect in mind. To identify a match, the new test relies on specially developed analytical software to compare DNA sequences in the sample to massive genomic databases covering all known pathogens.

Chiu and colleagues at the UCSF Center for Next-Gen Precision Diagnostics first developed this method to identify infectious agents in spinal fluid in cases of encephalitis and meningitis, notably helping to save a long-sick boy's life, and later validating the protocol for use as a clinical test that is now being ordered by physicians at hospitals nationwide. Chiu and collaborators also developed a similar blood test for sepsis, a leading killer of hospital patients, while other tests use respiratory fluid to diagnose infectious causes of pneumonia.

But each of these tests is designed to work only with specific body fluids, not all. Unfortunately, physicians are often uncertain of the origin of a patient's infection and must send off samples of several different body fluids simultaneously for lab analysis.

In the new study, the UCSF researchers, including Center for Next-Gen Precision Diagnostics co-founders Joe DeRisi, PhD, and Steve Miller, MD, PhD, compared performance of their new single-protocol "metagenomic" DNA test to gold-standard laboratory culture-based tests and now-standard PCR-based DNA tests, using two high-powered DNA sequencing technologies to diagnose bacterial or fungal infection. One was a portable, pocket-sized sequencer made by Oxford Nanopore Technologies, which can complete sequencing within six hours and to date has been used almost exclusively by research labs. The other was Illumina sequencing, which can simultaneously handle many samples in parallel and which already is used in some clinical labs (including at UCSF), but which requires more than 24 hours to complete.

The researchers analyzed body fluids -- 180 samples from in and around the lungs, the peritoneal cavity, pus-filled abscesses, the spinal cord, joints, and other sites such as tonsillar fluid and even vitreal (eye) fluid-- from 160 patients, 144 of whom were hospitalized.

Compared with gold-standard culture and PCR, the researchers diagnosed 79% of bacterial and 91% of fungal infections by Illumina sequencing, and 75% of bacterial and 91% of fungal infections by nanopore sequencing. Using the metagenomic DNA test, Chiu and colleagues were also able to diagnose infections in seven of 12 patients whose illnesses had remained undiagnosed after standard culturing or PCR-based DNA testing.

"We think this one metagenomic test can potentially replace all PCR-based DNA tests now being used to detect hundreds of organisms that can't be adequately cultured," Chiu said.

The researchers are now moving towards FDA regulatory approval in hopes of making this test a standard part of clinical practice at UCSF and elsewhere.

https://bit.ly/32JckMp

Fossil shark turns in to mystery pterosaur

Paleontologists have made a surprising discovery while searching through 100-year-old fossil collections from the UK—a new mystery species of pterosaur, unlike anything seen before.

Lead author of the project, University of Portsmouth Ph.D. student Roy Smith, discovered the mystery creature amongst fossil collections housed in the Sedgwick Museum of Cambridge and the Booth Museum at Brighton that were assembled when phosphate mining was at its peak in the English Fens between 1851 and 1900. These fossils found while workmen were digging phosphate nodules were frequently sold to earn a little bit of extra money.

It was while Smith was examining the fossils of shark spines that he made the amazing discovery. The fossils were actually fragments of jaws of toothless pterosaurs, which do indeed resemble shark fin spines but there are many subtle differences that allow them to be distinguished.

Pterosaurs with these types of beaks are better known at the time period from North Africa, so it would be reasonable to assume a likeness to the North African Alanqa. **Credit: Attributed to Davide Bonadonna**

Smith says: "One such feature are tiny little holes where nerves come to the surface and are used for sensitive feeding by the pterosaurs. Shark fin spines do not have these, but the early paleontologists clearly missed these features. Two of the specimens discovered can be identified as a pterosaur called Ornithostoma, but one additional specimen is clearly distinct and represents a new species. It is a palaeontological mystery.

"Unfortunately, this specimen is too fragmentary to be the basis for naming the new species. Sadly, it is doubtful if any more remains of this pterosaur will be discovered, as there are no longer any exposures of the rock from which the fossils came. But I'm hopeful that other museum collections may contain more examples, and as soon as the Covid restrictions are lifted I will continue my search".

Smith's supervisor, Professor Dave Martill, University of Portsmouth, says: "The little bit of beak is tantalizing in that it is small, and simply differs from Ornithostoma in subtle ways, perhaps in the way that a great white egret might differ from a heron. Likely the differences in life would have been more to do with color, call and behavior than in the skeleton".

"Pterosaurs with these types of beaks are better known at the time period from North Africa, so it would be reasonable to assume a likeness to the North African Alanqa (pictured below). This is extremely exciting to have discovered this mystery pterosaur right here in the UK. "This find is significant because it adds to our knowledge of these ancient and fascinating flying prehistoric reptiles, but also demonstrates that such discoveries can be made, simply by re-examining material in old collections."

More information: *Roy E. Smith et al, Edentulous pterosaurs from the Cambridge Greensand (Cretaceous) of eastern England with a review of Ornithostoma Seeley, 1871, Proceedings of the Geologists' Association (2020).* *DOI: 10.1016/j.pgeola.2020.10.004*

https://bit.ly/3kwHJYi

Printable ink guides cell growth, offers nerve injury hope

Bioconductive ink uses body's own electricity to guide nerve cell growth

Researchers have developed a neuron-growing ink that uses the body's own electrical signals to precisely guide the growth of nerve

cells. The bioconductive ink can be printed in lines to direct where neurons grow, cracking a major challenge in the emerging field of nerve engineering.

The team of researchers from Australia, India and Bangladesh have tested the ink on a biocompatible scaffold, with their promising lab results published in the journal *RSC Advances*.

Lead author, RMIT University's Dr Shadi Houshyar, said concentrating the growth of nerve cells in precisely ordered lines was essential to be able to reconnect nerves and heal traumatic nerve injuries.

"Nerve cells need to be meticulously guided to regrow between the broken ends of a nerve - if they just build up anywhere they will cause more pain or sensory problems," Houshyar said. "With our bioconductive ink, we can concentrate the neuron growth where we need it. "Our research is in early stages but with further development, we hope one day to enable damaged nerves to be fully reconnected, to improve the lives of millions of people worldwide."

Currently, there are limited options for rebuilding function when an injury results in large peripheral nerve gaps. Nerve grafts, where surgeons harvest nerves from elsewhere in the body to bridge across a gap, can lead to complications including painful neuromas, misalignment of neural cell growth and injury at the harvest site.

Although emerging alternative techniques such as artificial nerve guides exist, they often fail to achieve full functional or sensory recovery because they don't properly replicate nerve tissue.

Powering nerve cell regeneration

The new nerve-regenerating ink combines the neurotransmitter dopamine - known to help nerve cell survival - with a conductive carbon nanofibre and polymer.

The nanofibre and polymer enables the controlled release of dopamine from the ink, supporting the survival of developing neurons for longer. Because it is conductive, the nanofibre can also harness the power of bioelectricity - the electrical signals generated by the nervous system that play a key role in maintaining biological function and can accelerate wound healing.

"Using conductive materials allows free movement of electrons, stimulates cell growth and helps connect injured neural tissue," Houshyar, a Vice-Chancellor's Research Fellow in the RMIT School of Engineering, said.

As part of the research, the team also developed a biocompatible scaffold, so the ink could be printed in lines and tested with human cells. The study found the printed lines supported neural cell attachment and migration - both important for nerve regeneration.

Cell differentiation was also boosted, with the neural cells becoming more specialised as they grew along the lines.

"This supports proper communication with other neurons, which is promising for the establishment of neural circuits for sensory and motor processing - offering hope the technology could lead to a real recovery of nerve function," Houshyar said.

The next stage for the research is testing the ink and scaffold in pre-clinical animal trials, as well as exploring other applications.

"Our end goal is a nerve engineering solution that can direct the growth of the right nerve cells in the right places," she said.

"We're also keen to investigate how we can expand the potential uses of this technology, for speeding up wound healing and improving patient recovery."

The researchers acknowledge the support of the RMIT Microscopy and Microanalysis Facility.

'Three-Dimensional Directional Nerve Guide Conduits Fabricated with Dopamine Functionalized Conductive Carbon Nanofibre-based Nanocomposite Ink Printing', with Associate Professor Amitava Bhattacharyya from the PSG Institute of Advanced Studies (India) and collaborators from Jahangirnagar University (Bangladesh), is published in RSC Advances (DOI: 10.1039/d0ra06556k).

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

Babies buried under a mammoth-bone lid are the oldest known identical twins

Prehistoric grave contains the remains of a baby who died at birth and those of his twin, who survived for an additional six to seven weeks.

Ancient DNA has revealed that two baby boys carefully buried in the same grave more than 30,000 years ago were identical twins — the most ancient known from the archaeological record.

Maria Teschler-Nicola at the Natural History Museum Vienna, Ron Pinhasi at the University of Vienna and their colleagues examined two skeletons buried under a mammoth's shoulder blade at a site in Austria called Krems-Wachtberg, where hunter-gatherers camped 31,000 years ago.

Ancient hunter-gatherers buried an infant boy (left) with his identical twin (right), who had died more than a month earlier. **Credit: M. Teschler-Nicola et al./Commun. Biol. (CC BY)**

By comparing DNA in bone fragments with that from other recently discovered remains from the region, the researchers revealed that the skeletons belonged to twin boys. One died at birth, but the other lived for about 50 days and was added to the grave later, according to an analysis of teeth embedded in the babies' jawbones and the babies' positions in the burial site.

Both babies were buried with precious items: a necklace hung with snail-shell pendants for the newborn and a string of mammoth-ivory beads for the twin who survived for longer. A third boy, a three-month-old relative, was buried nearby. *Commun. Biol.* (2020)

https://go.nature.com/38H6X40

Tropical cyclones could last longer after landfall in a warming world

Tropical cyclones weaken after they reach land. But it emerges that for the North Atlantic basin, storms are weakening more slowly as regional sea surface temperatures increase.

Dan Chavas & Jie Chen

Tropical cyclones can cause substantial damage and death when they reach land, as a result of wind, storm surges and rainfall. It is known that tropical-cyclone intensity (measured by maximum wind speed) typically decreases rapidly after the storm reaches land[1]. However, existing models do not take into account whether and how this rate of storm decay after landfall depends on climate[1,2].

Writing in *Nature*, Li and Chakraborty[3] report that the rate at which tropical cyclones from the North Atlantic decay after landfall has changed since the 1960s — their intensity has been decreasing more slowly over time. This shift is mainly due to warming sea surface temperatures. The authors' work adds weight to growing concerns[4] that tropical cyclones might become more damaging in the future.

Li and Chakraborty analysed historical intensity data for storms that made landfall over North America between 1967 and 2018. They used the decrease in storm intensity over the 24 hours after landfall to define a timescale of decay for each storm. They then examined trends in this timescale.

The authors found a significant long-term shift towards slower decay (so storms maintain a higher intensity on land for longer). Furthermore, this trend aligned with long-term increases in regional mean sea surface temperature over the Gulf of Mexico and the western Caribbean, which are adjacent to land and supply the moisture for the storms before landfall. The changing timescales of

decay also correlate well with year-to-year variations in mean sea surface temperature (Fig. 1).

Li and Chakraborty next asked whether other factors could also contribute to the change in the timescale of decay. They found that a portion of the long-term trend could be attributed to an eastward shift in landfall location. By contrast, other factors — including the speed of storm movement at landfall and intensity at the time of landfall — were not important.

The authors bolstered their empirical findings by performing hurricane-landfall experiments using a simple, state-of-the-art atmospheric model. For a range of temperatures, they allowed a mature tropical cyclone to form over a water surface that had a fixed temperature. When each storm reached a fixed maximum wind speed, they mimicked landfall by instantaneously changing the surface beneath the storm from wet to dry. Under this model, the timescale of decay again increases with temperature.

The researchers then sought a physical explanation for why warming causes slower decay. The primary energy source for a tropical cyclone is the evaporation of water from the surface beneath the eyewall[5] (the band of cloud that surrounds the eye of the storm), which is rapidly cut off at landfall. But residual moisture in the storm provides a smaller, temporary, secondary source of energy[6]. The levels of this residual moisture are expected to increase with temperature on the basis of the laws of thermodynamics for moist air.

The authors tested the hypothesis that increased levels of residual moisture could cause slower decay using a second set of modelling experiments in which, in addition to drying the surface to mimic landfall, they removed all residual moisture in the atmosphere. These storms all showed identical timescales of decay, despite their different temperatures. Thus, it is the increased residual store of atmospheric moisture at warmer temperatures that slows the weakening of the storm.

A key outstanding question is the exact degree to which the decay rate depends on temperature. Although the empirical and modelling results are in qualitative agreement, temperature had a smaller effect on decay rate in the simulations than was estimated empirically. This difference might be due to the small size of the historical data set or to confounding factors in it. For example, there have been changes in the spatial distribution of landfall locations over time, and hence differences in the surface properties felt by the storms on land, such as surface moisture and roughness.

In addition, it is unclear whether the long-term trends seen in the historical data set might be affected by ongoing changes in the technologies with which researchers observe storms or in methods for estimating maximum storm wind speed over land. Information about these uncertainties is not readily available publicly, but an in-depth investigation of estimation practices would be worthwhile.

Analysis of historical data along coastal regions in other parts of the world, along with simulations over a broader range of temperatures and climates, could help to further test the robustness of the authors' findings for predicting future changes in decay rates. The effects of residual storm moisture also warrant further investigation to clarify how this effect can slow decay after landfall.

Li and Chakraborty's work highlights a key component of risk models that has been largely overlooked so far. Slower storm decay after landfall in the future would directly result in increases in total damage, and this would be exacerbated by increases in peak wind speed and total rainfall, both of which are expected to occur in a warming climate[7]. The extent of damage occurring inland depends on both the rate of storm decay and the speed of storm motion at landfall. Hence, a slower decay could also lead to increases in damage farther inland, although changes in the speed of motion

remain a point of contention[8,9]. Longer-lived storms might also increase the chances of interaction with the jet stream, which can sometimes produce hazardous weather that can extend much farther inland[10].

More generally, the current results indicate the need to broaden our thinking about how climate change affects tropical cyclones after landfall. We must take into account residual atmospheric effects from the adjacent ocean, landfall location and effects induced by the land surface itself[6]. Integrating this understanding into hurricane models should help to improve our predictions of the future risks posed by individual storms and over the long term.

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https://bit.ly/3nkZpYT

Cloth face masks that can be disinfected by the sun

A special type of cotton face mask that kills up to 99.9999% of bacteria and viruses within 60 minutes of daylight exposure

During the COVID-19 pandemic, many people have become accustomed to wearing cotton face masks in public places. However, viruses and bacteria that stick to the mask could be transferred elsewhere when the wearer removes or touches it. Now, researchers reporting in *ACS Applied Materials & Interfaces* have developed a special type of cotton face mask that kills up to 99.9999% of bacteria and viruses within 60 minutes of daylight exposure.

Face masks made of various cloth materials can filter nanoscale aerosol particles -- such as those released by a cough or sneeze -- potentially helping to reduce the spread of diseases, including COVID-19. But live bacteria and viruses on the surface of the mask could still be contagious. Peixin Tang, Gang Sun, Nitin Nitin and colleagues wanted to develop a new cotton fabric that would release reactive oxygen species (ROS) when exposed to daylight, killing microbes attached to the fabric's surfaces while being washable, reusable and safe for the wearer. Then, a person could disinfect their cloth mask during their lunch hour outside in the sun, or by spending a longer period of time under office or building lights, which are much less intense than sunlight.

The researchers made their antimicrobial fabrics by attaching positively charged chains of 2-diethylaminoethyl chloride (DEAE-Cl) to ordinary cotton. Then, they dyed the modified cotton in a solution of a negatively charged photosensitizer (a compound that releases ROS upon exposure to light), which attached to the DEAE chains by strong electrostatic interactions. The team found that a fabric made with a dye called rose Bengal as the photosensitizer killed 99.9999% of bacteria added to the fabric within 60 minutes of daylight exposure and inactivated 99.9999% of T7 bacteriophage -- a virus thought to be more resistant to ROS than some coronaviruses -- within 30 minutes. Further testing showed that the material could be handwashed at least 10 times and constantly exposed to daylight for at least 7 days without losing its antimicrobial activity. The fabric shows promise for making reusable, antibacterial/antiviral cloth face masks and protective suits, the researchers say.

The authors acknowledge funding from the COVID-19 Research Accelerator Funding Track Program at the University of California, Davis and the California Department of Pesticide Regulation.

The abstract that accompanies this paper can be viewed here.

https://bit.ly/3eYNahs

Yale scientists identify protein that protects against Lyme

Protein helps protect hosts from infection with the tick-borne spirochete that causes Lyme Disease

Yale researchers have discovered a protein that helps protect hosts from infection with the tick-borne spirochete that causes Lyme Disease, a finding that may help diagnose and treat this infection, they report Nov. 11 in the journal *PLOS Pathogens*.

Lyme Disease is the most common vector-borne disease in North America and is transmitted by ticks infected with the spirochete Borrelia burgdorferi. The course of the disease varies among individuals, with the majority experiencing mild symptoms easily treated by antibiotics. However, in some cases of untreated Lyme the infection can spread to the heart, joints, nervous system, and other organs.

For the study, the Yale team expressed more than 1,000 human genes in yeast and analyzed their interactions with 36 samples of B. burgdorferi. They found that one protein, Peptidoglycan Recognition Protein 1 (PGLYRP1), acts like an early warning signal to the immune system when exposed to the bacteria. When exposed to the Lyme spirochete, mice lacking PGLYRP1 had much higher levels of B. burgdorferi than mice with the protein and showed signs of immune system dysfunction, the researchers report. "Stimulating the ability of people to make more of this protein could help fight infection," said Yale's Erol Fikrig, the Waldemar Von Zedtwitz Professor of Medicine (Infectious Diseases) and professor of epidemiology (microbial diseases) and of microbial pathogenesis and co-corresponding author of the study.

Fikrig and his colleagues are also investigating whether people with higher levels of PGLYRP1 may be less susceptible to infection by B. burgdorferi, which would help explain why some infected individuals have better outcomes.

Yale's Noah Palm and Aaron Ring are co-corresponding authors of the paper. Akash Gupta, Gunjun Arora, and Connor Rosen of Yale are co-lead authors.

The work was primarily funded by the National Institutes of Health and the Steven & Alexandra Cohen Foundation, a nonprofit that supports Lyme and tick-borne disease research.

https://nyti.ms/3nmNKbZ

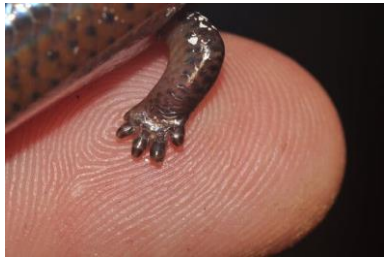
How Some Skinks Lost Their Legs and Then Evolved New Ones

The lizards have complicated a rule of thumb that in evolution, once you lose a body part, you don't regain it.

By Veronique Greenwood

In the rainforest in the Philippines, scientists laid out a tiny racetrack, just for skinks.

The racetrack and the high speed cameras surrounding it were part of research into a mysterious state of affairs. Skinks are lizards, but some species have lost their limbs over eons of evolution, giving them a snakelike look. However, other skinks whose ancestors jettisoned limbs have, for reasons still unknown, brought them back. They break an old rule of thumb in evolutionary biology, which holds that if you lose a complicated structure, you are unlikely to evolve it back.



Some skinks, like Brachymeles boulengeri, have more developed limbs with five fingers and toes. **Credit...Philip Bergmann**

Now, the researchers behind the racetrack write in Proceedings of the Royal Society B in a paper published Wednesday that skinks with limbs move faster and burrow better than their limbless compatriots. And the timing of limb gains and loss across the family tree of skinks in the Philippines appears to sync up with shifts in the local climate, which could have changed the texture of

the soil where they lived. As it grew drier, limbs disappeared, and as it grew damper, they sprouted back in some species, giving a rare glimpse into how, under the right evolutionary pressure, organisms can force limbs back into being.

On land, many legless creatures live in dry, sandy areas, said Philip Bergmann, a professor of biology at Clark University in Worcester, Mass., and an author of the new paper.

"A lot of people for decades, maybe even a century, have been suggesting that a snakelike form would be an adaptation for a burrowing lifestyle," Dr. Bergmann said.

In Asian jungles, however, skinks with and without limbs coexist in the same damp, tropical environment.

To see how skinks in these habitats actually move, the team captured 147 individuals of 13 different species. Some had no limbs, others had tiny ones, others had fully formed legs and feet. They encouraged the skinks to run along the racetrack and burrow in a tube of dirt, carefully recording their movements to analyze later in the lab.

Some species, like Brachymeles bicolandia, are more snake-like, with smaller limbs and fewer toes. **Credit...Philip Bergmann**

The Brachymeles boulengeri is much more lizard-like, with longer limbs and more toes. **Credit...Philip Bergmann**

The team found that skinks with limbs outperformed those without, moving and digging much faster. The limbless animals had their own manner of surviving in the forest, creeping slowly and keeping well out of sight rather than relying on speed.

Overlaying a reconstruction of the climate, based on published work by paleoclimate researchers, on the branching tree that contained all these species revealed interesting patterns. Sixty million years ago, when the skinks first lost their limbs, the area was much drier. Twenty million years ago, when some of them brought their limbs back, the climate had shifted to be wet and monsoonal.

"The climate in the past seems to correlate pretty nicely with our hypothesis," Dr. Bergmann said. Perhaps in wetter climes, limbs had advantages they had not had before.

The idea that complex structures, once they're gone, stay lost makes a certain amount of sense, Dr. Bergmann said. In theory, once the genes involved in making a limb stopped being used, they could run the risk of being damaged by random mutations and not being repaired, because they were no longer useful.

However, research has shown that many of these genes are actually involved in the development of many different parts of the body and need only be switched back on when needed, he went on.

"There is strong selection to maintain those genes," he said. "So you could activate them again in the right place."

https://wb.md/35sSnuS

'Test All Patients With Cancer': 1 in 8 Have Inherited Mutations

About 1 in 8 patients with cancer have inherited genetic mutations that may have contributed to the development of their cancers, but nearly half of these mutations would have been missed using current clinical guidelines.

Veronica Hackethal, MD

These findings come from the largest study of its kind so far, conducted in nearly 3000 patients with a wide range of cancer stages and types, including breast, colorectal, lung, ovarian, pancreatic, bladder, prostate, and endometrial cancers.

"This study tells us that the clinical practice guidelines are not very sensitive for identifying who does or doesn't have a genetic mutation that is predisposing them to cancer," commented first author Niloy Jewell Samadder, MD, director of the high-risk cancer clinic at the Mayo Clinic in Arizona, Phoenix, Arizona.

Finding a genetic mutation can alter clinical management of the cancer. "This really does open up treatment and management options that might not have been accessible to these patients," Samadder emphasized.

The results were published online on October 30 in *JAMA Oncology* and were presented simultaneously at the Society of Human Genetics. Samadder discusses details of the study in a video posted on YouTube. A clinician not involved in the study said the new results should lead to changes in practice. "For cancer patients, I think the debate is over. We should test everybody," Peter Beitsch, MD, surgical oncologist at the Dallas Surgical Group, told *Medscape Medical News.*

The Mayo Clinic is changing its daily practice at all four of its cancer centers. The changes will begin in the first quarter of 2021 at its Arizona campus. "Every cancer patient who comes to Mayo Clinic will be offered genomic evaluation that includes genetic testing to identify if they have an underlying genetic mutation that predisposes to their cancer and [helps physicians decide] how to incorporate that knowledge into designing the best surgical and treatment options for that patient and their family," Samadder said.

Study Details

The study included 2984 patients with cancer who were receiving care for a variety of solid tumor cancers at Mayo Clinic cancer centers in Arizona, Florida, Minnesota, and a community cancer center in Wisconsin. Patients were tested for about 84 genes using next-generation sequencing provided by Invitae.

Among participants, 13.3% (n = 397) tested positive for pathogenic mutations. Of these, about 70% (282 of 397 patients) carried moderate- and high-penetrance genes that increased their risk for cancer. For almost 28.2% (n = 42) of patients with high-penetrance mutations, changes were made in treatment as a result of genetic testing. These included changes in surgical management, immunotherapy, chemotherapy, or enrollment in a clinical trial for which they may otherwise have not been eligible.

Researchers also compared their universal testing approach to targeted testing recommended in guidelines from the National Comprehensive Cancer Network, the National Society of Genetic Counselors, and the American College of Medical Genetics.

They identified pathogenic mutations in 192 patients whose mutations would have been missed using guideline-recommended criteria, such as tumor pathology or family history. This represents 6.4% of all participants in the study (192 of 2984 patients) and 48.4% of patients who tested positive for pathogenic mutations (397 of 2984 patients).

"Genetic testing is underutilized in cancer care, both for patients and for their families, often due to outdated guidelines that restrict testing to a narrow group of high-risk patients. All cancer patients should have access to complete genetic information that can guide their care and inform their families' health," coauthor Robert Nussbaum, MD, chief medical officer of Invitae, said in a statement.

Some clinicians have been pushing for genetic testing of all patients with cancer, including Beitsch, who was lead author of a similar study in breast cancer patients published last year in the *Journal of Oncology*. That article made waves when the authors concluded that all breast cancer patients should have expanded panel genetic testing.

This new Mayo Clinic study extends the findings in breast cancer to "all cancer patients, not just breast cancer patients," Beitsch told *Medscape Medical News*.

Long-Running Debate

The new findings and opinions add to a long-running debate in oncology over the role of genetic testing and screening for pathogenic mutations.

Part of the debate about genetic testing has hinged on the question of costs, says Beitsch. When genetic testing first became available, it was conducted by hand, and costs were often prohibitive. Since then, genetic testing has been automated using next-generation sequencing, and the cost has decreased considerably.

"The Invitae cash price for an 80-plus gene panel is $250. That's [the cost of] a mani-pedi in Dallas. I don't discount that it's a lot of money for a lot of people. Yes, it's expensive, but it's a lot less expensive than it used to be," Beitsch said.

Another issue is that doctors are not entirely sure how to manage variants of uncertain significance (VUSs) when they are found. In the Mayo Clinic study, about half (47.4%; n = 1415) of participants had VUSs. The authors note that these results are consistent with past studies.

Beitsch says VUSs are a matter of education. To date, only about 2% of VUSs have been associated with cancer. The remainder, about 98%, do not affect treatment for patients who have already been diagnosed with cancer. "We all have VUSs. They're just minor variations in a gene. The vast majority of them have no consequence and don't alter the function of the gene," he said. "I tell everybody to ignore the VUSs [when found in patients with cancer]. Do not act on them at all. We just need to educate everybody to make sure they don't get stressed about it."

These comments echo guidance from the American Society of Breast Surgeons, which says that VUSs are DNA sequences that are not clinically actionable. This type of result needs to be considered as inconclusive, and patient management should not be influenced by such results.

However, VUSs are more significant if they are found in individuals who do not have cancer but who have a strong family history of cancer. In such cases, clinicians should be more aware, Beitsch emphasized. "Patients who have a VUS and don't have a cancer should absolutely pay more attention to their health. They got tested for a reason, and that reason is usually strong family history," Beitsch said.

He added that a major advantage of genetic testing is that it can enable cascade genetic testing of family members. Identifying pathogenic mutations in family members can lead them to undergo screening to detect early cancers, and preventive measures can be taken that may be lifesaving.

In the Mayo Clinic study, researchers offered genetic testing to family members of patients who tested positive for a pathogenic mutation. Testing was available free of charge for up to 90 days after a participant tested positive. In addition, family members were shown an educational video.

Nevertheless, only 17.6% (n = 70) of patients with pathogenic mutations had family members who underwent testing. Among these, 45% (79 of 176) of family members who were tested were found to carry pathogenic mutations.

"This really told us that financial barriers are not the only barrier to families understanding and undergoing preventive testing," Samadder said. "There are probably a number of other barriers — socioeconomic or emotional — that we have to deal with."

Genetic testing was provided by the Invitae Corporation. The study was supported by several grants, including a Mayo Transform the Practice Grant, and by Mayo Clinic's Center for Individualized Medicine. Two coauthors are employees of Invitae. Beitsch reports participating in a study 2 years ago that was funded by Invitae. He currently receives no financial support from Invitae. Several authors report receiving fees from one

or more of the following companies: Pfizer, Maze Therapeutics, Genome Medical, Astellas, and Merck. JAMA Oncol. Published online October 30, 2020. Abstract

https://bit.ly/3pvvCP9

Leprosy, ancient scourge of humans, found to assail wild chimpanzees

Finding could indicate an unknown source of leprosy in the wild and reveal new clues about a still-mysterious disease

By Kai Kupferschmidt

Conservation scientist Kimberley Hockings was worried. In 2017, photos from camera traps in Guinea-Bissau's Cantanhez National Park, where she works, revealed several chimpanzees with terrible lesions on their faces. Hockings emailed wildlife veterinarian Fabian Leendertz.

"I have NEVER seen this in chimps," Leendertz, who works at the Robert Koch Institute in Berlin, wrote back. Then a few months later, Leendertz saw a similar photo from his own research site in Ivory Coast, hundreds of kilometers away. Could it be the same disease?

Woodstock, a male chimpanzee at Taï National Park in Ivory Coast, has leprosy. **Tai Chimpanzee Project**

Now, a new preprint by the two researchers gives a surprising answer: Chimps in both West African sites suffer from leprosy, a disease never before documented in wild chimpanzees. The strains in each park appear unrelated, and they are unlikely to have come from contact with humans, the authors argue. The finding could indicate an unknown source of leprosy in the wild and reveal new clues about a still-mysterious disease.

Leprosy is an ancient ailment, but surprisingly little is known about where and when it emerged, or how exactly it spreads. The disease—and the terrible stigma it carries—once afflicted millions of people across the globe. But after a combination of antibiotics became standard therapy in the 1980s, cases plummeted and scientific interest waned. The difficulty of studying leprosy adds to the lack of interest, says co-author Charlotte Avanzi, a microbiologist at Colorado State University (CSU), Fort Collins. The bacteria that cause the disease, *Mycobacterium leprae* and the recently discovered *M. lepromatosis*, cannot be cultured in cells in the lab. The only way to multiply the pathogen is to inject it into armadillos or into the footpads of mice.

For years, researchers thought leprosy afflicted only humans. But over the past 2 decades, scientists have also found the pathogen circulating in nine-banded armadillos in the Americas and in red squirrels in the United Kingdom. Both species harbor the same bacterial genotype, called 3I, that has been linked to human infections in medieval Europe. In both cases, the pathogen appears to have jumped from humans to the animals. Scientists have also reported isolated leprosy cases in captive animals, including chimps. But the story in wild chimpanzees is shaping up to be very different. When a chimpanzee named Woodstock at Taï National Park in Ivory Coast started to show signs of leprosy, Leendertz decided to screen older fecal and necropsy samples from his library for the disease. He found traces of *M. leprae* in another chimpanzee that had been killed by a leopard in 2009. When researchers sequenced the pathogen's genome, they found it was of a rare genotype called 2F. In Guinea-Bissau, researchers collecting fecal samples also got lucky: One sample contained enough bacterium to sequence its full genome, which was another rare genotype called 4N/O.

Human diseases can spill over to chimpanzees with devastating consequences. But Leendertz thinks a recent transmission of leprosy from humans to chimps is unlikely, because the disease usually spreads only after prolonged, close contact, and there have

been no known leprosy cases among researchers or local assistants. (Although researchers study the chimps, they keep at least 6 meters of distance.) In addition, the genotypes responsible for both outbreaks are rare in humans, the researchers report today on the preprint server bioRxiv. Leendertz will not rule out two separate, ancient infections from humans. But, he concludes, "The most likely scenario is that there is some unidentified leprosy reservoir."

John Spencer, an immunologist who studies leprosy at CSU, says there is more and more evidence "that *Mycobacterium leprae* is not limited solely to existence in humans, but has other niches that it has adapted to."

Past work has hinted at that idea, says Anne Stone, an evolutionary geneticist at Arizona State University, Tempe, who was not part of the study. She has long suspected the leprosy bacterium may thrive in another reservoir, in part because of the leprosy genome's small size and other quirks. "That's really a signature of something that needs to live on another organism," she says. That signature appears to date back millions of years, to a time before humans, suggesting the bacterium had another host before we evolved.

"The data increasingly points to the possibility that something else than humans is actually the main host," Stone says. That could be an animal the chimpanzees hunt, for instance, or the leprosy bacterium might even live in the environment.

Rodents are a prime contender for the mystery host, Stone says, although amoeba and some insects have also been infected with leprosy in the lab. Leendertz and his colleagues are planning to look at all these possibilities.

It's an interesting new avenue for leprosy research, Avanzi says. "It's a very difficult disease," she says. "Any clue we can get about it from animals or anywhere is really, really helpful."

For the moment, the infected chimpanzees seem to be coping with their illness, although one is losing weight, Hockings says. Treating them is not really an option, Leendertz says. "Humans have to take antibiotics for months to treat leprosy. You just can't do that with these wild animals." For now, the disease does not appear to put the groups as a whole at risk, he says. "But it's an additional threat, of course, on top of poaching, habitat loss, and other diseases."

https://bit.ly/35xOvJ5

Canadian discovery: A potential game-changer to reverse alcohol intoxication

Developed at UHN, new simple method is proven to accelerate elimination of alcohol from the body

Toronto - A staggering 3 million deaths occur every year as result from harmful use of alcohol, according to the World Health Organization.

Present in alcoholic drinks, ethanol, normally referred to as 'alcohol', affects every part of the human body. Brain function, circulation and even nail growth are impacted. When a certain level of blood alcohol concentration is reached, the intoxication can damage organs and lead to death.

In a study published today in *Scientific Reports*, a Nature Research Journal, a team of researchers led by Dr. Joseph Fisher presents a proof of concept of a simple method that could become a game-changer in rescue therapy for severe alcohol intoxication, as well as just "sobering up."

Normally, 90% of the alcohol in the human body is cleared exclusively by the liver at constant rate that can't be increased. Currently there is no other method, short of dialysis, whereby alcohol can be removed from the blood. This leaves as the only options to treat life-threatening alcohol levels supportive measures such as giving oxygen, intravenous fluids, breathing assistance, and treating any heart issues with drugs.

The principle behind UHN team's approach is simply to recruit the lungs to breathe out the alcohol. The harder the breathing, it was

reasoned, the more alcohol is eliminated. The team found that indeed, hyperventilation eliminated the alcohol at least three times faster than through the liver alone.

"But you can't just hyperventilate, because in a minute or two you would become light-headed and pass out," explains Dr. Fisher, anesthesiologist and senior scientist at the Toronto General Hospital Research Institute (TGHRI).

When hyperventilating - breathing deeper and more rapidly than normal - the body eliminates carbon dioxide from the blood along with the alcohol. The decrease of this gas in the blood is the cause of symptoms such as light-headedness, tingling or numbness on hands and feet, and fainting.

Dr. Fisher and his team used a device that allows the patient to hyperventilate off the alcohol while returning precisely the amount of carbon dioxide to the body to keep it at normal levels in the blood--regardless of the extent of hyperventilation. The equipment is the size of a small briefcase and uses a valve system, some connecting tubes, a mask, and a small tank with compressed carbon dioxide.

"It's very basic, low-tech device that could be made anywhere in the world: no electronics, no computers or filters are required. "It's almost inexplicable why we didn't try this decades ago," says Dr. Fisher.

This study is the first scientific demonstration that the basic rate of alcohol elimination could be substantially exceeded by using hyperventilation. This study is a proof of concept performed in the laboratory with volunteers. The authors recommend following up with further validation studies to understand how this technology could be applied in a clinical setting.

Disclosure *- Dr. Joseph Fisher is the co-founder of Thornhill Medical, a for-profit spin off company from UHN. He is one of the inventors of the ClearMateTM, which was developed by Thornhill Medical for the elimination of volatile hydrocarbons, including for treatment of carbon monoxide poisoning.*

https://bit.ly/35xV2n3

Inclusion of patient headshots in electronic health records decreases order errors

In a study of Brigham patients, rate of wrong patient order entry decreased by 35 percent

Each year, health care practitioners at Brigham and Women's Hospital place over a million orders through the electronic health records (EHR) system. Even though studies indicate that practitioners place more than 99.9 percent of orders for the correct patients, researchers at the Brigham analyzed that remaining 0.1 percent to determine and address the root causes of wrong-patient order errors. In an effort to improve patient safety, the Brigham required headshots for participating patients to be displayed in their EHR as part of a quality improvement program in the Emergency Department. Analysis of the millions of orders placed for participating patients over a two-year span showed the rate of wrong patient order entry to be 35 percent lower for patients whose photos were included in their EHR. Results are published in *JAMA Network Open*.

"There's one specific solution to mitigating wrong-patient errors that turned out to be really effective: displaying patient's photos in their electronic chart. As a provider, these are patients that you know personally -- you've cared for them and you're going to quickly recognize that face," said Hojjat Salmasian, MD, MPH, PhD, of the Department of Quality and Safety at the Brigham.

Salmasian had previously collaborated on a project in which pop-up alerts were used to reduce wrong-patient errors. Unlike interruptive pop-up alerts, including patient photos in EHRs enables uninterrupted navigation and utilizes the natural human affinity for facial recognition. Promising results from smaller-scale studies looking at the implementation of patient photos to decrease wrong

patient order entry (WPOE) inspired Salmasian and his colleagues to pursue this larger-scale test at the Brigham.

The researchers focused on the Emergency Department, where providers often multitask and, consequently, have a higher rate of errors. In a retrospective cohort of patients admitted between July 2017 and June 2019, photos taken of willing patient participants and corresponding orders placed were analyzed for error. Of 2.5 million total orders placed across 71,851 unique patients, there was a decrease in errors of 35 percent. Salmasian emphasized the sheer volume of orders this 35 percent amasses to when considering the millions of orders placed per year at the Brigham, saying without this photo implementation an estimated 2 in every 1,000 orders may be placed incorrectly in the ED.

This improvement in error risk was slightly more detectable in white patients, a finding that illuminates implicit bias, treatment inequities, and the patient care impact of having a predominantly white patient population. The Brigham and Mass General Brigham have plans to include photos of all participating patients in their electronic health records. Despite the barrier COVID-19 has caused, with masks being required of all patients, hospitals locally and across the country plan to integrate this photo feature as soon as they are able. As requests to include a headshot in one's electronic health record increase, patients will begin to realize their actions -- even as small as uploading a headshot to a healthcare portal -- can have a huge impact on their health outcomes.

"It's important for all of us to realize that there are things that we can do as patients that directly impact the appropriateness and safety of care that we receive," said Salmasian. "If more patients engage in the care they receive, our health care system improves in both safety and quality."

Funding for this work was provided by the CRICO Risk Management Foundation and grant R01HS024713 from the AHRQ. Salmasian reported receiving grants from the Agency for Healthcare Research and Quality (AHRQ) during the conduct of the study.

Paper Cited:

Salmasian, H et al. "Association of Display of Patient Photographs in the Electronic Health Record with Wrong-Patient Order Entry Errors" JAMA Network Open
DOI: 10.1001/jamanetworkopen.2020.19652

https://bit.ly/2Utq1kJ

Diabetes drug can treat and reverse heart failure and reduce

Empagliflozin, a recently developed diabetes drug, can effectively treat and reverse heart failure

Empagliflozin, a recently developed diabetes drug, can effectively treat and reverse heart failure in both diabetic and non-diabetic patients, according to researchers at the Icahn School of Medicine at Mount Sinai.

Their clinical trial showed that this medication can improve the heart's size, shape, and function, leading to better exercise capacity and quality of life, which will reduce hospitalizations for heart failure patients. The results were presented on Friday, November 13, at the American Heart Association Scientific Sessions 2020 and simultaneously published in the *Journal of the American College of Cardiology*.

"Our clinical trial's promising results show this diabetes drug can ameliorate lives of heart failure patients with reduced ejection fraction, enhance their exercise capacity, and improve their quality of life with little to no side effects. We expect this work will help lead to U.S. Food and Drug Administration approval of empagliflozin for this patient population in the coming months," said first author Carlos Santos-Gallego, MD, postdoctoral fellow at the Icahn School of Medicine at Mount Sinai.

"Our study also identifies why this drug is effective: because it improves heart function, something that has not been understood until now," Dr. Santos-Gallego said. "Many doctors are afraid of prescribing a drug they do not understand, and our findings will help clinicians feel more comfortable giving this to patients once

approved. A cornerstone finding is that, although this drug was initially developed for diabetes, it is also incredibly effective in patients without diabetes."

Importantly, the researchers noted that the drug did not appear to cause hypoglycemia, or low blood sugar, in non-diabetic patients.

For the trial, known as "EMPATROPISM," researchers recruited 84 patients with chronic heart failure with reduced ejection fraction (EF)--the percentage of blood the left ventricle pumps with each contraction--and randomized them to treatment with empagliflozin or a placebo. All had baseline evaluations including cardiac magnetic resonance imaging, a cardiopulmonary exercise test on a bicycle wearing a face mask to text oxygen levels, a six-minute walk test, and quality-of-life questionnaires. Patients received treatment or placebo for six months, with some short safety visits at one and three months. At the six-month mark, patients went through the same tests.

Roughly 80 percent of the patients treated with empagliflozin showed significant improvement, and their hearts returned to near normal, the researchers found. This group had a 16.6 percent improvement in left ventricular ejection fraction at the six-month mark and their hearts pumped blood in a stronger way. Their hearts became smaller, less dilated because of less congestion and less fluid accumulation in the body, meaning that their heart failure became less severe, and the walls of the heart were less thick, meaning that the left ventricle could pump blood more easily. The placebo group showed no improvement; those patients either stayed at baseline or their condition got worse. They had a diminishing EF; their hearts were more dilated and thicker, and had an abnormal, more spherical, shape.

The study also showed that patients taking empagliflozin had roughly 10 percent improvement in their exercise levels, a statistically significant difference, while patients on the placebo arm showed no improvement. This demonstrated that the empagliflozin group became healthier, could do more everyday activities, and had an improved quality of life, putting those patients at less risk of hospitalization.

The study also identified, for the first time, why this drug is effective for treating heart failure. In heart failure, the heart goes through "adverse remodeling," in which the left ventricle dilates, becomes thicker (hypertrophic) and more spherical, and pumps in a weaker way with a lower ejection fraction. The researchers demonstrated that this drug lessens and reverses this adverse remodeling. It reduces the dilation and hypertrophy of the left ventricle, helps the left ventricle pump more strongly (increasing the ejection fraction), and changes the shape of the left ventricle, making it more elongated and less spherical.

"We were very surprised at how fast the benefits appeared with empagliflozin. The patients were already feeling better in the first few weeks of taking it. Another key issue is how safe this drug is; we saw no severe side effects, despite being an antidiabetic drug, no hypoglycemia was noticed. This shows that empagliflozin is a safe and potent treatment for heart failure with reduced ejection fraction independently of the diabetic status of the patient," explains co-author Juan Badimon, PhD, Professor of Medicine (Cardiology) and Director of the Atherothrombosis Research Unit at the Cardiovascular Institute at the Icahn School of Medicine at Mount Sinai.

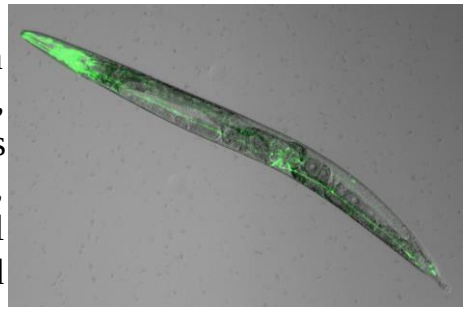
https://bit.ly/3kwcsF6

Worms reveal why melatonin promotes sleep

Research in C. elegans shows how melatonin activates the BK channel in the brain

Melatonin is used as a dietary supplement to promote sleep and get over jet lag, but nobody really understands how it works in the brain. Now, researchers at UConn Health show that melatonin helps

worms sleep, too, and they suspect they've identified what it does in us.



Our bodies produce melatonin in darkness. It's technically a hormone, but you can readily buy melatonin as a supplement in pharmacies, nutrition stores, and other retail shops. It's widely used by adults and often in children as well.

The Caennorhabditis elegans worm's neurons expressing the receptor for melatonin glow green. **Credit: Bojun Chen/UConn Health**

Melatonin binds to melatonin receptors in the brain to produce its sleep-promoting effects. Think of a receptor as a keyhole, and melatonin as the key. The two keyholes for melatonin are called MT1 and MT2 in human brain cells. But scientists didn't really know what happens when the keyhole is unlocked. Now UConn Health School of Medicine neuroscientists Zhao-Wen Wang and Bojun Chen and their colleagues have identified that process through their work with C. elegans worms, as reported in *PNAS* on Sept. 21. When melatonin fits into the MT1 receptor in the worm's brain, it opens a potassium channel known as the BK channel.

A major function of the BK channel in neurons is to limit the release of neurotransmitters, which are chemical substances used by neurons to talk to each other. In their search for factors related to the BK channel, the Wang and Chen labs found that a melatonin receptor is needed for the BK channel to limit neurotransmitter release. They subsequently found that melatonin promotes sleep in worms by activating the BK channel through the melatonin receptor. Worms that lack either melatonin secretion, the melatonin receptor, or the BK channel spend less time in sleep.

But wait--worms sleep?

Indeed they do, says Chen. There's actually been quite a lot of research on worm sleep, and researchers found that sleep is similar between worms and mammals like humans and mice.

Wang and Chen next plan to see if the melatonin-MT1-BK relationship holds in mice. The BK channel is involved in all kinds of bodily happenings, from epilepsy to high blood pressure. By learning more about the relationships between the BK channel, sleep, and behavioral changes, the researchers hope both to understand melatonin better and also help people who suffer from other diseases related to the BK channel.

https://bit.ly/2Ut6OJb

COVID-19 survival among elderly patients could be improved by arthritis drug

A type of arthritis drug may reduce the risk of dying for elderly patients with COVID-19.

This is the finding of a new international study, led by scientists at Imperial College London and the Karolinska Institutet, Sweden, published in the journal *Science Advances*.

In the early-stage study, 83 patients, with a median age of 81 and all suffering from moderate to severe COVID-19 infection, were given a drug called baricitinib. This medication is usually used to treat rheumatoid arthritis, and was initially identified by the Imperial team using artificial intelligence as a drug that could have anti-viral and anti-inflammatory effects.

In the study, the patients, who were in multiple hospitals across Italy and Spain, had a 71 per cent reduced risk of dying compared to patients who had not taken the drug. The study also found that 17 per cent of patients who were given the drug died or needed to go on a ventilator, compared to 35 per cent in the control group who were not given the medication.

The research team say the findings are being followed up with large-scale clinical trials.

Professor Justin Stebbing, co-lead author of the study from the Department of Surgery and Cancer at Imperial said: "We urgently need to find more effective treatments for COVID-19 while we wait for a vaccine to become widely available. This is one of the first COVID-19 treatments to go from computer to clinic and laboratory. It was first identified by an AI algorithm in February, which scanned thousands of potential drugs that could work against this virus.

"The study suggests this drug can aid recovery of patients with moderate to severe COVID-19, and may provide a new weapon in our arsenal against the virus. Large-scale clinical trials of this drug, to further investigate its potential, are now under way"

In the research, scientists from the Karolinska Institutet in Sweden together with the Imperial team grew miniature human organs in the lab, called organoids, to investigate how exactly the drug may combat COVID-19.

The findings revealed that the drug may help work in two ways: reduce organ damage caused by inflammation, and blocking the virus entering human cells.

When infected with the COVID-19 virus, called SARS-CoV-2, the body releases different types of inflammatory molecules, called chemokines and cytokines. These molecules act as the early warning system for the body, telling the immune system the body is under attack.

However, in the case of COVID-19, particular cytokine and chemokines, including those called interleukins and interferons, causes this warning system to spiral out of control, and trigger a so-called cytokine storm. This cytokine storm not only causes significant damage to the body's organs, but the study revealed it also helps the virus gain access inside human cells.

The study showed a particular cytokine, called an interferon, increases the number of receptors, or docking points, for the virus. By doing this it, in effect, lowers the drawbridge and lets the virus into the cells of the body.

The researchers revealed the drug blocks this process occurring and so increases survival from COVID-19. The research also suggested COVID-19 increases the activity of genes related to platelets, which can make the blood sticky and more likely to form clots. The drug baricitinib was shown to reduce the activity of the genes.

Professor Volker Lauschke, co-lead author from Karolinska Institutet in Sweden, explained: "This study confirms what AI predicted, and what we were hearing from patient case reports. For instance one case involved an 87-year-old severely unwell patient from Foggia, Italy, who showed rapid improvement after being given the drug, whereas her husband and son, who did not receive baricitinib, died. This study has also shone a light on exactly how this drug may protect us at the cellular level. This helps us understand why other types of drugs are proving beneficial, or not beneficial, as we as help identify other treatments which may tackle COVID-19."

Professor Stebbing added: "We have seen the top line results of a randomized study called the Adaptive Covid Treatment Trial-2 announced recently, showing benefits of baricitinib plus remdesivir, compared to remdesivir alone in over one thousand patients. Other very large trials occurring now include COV-BARRIER, and this will help create a fuller picture of the benefits and side effects of the oral medication (a small number of the patients in our study needed to stop the treatment due to problems with liver function). Further trials comparing baricitinib to other drugs in COVID-19 patients would also be helpful in improving outcomes."

Notes to editors:

'JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality' is published in the journal Science Advances. A full copy of the paper can be found on this link:
https://advances.sciencemag.org/lookup/doi/10.1126/sciadv.abe4724

https://bit.ly/2K1U6z1

Why does COVID-19 seem to spare children?

Vanderbilt University Medical Center study offers an answer

Researchers at Vanderbilt University Medical Center (VUMC) and their colleagues have determined a key factor as to why COVID-19 appears to infect and sicken adults and older people preferentially while seeming to spare younger children.

Children have lower levels of an enzyme/co-receptor that SARS-CoV-2, the RNA virus that causes COVID-19, needs to invade airway epithelial cells in the lung. The findings, published today in the *Journal of Clinical Investigation*, support efforts to block the enzyme to potentially treat or prevent COVID-19 in older people.

"Our study provides a biologic rationale for why particularly infants and very young children seem to be less likely to either get infected or to have severe disease symptoms," said Jennifer Sucre, MD, assistant professor of Pediatrics (Neonatology), who led the research with Jonathan Kropski, MD, assistant professor of Medicine.

Sucre and Kropski are co-corresponding authors of the paper. Bryce Schuler, MD, PhD, a resident in Pediatrics and Genetics at VUMC and postdoctoral fellow in the Vanderbilt Stimulating Access to Research in Residency program, is the paper's first author.

There is still much to learn about SARS-CoV-2. But this much is known: After a viral particle is inhaled into the lungs, protein "spikes" that stick out like nail studs in a soccer ball attach to ACE2, a receptor on the surfaces of certain lung cells.

A cellular enzyme called TMPRSS2 chops up the spike protein, enabling the virus to fuse into the cell membrane and "break into" the cell. Once inside, the virus hijacks the cell's genetic machinery to make copies of its RNA.

Sucre and Kropski, who have collaborated since 2016 on studies of lung diseases in premature infants and adults, wondered if TMPRSS2 had something to do with the greater severity of COVID-19 symptoms observed in older people compared to children.

"Our research has always focused on understanding lung development and how infant lungs differ from adult lungs in their vulnerability to injury," Sucre said. "In this study we actually took the opposite approach, and were able to see how the developing lung by its differences is protected from SARS-CoV-2 infection."

The researchers were well equipped to begin such a study. As members of the international Human Cell Atlas (HCA) Lung Biological Network, they and their colleagues had built a dataset on lung development in the mouse using a technique called single-cell RNA-sequencing.

The technique can detect the expression of genes in individual cells of tissues such as the lung. In this way the researchers were able to track the expression of genes known to be involved in the body's response to COVID-19 over time.

They found that while the gene for ACE2 was expressed at low levels in the mouse lung, "TMPRSS2 stood out as having a really striking trajectory of increased expression during development," Schuler said.

With the help of VUMC pathologists, the researchers obtained and analyzed human lung specimens collected from donors of different ages, and confirmed a similar trajectory in TMPRSS2 expression to what they'd found in mice.

"What we found is that expression of (TMPRSS2) goes up significantly with aging, and we see that at the level of the gene and at the level of the protein," Sucre said. "We see a lot more TMPRSS2 in older individuals, in both humans and mice."

The researchers also used fluorescent probes to analyze autopsy specimens from three patients who died of COVID-19, and found the virus in three types of cells that express TMPRSS2.

TMPRSS2 is well known for its role in the development of prostate cancer. Drugs that block the enzyme and which have been approved for the treatment of advanced prostate cancer currently are being tested clinically as potential treatments for COVID-19.

The new findings reported today support further investigation.

"We do think TMPRSS2 could be an attractive target both in treatment and potentially as a prophylaxis for (preventing infection in) people at high risk of COVID exposure," Sucre said.

The research was supported by grants from the National Institutes of Health.

https://wb.md/32QeU30

'Breakthrough Finding' Reveals Why Certain COVID Patients Die

Why does one 40-year-old get really sick and another one not even need to be admitted?"

Liz Szabo

Dr. Megan Ranney has learned a lot about COVID-19 since she began treating patients with the disease in the emergency department in February.

But there's one question she still can't answer: What makes some patients so much sicker than others?

Advancing age and underlying medical problems explain only part of the phenomenon, said Ranney, who has seen patients of similar age, background and health status follow wildly different trajectories.

"Why does one 40-year-old get really sick and another one not even need to be admitted?" asked Ranney, an associate professor of emergency medicine at Brown University.

In some cases, provocative new research shows, some people — men in particular — succumb because their immune systems are hit by friendly fire. Researchers hope the finding will help them develop targeted therapies for these patients.

In an international study in Science, 10% of nearly 1,000 COVID patients who developed life-threatening pneumonia had antibodies that disable key immune system proteins called interferons. These antibodies — known as autoantibodies because they attack the body itself — were not found at all in 663 people with mild or asymptomatic COVID infections. Only four of 1,227 healthy individuals had the autoantibodies. The study, published on Oct. 23, was led by the COVID Human Genetic Effort, which includes 200 research centers in 40 countries.

"This is one of the most important things we've learned about the immune system since the start of the pandemic," said Dr. Eric Topol, executive vice president for research at Scripps Research in San Diego, who was not involved in the new study. "This is a breakthrough finding." (Topol is also editor-in-chief of Medscape.)

In a second Science study by the same team, authors found that an additional 3.5% of critically ill patients had mutations in genes that control the interferons involved in fighting viruses. Given that the body has 500 to 600 of these genes, it's possible researchers will find more mutations, said Qian Zhang, lead author of the second study.

Interferons serve as the body's first line of defense against infection, sounding the alarm and activating an army of virus-fighting genes, said virologist Angela Rasmussen, an associate research scientist at the Center of Infection and Immunity at Columbia University's Mailman School of Public Health.

"Interferons are like a fire alarm and a sprinkler system all in one," said Rasmussen, who wasn't involved in the new studies.

Lab studies show interferons are suppressed in some people with COVID-19, perhaps by the virus itself.

Interferons are particularly important for protecting the body against new viruses, such as the coronavirus, which the body has never encountered, said Zhang, a researcher at Rockefeller

University's St. Giles Laboratory of Human Genetics of Infectious Diseases.

When infected with the novel coronavirus, "your body should have alarms ringing everywhere," said Zhang. "If you don't get the alarm out, you could have viruses everywhere in large numbers."

Significantly, patients didn't make autoantibodies in response to the virus. Instead, they appeared to have had them before the pandemic even began, said Paul Bastard, the antibody study's lead author, also a researcher at Rockefeller University.

For reasons that researchers don't understand, the autoantibodies never caused a problem until patients were infected with COVID-19, Bastard said. Somehow, the novel coronavirus, or the immune response it triggered, appears to have set them in motion.

"Before COVID, their condition was silent," Bastard said. "Most of them hadn't gotten sick before."

Bastard said he now wonders whether autoantibodies against interferon also increase the risk from other viruses, such as influenza. Among patients in his study, "some of them had gotten flu in the past, and we're looking to see if the autoantibodies could have had an effect on flu."

Scientists have long known that viruses and the immune system compete in a sort of arms race, with viruses evolving ways to evade the immune system and even suppress its response, said Sabra Klein, a professor of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health.

Antibodies are usually the heroes of the immune system, defending the body against viruses and other threats. But sometimes, in a phenomenon known as autoimmune disease, the immune system appears confused and creates autoantibodies. This occurs in diseases such as rheumatoid arthritis, when antibodies attack the joints, and Type 1 diabetes, in which the immune system attacks insulin-producing cells in the pancreas.

Although doctors don't know the exact causes of autoimmune disease, they've observed that the conditions often occur after a viral infection. Autoimmune diseases are more common as people age.

In yet another unexpected finding, 94% of patients in the study with these autoantibodies were men. About 12.5% of men with life-threatening COVID pneumonia had autoantibodies against interferon, compared with 2.6% of women.

That was unexpected, given that autoimmune disease is far more common in women, Klein said.

"I've been studying sex differences in viral infections for 22 years, and I don't think anybody who studies autoantibodies thought this would be a risk factor for COVID-19," Klein said.

The study might help explain why men are more likely than women to become critically ill with COVID-19 and die, Klein said.

"You see significantly more men dying in their 30s, not just in their 80s," she said.

Akiko Iwasaki, a professor of immunobiology at the Yale School of Medicine, noted that several genes involved in the immune system's response to viruses are on the X chromosome.

Women have two copies of this chromosome — along with two copies of each gene. That gives women a backup in case one copy of a gene becomes defective, Iwasaki said.

Men, however, have only one copy of the X chromosome. So if there is a defect or harmful gene on the X chromosome, they have no other copy of that gene to correct the problem, Iwasaki said.

Bastard noted that one woman in the study who developed autoantibodies has a rare genetic condition in which she has only one X chromosome.

Scientists have struggled to explain why men have a higher risk of hospitalization and death from COVID-19. When the disease first appeared in China, experts speculated that men suffered more from

the virus because they are much more likely to smoke than Chinese women.

Researchers quickly noticed that men in Spain were also more likely to die of COVID-19, however, even though men and women there smoke at about the same rate, Klein said.

Experts have hypothesized that men might be put at higher risk by being less likely to wear masks in public than women and more likely to delay seeking medical care, Klein said.

But behavioral differences between men and women provide only part of the answer. Scientists say it's possible that the hormone estrogen may somehow protect women, while testosterone may put men at greater risk. Interestingly, recent studies have found that obesity poses a much greater risk to men with COVID-19 than to women, Klein said.

Yet women have their own form of suffering from COVID-19.

Studies show women are four times more likely to experience long-term COVID symptoms, lasting weeks or months, including fatigue, weakness and a kind of mental confusion known as "brain fog," Klein noted.

As women, "maybe we survive it and are less likely to die, but then we have all these long-term complications," she said.

After reading the studies, Klein said, she would like to learn whether patients who become severely ill from other viruses, such as influenza, also harbor genes or antibodies that disable interferon.

"There's no evidence for this in flu," Klein said. "But we haven't looked. Through COVID-19, we may have uncovered a very novel mechanism of disease, which we could find is present in a number of diseases."

To be sure, scientists say that the new study solves only part of the mystery of why patient outcomes can vary so greatly.

Researchers say it's possible that some patients are protected by past exposure to other coronaviruses. Patients who get very sick also may have inhaled higher doses of the virus, such as from repeated exposure to infected co-workers.

Although doctors have looked for links between disease outcomes and blood type, studies have produced conflicting results.

Screening patients for autoantibodies against interferons could help predict which patients are more likely to become very sick, said Bastard, who is also affiliated with the Necker Hospital for Sick Children in Paris. Testing takes about two days. Hospitals in Paris can now screen patients on request from a doctor, he said.

Although only 10% of patients with life-threatening COVID-19 have autoantibodies, "I think we should give the test to everyone who is admitted," Bastard said. Otherwise, "we wouldn't know who is at risk for a severe form of the disease."

Bastard said he hopes his findings will lead to new therapies that save lives. He notes that the body manufactures many types of interferons. Giving these patients a different type of interferon — one not disabled by their genes or autoantibodies — might help them fight off the virus.

In fact, a pilot study of 98 patients published Thursday in the Lancet Respiratory Medicine journal found benefits from an inhaled form of interferon. In the industry-funded British study, hospitalized COVID patients randomly assigned to receive interferon beta-1a were more than twice as likely as others to recover enough to resume their regular activities.

Researchers need to confirm these findings in a much larger study, said Dr. Nathan Peiffer-Smadja, a researcher at Imperial College London who was not involved in the study but wrote an accompanying editorial. Future studies should test patients' blood for genetic mutations and autoantibodies against interferon, to see if they respond differently than others.

Peiffer-Smadja notes that inhaled interferon may work better than an injected form of the drug because it's delivered directly to the

lungs. While injected versions of interferon have been used for years to treat other diseases, the inhaled version is still experimental and not commercially available.

And doctors should be cautious about interferon for now, because a study led by the World Health Organization found no benefit to an injected form of the drug in COVID patients, Peiffer-Smadja said. In fact, there was a trend toward higher mortality rates in patients given interferon, although this finding could have been due to chance. Giving interferon later in the course of disease could encourage a destructive immune overreaction called a cytokine storm, in which the immune system does more damage than the virus.

Around the world, scientists have launched more than 100 clinical trials of interferons, according to clinicaltrials.gov, a database of research studies from the National Institutes of Health.

Until larger studies are completed, doctors say, Bastard's findings are unlikely to change how they treat COVID-19.

Dr. Lewis Kaplan, president of the Society of Critical Care Medicine, said he treats patients according to their symptoms, not their risk factors.

"If you are a little sick, you get treated with a little bit of care," Kaplan said. "You are really sick, you get a lot of care. But if a COVID patient comes in with hypertension, diabetes and obesity, we don't say, 'They have risk factors. Let's put them in the ICU.' "

https://wb.md/2K730LD

SAMSON Answers the Statin Side Effect Question

The novel and elegant SAMSON trial largely answers the lingering question of statin side effects.

John Mandrola, MD

This has major implications because statins may be *the* most studied class of any drug. More than 130,000 patients have been enrolled in placebo-controlled trials; the results show a consistent 25% relative reduction in future cardiac events.

Yet many patients discontinue the drug because of adverse effects, most often myalgia. Large observational studies report a 20% to 50% higher rate of myalgia in statin users vs nonusers.

But in blinded randomized controlled trials (RCTs), people taking statins have almost the same rates of minor adverse effects as those taking placebo.

One way to explain the discrepancy between the observational studies and the RCTs is that statin trials have run-in periods that exclude patients who report adverse effects. Another explanation is the nocebo effect—when a negative expectation produces a negative outcome.

An Italian group has published one of the best examples of nocebo effects. They gave the β-blocker atenolol to three groups of men: one group was given no information, another group was informed about the drug but not any side effects, and a third group was told about possible erectile dysfunction. The rates of erectile dysfunction in each group were 3%, 15%, and 31%, respectively.

The SAMSON Trial

In the SAMSON trial, presented at the 2020 American Heart Association (AHA) Scientific Sessions and simultaneously published in the *New England Journal of Medicine,* James Howard and colleagues at the Imperial College London tested the nocebo effect of statins.

They used the so-called n-of-1 trial design in which each patient serves as their own control. This design is nifty because it mirrors what clinicians do in practice. You start a drug and see if it makes the person feel better; if you aren't sure, you stop it, observe for a time, and then restart.

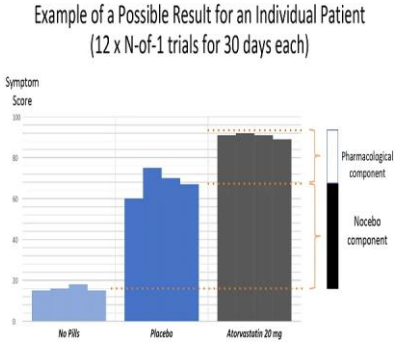
The key difference in SAMSON is that patients and doctors were blinded to the treatment. The trial randomly assigned 60 patients

who had previously stopped statins because of side effects to 12 one-month periods consisting of no medications, placebo, and statin. All but 11 patients completed the 12-month trial.

Patients recorded symptom intensity (0-100) each day on a smartphone app.

The primary outcome of the study was the ratio between excess symptom intensity caused by the placebo and excess symptom intensity caused by the statin.

The graph below depicts how the nocebo proportion was calculated. First, the researchers recorded the difference in symptom scores between taking no pills and a placebo.



This is the nocebo proportion (ie, the ill effects from the negative expectations of the pill).

The authors then recorded the symptom score from the statin, which includes both the nocebo effect and the pharmacologic effects of the drug.

Three Main Results

The mean symptom score for all patients was 8.0 during no-pill months, 15.4 during placebo months, and 16.3 during the statin months.

The difference in symptom scores between the placebo and statin months and the no-pill months was highly significant ($P < .0001$).

However, the difference in symptom scores between the placebo and statin months was not significant ($P = .39$).

To calculate the nocebo effect, they divided the symptoms score of the nocebo component by the statin proportion, for a nocebo ratio of 0.9:

symptom intensity on placebo (15.4) – symptom intensity on no pills (8.0)

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symptom intensity on statins (16.3) – symptom intensity on no pills (8.0)

The authors concluded that patients really do get symptoms from taking statin tablets. But, crucially, 90% of these symptoms are elicited by placebo pills too.

Statin side effects, therefore, are mainly caused by the act of taking pills. Six months after completing the trial, 30 of the 60 patients who were shown their personal results had successfully restarted statins.

My Comments

The results of any trial ought to be considered in the context of prior data.

Before SAMSON, the evidence for nocebo effects of statins was strong. The most convincing statin RCT in this regard was the lipid-lowering arm of the ASCOT trial, which compared atorvastatin vs placebo in 10,000 patients.

ASCOT-LLA had both a blinded phase and open-label continuation. In the blinded phase, there were no significant differences in muscle-related symptoms, but in the open-label phase, significantly more patients in the statin arm reported muscle symptoms.

We clinicians can use the SAMSON results the same way the Imperial College researchers used them: to convince some patients previously intolerant to statins to restart a drug that lowers cardiac events. That is a big deal.

Another general message of SAMSON is for clinical trialists. If expectations can have this large of an effect, imagine the expectation differential between those in the procedure arm of, say, an atrial fibrillation ablation vs drug trial. Or in a percutaneous coronary intervention (PCI) vs medical therapy trial? Expectations are especially relevant with measurement of subjective bias–prone outcomes, such as quality of life.

My favorite message of SAMSON is how it informs the art of medicine. Experienced clinicians well know that getting the best

outcome from a drug or procedure transcends pharmacology or physiology.

It means managing the complex neurophysiology of placebo and nocebo effects. Such effects may stem from simple expectations of reward or harm, social learning (think Internet), and even Pavlovian conditioning.

Clinicians must be mindful of our words and actions. Yes, patients ought to be informed, but it also makes sense to use all the tools of human nature to get a positive outcome.

The practices of showing a patient and her family a beautiful angiographic result after a PCI or being optimistic after an AF ablation should not be discounted. And when we prescribe a treatment, there is every reason to be positive.

The word "doctor" originated from the Latin verb "docere"—to teach. I will save the SAMSON trial on my phone or computer and use it to teach patients about the power of expectations and the nocebo effect of statins.

When, for instance, a patient reports statin side effects, rather than reduce the dose of the statin, which reinforces that the drug is causing the symptom, a better tack would be to pull out the SAMSON trial and teach about the nocebo effect.

Yet empathy remains vital. Patients who report statin side effects are having real symptoms; they shouldn't be dismissed. SAMSON simply says the side effect isn't from the *statin* but from the *statin pill.*

The SAMSON investigators have beautifully shown that being a healer means more than writing a prescription or moving a catheter. For that I say, thank you.

John Mandrola practices cardiac electrophysiology in Louisville, Kentucky, and is a writer and podcaster for Medscape. He espouses a conservative approach to medical practice. He participates in clinical research and writes often about the state of medical evidence.

https://bit.ly/3pz8qPO

How a Queensland sea sponge is helping scientists unravel a 700-million-year-old mystery of evolution

Humans, mice, zebrafish — and most likely the entire animal kingdom — share enhancer regions with a sea sponge that comes from the Great Barrier Reef

Emily S Wong *

Many human traits, such as height and disease susceptibility, depend on genes that are encoded in our DNA. These genes are switched on and off and further fine-tuned by important but hard-to-find regions in the genome.

A particularly important class of these regions are known as enhancers, which boost the likelihood that a particular gene will be activated. Trying to find enhancers based on the genome sequence alone is incredibly difficult, like finding a light switch in a dark room. That's why, until now, there has not been a single example of a DNA sequence enhancer that has been found to be similar right across the animal kingdom.

In a new study published in Science, we found that humans, mice, zebrafish — and most likely the entire animal kingdom — share enhancer regions with a sea sponge that comes from the Great Barrier Reef. Because sea sponges and humans last shared a common ancestor more than 700 million years ago, this means the functional mechanism has been preserved across all this time.

What we did

Our study involved a team of researchers from the Victor Chang Cardiac Research Institute, The University of Queensland, The Centenary Institute, and Monash University. We started by collecting sea sponge samples from the Great Barrier Reef, near Heron Island.

At the University of Queensland, we extracted enhancer DNA from the sea sponge and injected it into a single cell from a zebrafish

embryo. We found that while the sea sponge enhancer sequences were very different from zebrafish enhancer sequences, they still worked: they successfully and consistently drove the expression of a fluorescent protein in certain types of zebrafish cells.

Based on computational predictions, we also identified and tested similar enhancers from humans and mice, to show that these sequences drive the expression of a fluorescent protein in similar zebrafish cell types during development.

We discovered that despite differences between the genetic sequences of sponges and humans due to millions of years of evolution, we could identify a similar set of genomic instructions that controls gene expression in both organisms.

What this means

Our findings represent a fundamental discovery in understanding the connection between our genomes and our physical traits.

The sections of DNA that are responsible for controlling gene expression are notoriously difficult to find, study and understand. Even though they make up a significant part of the human genome, researchers are only beginning to understand this genetic "dark matter".

The work is helping us learn to "read" and understand the human genome, which is amazingly complex. Knowing more about how our genes operate will also help us understand what goes wrong in disease. An improved understanding of the genome will also help us understand how animals evolve.

Emily S Wong does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond their academic appointment.

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https://bit.ly/38Nisak

Ancient bust of Greek god Hermes found during Athens sewage works

The Greek Culture Ministry said that the head is one of many that served as street markers in ancient Athens

The head of an ancient statue of the Greek god Hermes has been unearthed during excavations in central Athens. Photo: Greek Culture Ministry / AFP

A bust of the ancient god Hermes, in good condition, was discovered in central Athens during sewage works, authorities said on Sunday.

The Greek Culture Ministry said that the head, one of many that served as street markers in ancient Athens, was found on Friday and it appears to be from around 300BC – that is, either from the late fourth century BC or the early third century. It depicts Hermes at "a mature age," the ministry said, in contrast to his usual depictions as youthful.

The head is in the style of famed Greek sculpture Alcamenes, who flourished in the second half of fifth century BC, the ministry said.

After serving as a street marker, the head, at some point, had been built into the wall of a drainage duct, the ministry said.