https://bit.ly/3jyLhdj

# Earth to birds: Take the next left

***Scientists have long thought that avian migration is guided by the magnetic field, but how, exactly? The search has led to three very different hypotheses.***

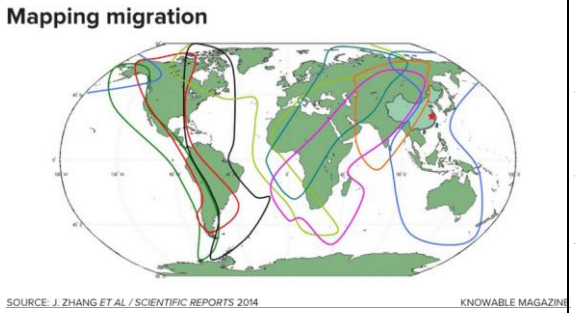
**By Sophie Fess**

Every fall, the bar-tailed godwit takes to wing and flies nonstop from Alaska to New Zealand — a journey of 7,000-plus miles. Countless other birds head off too, bound for warmer spots before returning in the spring. How they do it without getting lost remains mysterious to this day.

Scientists are convinced birds must be using some type of biologically based magnetic compass, but they have yet to figure out how such a system would work. Now the field is heating up, and the latest research is pointing away from one long-standing theory and bolstering some intriguing alternatives.

Clues have been piling up for decades. Back in the 1960s, researchers discovered that European robins can somehow sense Earth's magnetic field. In the decades since, scientists learned that robins and a variety of other bird species use the field, which is created by movement of iron in Earth's core, as a navigational aid. The birds combine this guide with information deduced from the sun, the stars and geographical landmarks to complete their voyages.

But a vexing question that remains is what sort of biological receptor birds use to detect the magnetic field.




***This map shows the eight main migratory routes that billions of birds follow each year. Some species travel tens of thousands of miles between their breeding and wintering grounds. Scientists believe that birds use some sort of biological compass to find their way, but how such a system would work remains mysterious.***

"Key experiments by a group in Germany definitively showed that a magnetic sense exists. Now, more than 50 years later, we still don't really understand how it works," says neuroscientist David Keays of the Research Institute of Molecular Pathology in Vienna.

Today, researchers are focusing on three possible ways that a magnetic sense could work. One idea involves a form of iron with magnetic properties, called magnetite, acting as a sort of compass within cells that rotates to align with the magnetic field. Another contender, known as the radical-pair mechanism, hinges on a chemical reaction in a bird's eye that is influenced by Earth's magnetic field. A third hypothesis suggests that as a bird moves through Earth's magnetic field, small currents are generated in the creature's inner ear. In all three of these scenarios, signals are produced and passed on to the bird's brain to be processed and translated into directions. Here's a look at each of them.

## Testing their metal

The magnetite idea has been studied the longest. Though it is biologically possible — certain kinds of swimming bacteria use the iron mineral to orient themselves — evidence in higher animals remains elusive, with scattered reports that are not always reproducible.

"The history of the magnetite literature in vertebrates is basically, 'I find magnetite here,' 'I find magnetite here,' 'I find magnetite here,' but it's not getting much further than that yet," says biologist Henrik Mouritsen, who investigates magnetoreception in European robins and blackcaps and coauthored a 2016 overview of the topic in the *Annual Review of Biophysics*.

Mouritsen, of the University of Oldenburg in Germany, would like to test the magnetite hypothesis using a classic tool of biologists: Remove something from the animal and see what happens to its behavior. If magnetite is critical for navigation, destroying the magnetite-containing cells would affect the birds' ability to find their way. But for this research strategy to work, scientists need to know

just where to find magnetite in the robins. And even if they find it, "it's a long way from showing a cell contains iron to showing it's magnetite connected to nerve tissue that has any biological relevance," Mouritsen says.

One major knock against the magnetite theory is that a bird's compass senses only the axis of the magnetic field and not its polarity, says chemist Peter Hore of the University of Oxford, a coauthor on the *Annual Reviews* paper. Unlike the compass needles used by people, which rely on the magnetic field's polarity to point toward the magnetic North Pole, birds know which direction the nearest pole is but can't distinguish between north and south. So when scientists invert the magnetic field in the lab, birds don't sense a change and continue to head in the same direction.

But magnetite particles would respond to a flipped field by pointing in the opposite direction, just like a compass needle would. If birds were depending on magnetite, they would sense the change and turn around to head in the opposite direction.

**The eyes have it?**

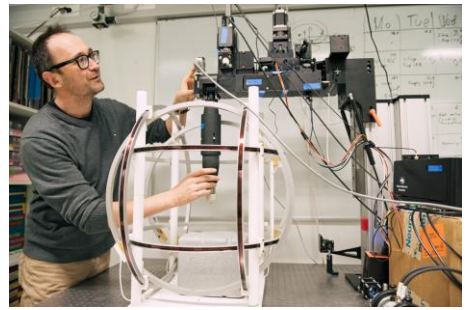
The weight of evidence gathered by scientists tilts toward another idea known as the radical-pair hypothesis, Hore says. Mouritsen also favors this idea, which is based on a protein in birds' eyes called cryptochrome. When light hits cryptochrome, reactions within the protein generate a pair of molecules, called a radical pair. The two molecules in the pair each have an odd number of electrons, leaving each with a single, unpaired electron. These two extra electrons can have spins that are in the same (or parallel) direction, or in the opposite (antiparallel) direction, and they can also flip between these two states.

According to the radical-pair hypothesis, Earth's magnetic field influences how likely the spins are to be parallel or antiparallel. How those spins are then translated into a compass isn't certain, but scientists suspect that in a biochemical reaction in the bird's eye, the two spin states could lead to different amounts of chemical products being made. The products could then influence signals sent from the bird's retina to its brain, making it aware of the magnetic field.

A mechanism based on radical pairs instead of magnetite could potentially allow birds to detect magnetic fields, Keays agrees. But because the radical-pair system depends on light hitting birds' eyes, he thinks there is probably more than one mechanism at work. "It seems counterintuitive to have a light-dependent magnetic sensor when you are flying at night," he says.

**Or maybe the ears do**

Keays is testing a long-forgotten hypothesis, first proposed in 1882, that as a bird flies through Earth's magnetic field, tiny electric currents are generated in its ear. This would happen through electromagnetic induction, akin to how a magnet that moves through a coiled wire creates an electric current in the wire. Extremely sensitive receptors would pick up the small voltages induced in the bird's inner ear and send signals to the brain.



***Neuroscientist David Keays works with an apparatus containing Helmholz coils that he uses to test the magnetic sense of pigeons. When electric current flows through the coils, a magnetic field is generated and Keays analyzes how neurons in the pigeons' brains respond.*** **Credit: Lukas Beck**

Electromagnetic induction is thought to be plausible in sharks and skates, which can sense electric currents in seawater. That same electrosensory system could potentially function as a sort of biological wire in which currents could be induced, allowing the animals to sense Earth's magnetic field.

To test whether induction could work in a land animal like birds, Keays built a simple, scaled model of a pigeon's inner ear: a plastic tube filled with conductive fluid. When he put the model in a rotating magnetic field, sure enough, a small current was induced. Keays suspects the pigeon behavior of rapid head-turning to scan the environment during flight may also serve to boost the voltage in the

birds' ears. He has also discovered a very sensitive electroreceptor in the pigeon's inner ear, which is exactly where it would be needed for induction to work.

Though scientists in the field are finding many new and intriguing pieces of evidence, the definitive test that will finally reveal how birds "feel" the magnetic field has yet to be devised, Hore says. "What we need is a killer experiment that would have the power to show, once and for all, whether it really is radical pairs and whether it really is cryptochrome. But it's actually very hard to come up with something."

***https://bit.ly/2WVx0xQ***

## Older adults who can really smell the roses may face lower likelihood of dementia

***Vision, hearing, touch, olfaction linked to cognition, UCSF study shows***

Seniors who can identify smells like roses, turpentine, paint-thinner and lemons, and have retained their senses of hearing, vision and touch, may have half the risk of developing dementia as their peers with marked sensory decline.

In a study by UC San Francisco, researchers tracked close to 1,800 participants in their seventies for a period of up to 10 years to see if their sensory functioning correlated with the development of dementia. At the time of enrollment, all participants were dementia-free, but 328 participants (18 percent) developed the condition over the course of the study.

Among those whose sensory levels ranked in the middle range, 141 of the 328 (19 percent) developed dementia. This compares with 83 in the good range (12 percent) and 104 (27 percent) in the poor range, according to the study, which publishes in *Alzheimer's and Dementia: The Journal of the Alzheimer's Association* on July 20, 2020.

Previous research has centered on the link between dementia and individual senses, but the UCSF researchers' focus was on the additive effects of multiple impairments in sensory function, which emerging evidence shows are a stronger indicator of declining cognition.

"Sensory impairments could be due to underlying neurodegeneration or the same disease processes as those affecting cognition, such as stroke," said first author Willa Brenowitz, PhD, of the UCSF Department of Psychiatry and Behavioral Sciences, and the Weill Institute for Neurosciences. "Alternatively, sensory impairments, particularly hearing and vision, may accelerate cognitive decline, either directly impacting cognition or indirectly by increasing social isolation, poor mobility and adverse mental health."

While multiple impairments were key to the researchers work, the authors acknowledged that a keen sense of smell, or olfaction, has a stronger association against dementia than touch, hearing or vision. Participants whose smell declined by 10 percent had a 19 percent higher chance of dementia, versus a 1-to-3-percent increased risk for corresponding declines in vision, hearing and touch.

"The olfactory bulb, which is critical for smell, is affected fairly early on in the course of the disease," said Brenowitz. "It's thought that smell may be a preclinical indicator of dementia, while hearing and vision may have more of a role in promoting dementia."

The 1,794 participants were recruited from a random sample of Medicare-eligible adults in the Health, Aging and Body Composition study. Cognitive testing was done at the beginning of the study and repeated every other year. Dementia was defined by testing that showed a significant drop from baseline scores, documented use of a dementia medication or hospitalization for dementia as a primary or secondary diagnosis.

Multisensory testing was done in the third-to-fifth year and included hearing (hearing aids were not allowed), contrast-sensitivity tests for vision (glasses were permitted), touch testing in which vibrations were measured in the big toe, and smell, involving identifying distinctive odors like paint-thinner, roses, lemons, onions and turpentine.

The researchers found that participants who remained dementia-free generally had higher cognition at enrollment and tended to have no sensory impairments. Those in the middle range tended to have

multiple mild impairments or a single moderate-to-severe impairment. Participants at higher risk had multiple moderate-to-severe impairments.

"We found that with deteriorating multisensory functioning, the risk of cognitive decline increased in a dose-response manner," said senior author Kristine Yaffe, MD, of the UCSF departments of Psychiatry and Behavioral Sciences, Epidemiology and Biostatistics, and Neurology, as well as the San Francisco VA Health Care System. "Even mild or moderate sensory impairments across multiple domains were associated with an increased risk of dementia, indicating that people with poor multisensory function are a high-risk population that could be targeted prior to dementia onset for intervention."

The 780 participants with good multisensory function were more likely to be healthier than the 499 participants with poor multisensory function, suggesting that some lifestyle habits may play a role in reducing risks for dementia. The former group was more likely to have completed high school (85 percent versus 72.1 percent), had less diabetes (16.9 percent versus 27.9 percent) and were marginally less likely to have cardiovascular disease, high-blood pressure and stroke.

***Co-Author:*** *Allison Kaup, PhD, of UCSF, San Francisco VA Health Care System and the Neurology Center of Southern California.*

***Funding:*** *National Institutes of Health, National Institute on Aging and Alzheimer's Association.*

***https://bbc.in/3eWn25w***

## Coronavirus: Protein treatment trial 'a breakthrough'

***The preliminary results of a clinical trial suggest a new treatment for Covid-19 reduces the number of patients needing intensive care, according to the UK company that developed it.***

**By Justin Rowlatt BBC News**

The treatment from Southampton-based biotech Synairgen uses a protein called interferon beta which the body produces when it gets a viral infection. The protein is inhaled directly into the lungs of patients with coronavirus, using a nebuliser, in the hope that it will stimulate an immune response.

The initial findings suggest the treatment cut the odds of a Covid-19 patient in hospital developing severe disease - such as requiring ventilation - by 79%. Patients were two to three times more likely to recover to the point where everyday activities were not compromised by their illness, Synairgen claims.

It said the trial also indicated "very significant" reductions in breathlessness among patients who received the treatment.

In addition, the average time patients spent in hospital is said to have been reduced by a third, for those receiving the new drug - down from an average of nine days to six days.

The double-blind trial involved 101 volunteers who had been admitted for treatment at nine UK hospitals for Covid-19 infections.

Half of the participants were given the drug, the other half got what is known as a placebo - an inactive substance.

**Unconfirmed results**

Stock market rules mean Synairgen is obliged to report the preliminary results of the trial.

The results have not been published in a peer-reviewed journal, nor has the full data been made available; so the BBC cannot confirm the claims made for the treatment. But if the results are as the company says, it will be a very important step forward in the treatment of coronavirus infections. The scientist in charge of the trial, Tom Wilkinson, says if the results are confirmed in larger studies the new treatment will be "a game changer".

The trial was relatively small but the signal that the treatment benefits patients was unusually strong, he says. "We couldn't have expected much better results than these," Synairgen chief executive Richard Marsden told the BBC. He described the results as "a major breakthrough in the treatment of hospitalised Covid-19 patients".

**What happens next?**

Mr Marsden said the company will be presenting its findings to medical regulators around the world in the next couple of days to see what further information they require in order to approve the treatment.

That process could take months, although the British government, like many others, has said it will work as fast as possible to get promising coronavirus treatments approved. It is possible it could be given emergency approval, as the anti-viral drug remdesivir was in May.

Another possibility is that permission will be given for more patients to receive the treatment with the effects being carefully monitored to confirm it is safe and effective.

If it does get approval, the drug and the nebulisers used to deliver it would then need to be manufactured in large quantities.

Mr Marsden says he instructed companies to start producing supplies back in April to ensure they would be available should the results be positive. He says he expects Synairgen to be able to deliver "a few 100,000" doses a month by the winter.

**How does the treatment work?**

Interferon beta is part of the body's first line of defence against viruses, warning it to expect a viral attack. The coronavirus seems to suppress its production as part of its strategy to evade our immune systems.

The new drug is a special formulation of interferon beta delivered directly to the airways via a nebuliser which makes the protein into an aerosol. The idea is that a direct dose of the protein in the lungs will trigger a stronger anti-viral response, even in patients whose immune systems are already weak.

Interferon beta is commonly used in the treatment of multiple sclerosis. Previous clinical trials conducted by Synairgen have shown that it can stimulate an immune response and that patients with asthma and other chronic lung conditions can comfortably tolerate the treatment.

**How was the treatment tested?**

No-one involved in the trial knew which patients have been given which treatment until it was over. "If you know it's a drug, your mind might have a bias," explained Sandy Aitken, one of the nurses who administered the new drug to patients at Southampton Hospital.

Synairgen's drug trial was the template for the Accord programme, a fast-track clinical trial scheme set up by the UK government in April to accelerate the development of new drugs for patients with Covid-19.

The Synairgen team believes the drug could be even more effective at the early stages of infection. A trial exploring the effects of giving patients who are in high-risk groups the new drug as soon as they are confirmed as having Covid-19 has struggled to find volunteers because there are so few new infections at the moment.

**What do other experts say?**

Expert in emergency medicine Prof Steve Goodacre, from the University of Sheffield, said: "These results are not interpretable. We need the full details and, perhaps more importantly, the trial protocol. The trial should have been registered and a protocol made available before any analysis was undertaken."

Prof Naveed Sattar, professor of metabolic medicine at the University of Glasgow, said: "The results seem very impressive, and although accepted that the trial is small with just over 100 participants, a 79% reduction in disease severity could be a game changer.

"It would be good to see the full results once presented and peer-reviewed to make sure they are robust and the trial conduct was rigorous. Also, with small numbers comes less certainty on the true level of benefit, or whether benefits vary between people with differing risk characteristics. Such work would require a larger trial but, even so, these results are very exciting."

***https://bit.ly/3eTLyUR***

## Coronavirus antibodies fall dramatically in first 3 months after mild cases of COVID-19

***Antibodies decrease by roughly half every 36 days on average***

***Correction Note:***

*Due to a math miscalculation in the study, a previous version of this release contained an error in the rate at which COVID-19 antibodies decline after infection. The correct rate is 36 days, not 73 as previously reported, which is actually a more dramatic rate of decay. The change is reflected under the findings section of the release.*

**FINDINGS**

A study by UCLA researchers shows that in people with mild cases of COVID-19, antibodies against SARS-CoV-2 -- the virus that causes the disease -- drop sharply over the first three months after infection, decreasing by roughly half every 36 days on average. If sustained at that rate, the antibodies would disappear within about a year.

**BACKGROUND**

Previous reports have suggested that antibodies against the novel coronavirus are short-lived, but the rate at which they decrease has not been carefully defined. This is the first study to carefully estimate the rate at which the antibodies disappear.

**METHOD**

The researchers studied 20 women and 14 men who recovered from mild cases of COVID-19. Antibody tests were conducted at an average of 36 days and 82 days after the initial symptoms of infection.

**IMPACT**

The findings raise concerns about antibody-based "immunity passports," the potential for herd immunity and the reliability of antibody tests for estimating past infections. In addition, the findings may have implications for the durability of antibody-based vaccines.

***AUTHORS***

*F. Javier Ibarrondo, Dr. Jennifer Fulcher, Dr. David Goodman-Meza, Julie Elliott, Christian Hofmann, Mary Hausner, Kathie Ferbas, Dr. Nicole Tobin, Dr. Grace Aldrovandi and Dr Otto Yang, all of UCLA.*

***JOURNAL***

*The research is published in the peer-reviewed New England Journal of Medicine.*

***FUNDING***

*The AIDS Healthcare Foundation, the Doris Duke Charitable Foundation, the National Institutes of Health, the James B. Pendleton Charitable Trust and the McCarthy Family Foundation funded the study.*

***https://bit.ly/2ZUsT6U***

## Researchers accidentally breed sturddlefish

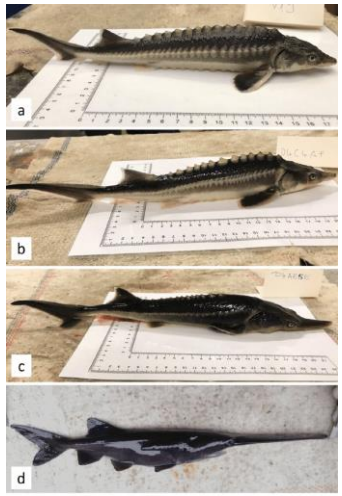
### *Cross between an American Paddlefish and a Russian Sturgeon*

**by Bob Yirka , Phys.org**

A team of researchers working at Hungary's National Agricultural Research and Innovation Centre, Research Institute for Fisheries and Aquaculture, has accidentally bred a new kind of fish—dubbed the sturddlefish by some observers, it is a cross between an American Paddlefish and a Russian Sturgeon. In their paper published in the journal *Genes*, the group describes accidentally breeding the fish and what they learned by doing so.

In the past, scientists and others have bred animals from different species for various reasons, from research to utility—mules (crossed between donkeys and horses) are considered to have beneficial traits from both animals, and ligers (a cross between lions and tigers) have helped researchers understand their respective genetic backgrounds.

In this new effort, the researchers claim that they were not trying to create a new type of fish, they were instead attempting to apply gynogenesis (a type of reproduction in which sperm is used from one creature to fertilize an egg, but its DNA is ignored) using American paddlefish and Russian sturgeon. To their surprise, the eggs produced fish that grew to adults.




In studying the hundreds of offspring produced, which some on the internet have named sturddlefish, the researchers found that they fell into one of three main categories: those that looked mostly like their mothers, those that looked mostly like their fathers and those that inherited features of both parents.

**Credit: Genes. DOI: 10.3390/genes11070753**

Both of the parent fish are endangered, and they would not have had any chance of reproducing in the wild—as their names suggest, the paddlefish live in the U.S. and the sturgeon live in Russia. They are both considered to be "living fossils" by scientists because they have not changed very much over a very long period of time. The researchers note that it is believed their last common ancestor went as far back as 184 million years ago—when the dinosaurs were still

roaming the Earth. They also note that the two fish species have more in common than many might think—they both have spiral valve intestines, for example, and scaleless skin and cartilaginous endoskeletons. The researchers also believe the offspring, like most crossbred offspring, are infertile.

***More information:*** *Jenő Káldy et al. Hybridization of Russian Sturgeon (Acipenser gueldenstaedtii, Brandt and Ratzeberg, 1833) and American Paddlefish (Polyodon spathula, Walbaum 1792) and Evaluation of Their Progeny, Genes (2020). DOI: 10.3390/genes11070753*

***https://bbc.in/2CAllO4***

## Coronavirus: 'Infection here for many years to come'

***The UK will be living with coronavirus for many years to come and even a vaccine is unlikely to eliminate it for good, experts are warning.***

Wellcome Trust director Prof Sir Jeremy Farrar told the House of Commons' Health Committee "things will not be done by Christmas".

He went on to say humanity would be living with the virus for "decades". It comes after the prime minister said last week he hoped for a return to normality by Christmas.

Boris Johnson made the comments as he set out plans to further ease restrictions, including the opening of leisure centres and indoor swimming pools later this month and the prospect of mass gatherings being allowed from the autumn.

But experts giving evidence to the cross-party group of MPs said it was important to be realistic that the virus would still be here.

Sir Jeremy, a member of Sage, the government advisory body, said the world would be living with Covid-19 for "very many, many years to come". "Things will not be done by Christmas. This infection is not going away, it's now a human endemic infection.

"Even, actually, if we have a vaccine or very good treatments, humanity will still be living with this virus for very many, many years.... decades to come."

He urged against complacency during the summer, saying the period was a "crucial phase" to prevent a second wave. "If we have any sense of complacency of 'this is behind us', then we will undoubtedly have a second wave, and we could easily be in the same situation again."

He said it was important to further build up testing capacity as well as investing in treatments and vaccines.

### Vaccine 'unlikely to have durable effect'

Prof Sir John Bell, of the University of Oxford, said he thought it was unlikely that Covid-19 would ever be eliminated despite the positive news announced on Monday that trials by his university had triggered an immune response - an important step in developing a vaccine.

"The reality is that this pathogen is here forever, it isn't going anywhere," he told MPs. "Look at how much trouble they've had in eliminating, for example, polio, that eradication programme has been going on for 15 years and they're still not there.

"So this is going to come and go, and we're going to get winters where we get a lot of this virus back in action.

"The vaccine is unlikely to have a durable effect that'll last for a very long time, so we're going to have to have a continual cycle of vaccinations, and then more disease, and more vaccinations and more disease. "So I think the idea that we're going to eliminate it across the population, that's just not realistic."

### Chief adviser defends government record

The government's chief medical adviser was also quizzed by MPs.

Prof Chris Whitty was asked at length about the UK's record so far in tackling coronavirus. He defended moves to end attempts at trying to contain the virus in March, while defending the actions of ministers accused of announcing lockdown too late.

Crucial evidence about the scale of the outbreak and modelling about how quickly it could spread was presented to ministers on 16 March.

But it was a full week later that a total lockdown was announced.

Prof Whitty said it was not a "huge delay" given the "enormity" of the decision. He also pointed out that others steps were taken in the meantime, including the closing of schools.

Meanwhile, Health Secretary Matt Hancock has defended the government's record on testing - and his decision to set the target of providing 100,000 tests a day by the end of April.

The move has been criticised with some describing it as arbitrary.

But Mr Hancock told the Science and Technology Committee, which was sitting after the Health Committee, that it was important because of the need to "scale up" at an unprecedented speed.

"The point of the big, hairy, audacious goal is to say to the whole system, 'this is where we're going, you do your bit, let's get there'."

**UK coronavirus statistics:**

- ***45,422 people had died in hospitals, care homes and the wider community after testing positive for coronavirus in the UK as of 5pm on Monday, up by 110 from the day before***
- ***Separate figures published by the UK's statistics agencies show there have now been 56,100 deaths registered in the UK where Covid-19 was mentioned on the death certificate***
- ***In the 24-hour period up to 9am on Tuesday, there had been a further 445 lab-confirmed cases. Overall, a total of 295,817 cases have been confirmed since the outbreak began***

***https://bit.ly/2WUGhWG***

## Non-invasive blood test can detect cancer four years before conventional diagnosis methods

***Detects stomach, esophageal, colorectal, lung and liver cancer.***

An international team of researchers has developed a non-invasive blood test that can detect whether an individual has one of five common types of cancers, four years before the condition can be diagnosed with current methods. The test detects stomach, esophageal, colorectal, lung and liver cancer.

Called PanSeer, the test detected cancer in 91% of samples from individuals who had been asymptomatic when the samples were collected and were only diagnosed with cancer one to four years later. In addition, the test accurately detected cancer in 88% of samples from 113 patients who were already diagnosed when the samples were collected. The test also recognized cancer-free samples 95% of the time. ß

In addition, the test accurately detected cancer in 88% of samples from 113 patients who already diagnosed with five common cancer types. The test also recognized cancer-free samples 95% of the time.

The study is unique in that researchers had access to blood samples from patients who were asymptomatic and had not yet been diagnosed. This allowed the team to develop a test that can find cancer markers much earlier than conventional diagnosis methods. The samples were collected as part of a 10-year longitudinal study launched in 2007 by Fudan University in China.

"The ultimate goal would be performing blood tests like this routinely during annual health checkups," said Kun Zhang, one of the paper's corresponding authors and professor and chair of the Department of Bioengineering at the University of California San Diego. "But the immediate focus is to test people at higher risk, based on family history, age or other known risk factors."

Early detection is important because the survival of cancer patients increases significantly when the disease is identified at early stages, as the tumor can be surgically removed or treated with appropriate drugs. However, only a limited number of early screening tests exist for a few cancer types.

Zhang and colleagues present their work in the July 21, 2020 issue of *Nature Communications*. The team includes researchers at Fudan University and at Singlera Genomics, a San Diego and Shanghai based startup that is working to commercialize the tests based on advances originally made in Zhang's bioengineering lab at the UC San Diego Jacobs School of Engineering.

The researchers emphasize that the PanSeer assay is unlikely to predict which patients will later go on to develop cancer. Instead, it is most likely identifying patients who already have cancerous growths, but remain asymptomatic for current detection methods. The team concluded that further large-scale longitudinal studies are needed to

confirm the potential of the test for the early detection of cancer in pre-diagnosis individuals.

**Taizhou Longitudinal Study**

Blood samples in the *Nature Communications* study were collected as part of the Taizhou Longitudinal Study, which has collected plasma samples from over 120,000 individuals between 2007 and 2017. Each individual gave blood samples over a 10-year period and underwent regular check-ins with physicians. In all, over 1.6 million specimens have been collected and archived to date.

Once a person was diagnosed with cancer, the researchers had access to blood samples taken one to four years before these patients even started to show symptoms.

The team was able to examine samples from both healthy and sick individuals from the same cohort. The authors performed an analysis on plasma samples obtained from 605 asymptomatic individuals, 191 of whom were later diagnosed with cancer. They also profile plasma samples from an additional 223 diagnosed cancer patients as well as 200 primary tumour and normal tissue samples.

**DNA methylation based diagnosis method**

Zhang and his lab have been developing for over a decade methods to detect cancer based on a biological process called DNA methylation analysis. The method screens for a particular DNA signature called CpG methylation, which is the addition of methyl groups to multiple adjacent CG sequences in a DNA molecule. Each tissue in the body can be identified by its unique signature of methylation haplotypes. They did an early-stage proof-of-concept study that was published in a 2017 paper in *Nature Genetics*.

Zhang cofounded Singlera Genomics, which licensed technology he developed at UC San Diego. In the past few years, Singlera Genomics has been working to improve and eventually commercialize early cancer detection tests, including the PanSeer test, which was used in the *Nature Communications* study. Zhang is now the company's scientific advisor.

Zhang, Singlera Genomics and additional collaborators have been working to make a formal demonstration that cancer can be detected in the blood prior to conventional diagnosis. The July 2020 *Nature Communications* publication is the outcome of that effort.

*Conflict of interest statement:*
*Jeffrey Gole, Athurva Gore, Qiye He, Jun Min, Xiaojie Li, Lei Cheng, Zhenhua Zhang, Hongyu Niu, Zhe Li, Zhe Li, Han Shi, Justin Dang, Catie McConnell, and Rui Liu are employees of Singlera Genomics. Yuan Gao and Rui Liu are board members of Singlera Genomics. Jeffrey Gole, Athurva Gore, and Rui Liu are inventors on a patent (US62/657,544) held by Singlera Genomics that covers basic aspects of the library preparation method used in this paper. Kun Zhang is a co-founder, equity holder, and paid consultant of Singlera Genomics. The terms of these arrangements are being managed by the University of California San Diego in accor- dance with its conflict of interest policies.*

***Funding***
*The Taizhou Longitudinal Study study was supported by the National Key Research and Development Program of China (grant number: 2017YFC0907000, 2017YFC0907500, 2019YFC1315800, 2019YF101103, and 2016YFC0901403), the National Natural Science Foundation of China (grant number: 91846302 and 81502870), the Key Basic Research grants from the Science and Technology Commission of Shanghai Municipality (grant number: 16JC1400501), the International S&T Cooperation Program of China (grant number: 2015DFE32790), the Shanghai Municipal Science and Technology Major Pro- ject program (grant number: 2017SHZDZX01), the International Science and Technol- ogy Cooperation Program of China (grant number: 2015DFE32790), and the 111 Project (B13016). Funding for the DNA methylation assays was provided by Singlera Genomics.*

*Non-invasive early detection of cancer four years before conventional diagnosis using a blood test*

https://doi.org/10.1038/s41467-020-17316-z

*Xingdong Chen1,2,3,12, Jeffrey Gole4,12, Athurva Gore4,12, Qiye He5,12, Ming Lu2,6,12, Jun Min4, Ziyu Yuan2, Xiaorong Yang2,6, Yanfeng Jiang1,2, Tiejun Zhang7, Chen Suo7, Xiaojie Li5, Lei Cheng5, Zhenhua Zhang5, Hongyu Niu5, Zhe Li5, Zhen Xie5, Han Shi4, Xiang Zhang8, Min Fan9, Xiaofeng Wang1,2, Yajun Yang1,2, Justin Dang4, Catie McConnell4, Juan Zhang2, Jiucun Wang1,2,3, Shunzhang Yu2,7, Weimin Ye2,10?, Yuan Gao4, Kun Zhang 11, Rui Liu4,5 & Li Jin1,2,3*

*1 State Key Laboratory of Genetic Engineering and Collaborative Innovation Center for Genetics and Development, School of Life Sciences, Fudan University, 200438 Shanghai, China. 2 Taizhou Institute of Health Sciences, Fudan University, 225300 Taizhou, Jiangsu, China. 3 Human Phenome Institute, Fudan University, 201203 Shanghai, China. 4 Singlera Genomics Inc., La Jolla, CA 92037, USA. 5 Singlera Genomics (Shanghai) Ltd., 201203 Shanghai, China. 6 Clinical Epidemiology Unit, Qilu Hospital of Shandong University, 250012 Jinan, Shandong, China. 7 Department of Epidemiology, School of Public Health, Fudan University, 200032 Shanghai, China. 8 Taizhou Disease Control and Prevention Center, 225300 Taizhou, Jiangsu, China. 9 Taixing Disease Control and Prevention Center, 225400 Taizhou, Jiangsu, China. 10 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 17177 Stockholm, Sweden. 11 Department of Bioengineering, University of California at San Diego, La Jolla, CA 92093, USA. 12These authors contributed equally: Xingdong Chen, Jeffrey Gole, Athurva Gore, Qiye He, Ming Lu. ?email: weimin.ye@ki.se; gary.gao@singleragenomics.com; kzhang@bioeng.ucsd.edu; rliu@singleragenomics.com; lijin@fudan.edu.cn*

https://bit.ly/39ob9nL

# Genetic variant may explain why some women don't need pain relief during childbirth

***May be carriers of a key genetic variant that acts a natural epidural***

Women who do not need pain relief during childbirth may be carriers of a key genetic variant that acts a natural epidural, say scientists at the University of Cambridge. In a study published today in the journal *Cell Reports*, the researchers explain how the variant limits the ability of nerve cells to send pain signals to the brain.

Childbirth is widely recognised as a painful experience. However, every woman's experience of labour and birth is unique, and the level of discomfort and pain experienced during labour varies substantially between women.

A collaboration between clinicians and scientists based at Addenbrooke's Hospital, part of Cambridge University Hospitals NHS Foundation Trust (CUH), and the University of Cambridge sought to investigate why some mothers report less pain during labour.

A group of women was recruited and characterised by the team led by Dr Michael Lee from the University's Division of Anaesthesia. All the women had carried their first-born to full term and did not request any pain relief during an uncomplicated vaginal delivery. Dr Lee and colleagues carried out a number of tests on the women, including applying heat and pressure to their arms and getting them to plunge their hands into icy water.

Compared to a control group of women that experienced similar births, but were given pain relief, the test group showed higher pain thresholds for heat, cold and mechanical pressure, consistent with them not requesting pain relief during childbirth. The researchers found no differences in the emotional and cognitive abilities of either group, suggesting an intrinsic difference in their ability to detect pain.

"It is unusual for women to not request gas and air, or epidural for pain relief during labour, particularly when delivering for the first time," said Dr Lee, joint first author. "When we tested these women, it was clear their pain threshold was generally much higher than it was for other women."

Next, senior co-author, Professor Geoff Woods, and his colleagues at the Cambridge Institute for Medical Research sequenced the genetic code of both groups of women and found that those in the test group had a higher-than-expected prevalence of a rare variant of the gene KCNG4. It's estimated that one approximately 1 in 100 women carry this variant.

KCNG4 provides the code for the production of a protein that forms part of a 'gate', controlling the electric signal that flows along our nerve cells. As the joint first author Dr Van Lu showed, sensitivity of this gatekeeper to electric signals that had the ability to open the gate and turn nerves on was reduced by the rare variant.

This was confirmed in a study involving mice led by Dr Ewan St. John Smith from the Department of Pharmacology, who showed that the threshold at which the 'defective' gates open, and hence the nerve cell switches 'on', is higher - which may explain why women with this rare gene variant experience less pain during childbirth.

Dr St. John Smith, senior co-author, explained: "The genetic variant that we found in women who feel less pain during childbirth leads to a 'defect' in the formation of the switch on the nerve cells. In fact, this defect acts like a natural epidural. It means it takes a much greater signal - in other words, stronger contractions during labour - to switch it on. This makes it less likely that pain signals can reach the brain."

"Not only have we identified a genetic variant in a new player underlying different pain sensitivities," added senior co-author Professor Frank Reimann, "but we hope this can open avenues to the development of new drugs to manage pain."

"This approach of studying individuals who show unexpected extremes of pain experience also may find wider application in other contexts, helping us understand how we experience pain and develop new drugs to treat it," said Professor David Menon, senior co-author.

*The research was support by the Addenbrooke's Charitable Trust, the National Institute for Health Research Cambridge Biomedical Research Centre, Wellcome Trust, Rosetrees Trust and the BBSRC.*

***Reference***

*Lee, M.C. et al (2020). Human labour pain is influenced by the voltage-gated potassium channel Kv6.4 subunit. Cell Reports; 21 July 2020; DOI: 10.1016/j.celrep.2020.107941*

***https://go.nature.com/3jJaX7p***

# Controversial cave discoveries suggest humans reached Americas much earlier than thought

***Archaeologists say stone artefacts point to occupation more than 30,000 years ago — but not everyone is convinced.***

**Colin Barras**

Archaeologists excavating a cave in the mountains of central Mexico have unearthed evidence that people occupied the area more than 30,000 years ago — suggesting that humans arrived in North America at least 15,000 years earlier than thought.

The discovery, which includes hundreds of ancient stone tools, is backed up by a fresh statistical analysis that incorporates data from other sites. But the conclusion has stirred controversy among some researchers.

"When I see a claim being made that is so dramatic, then the evidence has to be there to substantiate the claim," says archaeologist Kurt Rademaker at Michigan State University in East Lansing.

The first humans in the Americas came from East Asia, but when they began to arrive is hotly debated. Some researchers think that it could have been as early as 130,000 years ago, although most of the archaeological evidence supporting this theory is disputed. For instance, some of the stone artefacts are so simple that sceptics say they were probably produced by natural geological processes rather than by people. The mainstream view is that the peopling of the Americas began about 15,000 or 16,000 years ago — based on genetic evidence and artefacts found at sites including the 14,000-year-old Monte Verde II in Chile.

The latest discoveries, published on 22 July in *Nature*[1], question that consensus. Since 2012, a team led by Ciprian Ardelean at the Autonomous University of Zacatecas in Mexico has been excavating Chiquihuite Cave, which is 2,740 metres above sea level in the country's Astillero Mountains. The researchers found almost 2,000 stone tools, 239 of which were embedded in layers of gravel that have been carbon dated to between 25,000 and 32,000 years old.

There are so few of these oldest tools that Ardelean thinks the site was visited only occasionally, perhaps used as a refuge every few decades, during particularly severe winters. At the height of the last ice age, 26,000 years ago, North America would have been a dangerous place. "There must have been horrible storms, hail, snow," he says. He adds that the Chiquihuite Cave is well insulated and could have provided shelter to any humans who were around to witness the blizzards.

## Troublesome data

The team makes a good case for ancient human occupation, says François Lanoë, an archaeologist and anthropologist at the University of Arizona in Tucson. But he adds that data from caves are "notoriously troublesome" to interpret. Stone tools might have been shifted into deeper layers by geological or biological activity — perhaps moved by burrowing animals — making them seem older than they really are.

That's assuming they really are stone tools. "If an artefact is a stone tool, you see numerous chips removed from the edge," says Rademaker. He sees no clear evidence of this in the images in the paper — a point echoed by archaeologist Ben Potter at Liaocheng University in China.

Ardelean admits that some of the tools might have shifted into lower layers, although he says the 239 oldest tools lie beneath an impenetrable layer of mud formed during the height of the last ice age, so they must be at least that old. He insists they are tools — in fact, he thinks some have telltale marks suggesting that they were made by

novices learning from experts. “Somebody was teaching somebody else at this site,” he says.

Aside from the stone tools, the team found relatively little evidence of human presence. Geneticists led by Eske Willerslev at the University of Copenhagen searched for ancient human DNA in the cave dirt, but with no luck. “Of course, I was disappointed,” says Ardelean.

***One of the limestone artefacts found at the site.*** **Credit: Ciprian Ardelean**

## Early settlers

In a second study, also published in *Nature*[2], two of Ardelean’s co-authors — archaeologists Thomas Higham and Lorena Becerra-Valdivia at the University of Oxford, UK — combined the Chiquihuite Cave evidence with data from 41 other archaeological sites in North America and a region of eastern Siberia and western Alaska called Beringia, and built a statistical model of early human settlement. They concluded that people were present across North America much earlier than the accepted date of 15,000–16,000 years ago.

Some archaeologists think that it is time to take these ideas seriously. “The growing body of evidence for people in Beringia before 15,000 years ago renders their appearance in places like Mexico 20,000 or 30,000 years ago less surprising,” says John Hoffecker, an archaeologist at the University of Colorado Boulder.

Others disagree. Collins says Becerra-Valdivia and Higham assume that early sites such as Chiquihuite Cave and Bluefish Caves[3] in Yukon, Canada, where artefacts have been dated to 24,000 years ago, offer unambiguous evidence of human activity. “This is far from the case,” he says.

Becerra-Valdivia accepts that evidence from most sites — with the exception of Monte Verde II — is disputed, but says that the analysis purposely omitted information from the most controversial sites, to make its case stronger.

If there were people in North America so early, it’s unclear what happened to them. “There continues to be no convincing genetic evidence of a pre-15,000-years-ago human presence in the Americas,” says geneticist David Reich at Harvard Medical School in Boston, Massachusetts

Ardelean says there is a simple reason why genetic studies[4] suggest that humans spread across the Americas only relatively recently: early groups such as the one he thinks was present at Chiquihuite Cave didn’t survive to contribute to modern gene pools. “I definitely advocate for the idea of lost groups,” he says.

*doi: 10.1038/d41586-020-02190-y*

***References***


1. *Ardelean, C. F. et al. Nature https://doi.org/10.1038/s41586-020-2509-0 (2020).* *Article* *Google Scholar*
2. *Becerra-Valdivia, L. & Higham, T. Nature https://doi.org/10.1038/s41586-020-2491-6 (2020).* *Article* *Google Scholar*
3. *Bourgeon, L., Burke, A. & Higham, T. PLoS ONE* ***12****, e0169486 (2017).* *PubMed* *Article* *Google Scholar*
4. *Posth, C. et al. Cell* ***175****, 1185–1197.e22 (2018).* *PubMed* *Article* *Google Scholar*

*Download references*


***https://bit.ly/32SK3DU***

# Chocolate is good for the heart

***Eating chocolate at least once a week is linked with a reduced risk of heart disease***

Sophia Antipolis - Eating chocolate at least once a week is linked with a reduced risk of heart disease, according to research published today in the *European Journal of Preventive Cardiology*, a journal of the European Society of Cardiology (ESC).1

"Our study suggests that chocolate helps keep the heart's blood vessels healthy," said study author Dr. Chayakrit Krittanawong of Baylor College of Medicine, Houston, Texas.

"In the past, clinical studies have shown that chocolate is beneficial for both blood pressure and the lining of blood vessels," he continued. "I wanted to see if it affects the blood vessels supplying the heart (the coronary arteries) or not. And if it does, is it beneficial or harmful?"

The researchers conducted a combined analysis of studies from the past five decades examining the association between chocolate consumption and coronary artery disease (the blockage of the coronary arteries). The analysis included six studies with a total of 336,289 participants who reported their chocolate consumption.

During a median follow-up of nearly nine years, 14,043 participants developed coronary artery disease and 4,667 had a heart attack (when coronary artery disease progresses and the flow of blood to the heart is suddenly blocked).

Compared with consuming chocolate less than once a week, eating chocolate more than once a week was associated with an 8% decreased risk of coronary artery disease.

Dr. Krittanawong said: "Chocolate contains heart healthy nutrients such as flavonoids, methylxanthines, polyphenols and stearic acid which may reduce inflammation and increase good cholesterol (high-density lipoprotein or HDL cholesterol)."

He noted that the study did not examine whether any particular type of chocolate is more beneficial and whether there is an ideal portion size. "Chocolate appears promising for prevention of coronary artery disease, but more research is needed to pinpoint how much and what kind of chocolate could be recommended," he said.

While it's not clear how much chocolate is optimal, Dr. Krittanawong warned against overeating. He said: "Moderate amounts of chocolate seem to protect the coronary arteries but it's likely that large quantities do not. The calories, sugar, milk, and fat in commercially available products need to be considered, particularly in diabetics and obese people."

***References***

*1Krittanawong C, Narasimhan B, Wang Z, et al. Association between chocolate consumption and risk of coronary artery disease: a systematic review and meta-analysis. Eur J Prev Cardiol. 2020. doi:10.1177/2047487320936787.*

***https://bit.ly/3g3Rlse***

## Buckwheat enhances the production of a protein that supports the longevity

***Buckwheat-based diet helps increase the level of SIRT1 that protects all the cells of the body and enhances longevity***

A healthy low-calorie diet that contains plant products can help us improve the level of sirtuin 1 (SIRT1) protein production that is known to increase life expectancy. A team of scientists from Krasnoyarsk conducted an experiment to see how buckwheat affected the health of rats. The only known method to optimize the level of this protein is a calorie restriction. But why will healthy people be subjected to calorie restriction without any medical emergency? According to the researchers, a buckwheat-based diet helps to increase the level of SIRT1 protein that protects all the cells of the body and enhances longevity. In the same time, there is no need to starve. The results of the study were published in the *Journal of Cereal Science*.

With increased stress levels and wide availability of junk food, today we have to take special care about our health. Vitamins and amino acids are precursors of important regulatory and building molecules in our bodies, and a diet rich in them can help keep one's digestive system healthy and support it in case of any health issues. On the contrary, an unbalanced diet or overeating can cause various diseases, including cancers.

SIRT1 is a protein that senses nutrient status of cells. When SIRT1 levels in a cell are intentionally increased, its aging process slows down, and its stress resistance improves. However, the excess of SIRT1 in the organs and tissues of a living being is a sign of hunger which may lead to anemia and other negative effects.

A team of biologists from the School of Fundamental Biology and Biotechnology of Siberian Federal University added 30% buckwheat (which is rich in nutrients) to the diet of rats and studied its impact on their health. The animals were divided into three groups with eight rats in each. The first (control) group got a regular amount of feed; in

the second (calorie restriction group) the portions were reduced by 30%, and the third (experimental) group got regular feed with the addition of ground buckwheat that amounted up to 30% of the total feed weight. Buckwheat contains dietary fiber that could be only partially digested by humans and rats. In view of that, the scientists calculated the daily feed volume for the third group for it to have the same nutritional value as the diet of the second group.

After eight weeks of the experiment, samples were taken from the blood, liver, kidneys, and stomach of the animals to measure the content of SIRT1. To do so, the scientists used molecules that produce a colored substance after linking with SIRT1. Moreover, the team monitored the weight of the rats in the course of the experiment. The animals from the third group gained more weight than the ones from the second group, even though both groups consumed an equal amount of calories. This observation indicates that buckwheat ensures proper growth and development in the long run. Though the highest level of SIRT1 production was registered in the calorie restriction group. However, this effect was achieved at the cost of lowering body and organ weights. In the experimental group the levels of the protein were higher than in the control group, but no weight loss was observed.

"The results of the study show that a diet that includes buckwheat has the effect of calorie restriction, because this grain contains a lot of indigestible fiber. Buckwheat is a low calorie product, and when added to a diet, it increases the production of SIRT1. This protein, in turn, protects the cells of the digestive system without causing hunger and loss of growth in animals. We believe that other plant products, such as grain, vegetables, fruit, or nuts, have similar effect on SIRT1 production and on the health in general. If you want a healthy and long life, eat more of them", said Shubhra Pande, the author of the research and the Post-doctoral fellow of the Department of Biophysics at the School of Fundamental Biology and Biotechnology of Siberian Federal University.

***https://nyti.ms/3q2R6hd***

## Can You Get Covid-19 Again? It's Very Unlikely, Experts Say

***Reports of reinfection instead may be cases of drawn-out illness. A decline in antibodies is normal after a few weeks, and people are protected from the coronavirus in other ways.***

**By Apoorva Mandavilli**

The anecdotes are alarming. A woman in Los Angeles seemed to recover from Covid-19, but weeks later took a turn for the worse and tested positive again. A New Jersey doctor claimed several patients healed from one bout only to become reinfected with the coronavirus. And another doctor said a second round of illness was a reality for some people, and was much more severe.

These recent accounts tap into people's deepest anxieties that they are destined to succumb to Covid-19 over and over, feeling progressively sicker, and will never emerge from this nightmarish pandemic. And these stories fuel fears that we won't be able to reach herd immunity — the ultimate destination where the virus can no longer find enough victims to pose a deadly threat.

But the anecdotes are just that — stories without evidence of reinfections, according to nearly a dozen experts who study viruses. "I haven't heard of a case where it's been truly unambiguously demonstrated," said Marc Lipsitch, an epidemiologist at the Harvard T.H. Chan School of Public Health.

Other experts were even more reassuring. While little is definitively known about the coronavirus, just seven months into the pandemic, the new virus is behaving like most others, they said, lending credence to the belief that herd immunity can be achieved with a vaccine.

It may be possible for the coronavirus to strike the same person twice, but it's highly unlikely that it would do so in such a short window or to make people sicker the second time, they said. What's more likely is that some people have a drawn-out course of infection, with the virus taking a slow toll weeks to months after their initial exposure.

People infected with the coronavirus typically produce immune molecules called antibodies. Several teams have recently reported that the levels of these antibodies decline in two to three months, causing some consternation. But a drop in antibodies is perfectly normal after an acute infection subsides, said Dr. Michael Mina, an immunologist at Harvard University.

Many clinicians are "scratching their heads saying, 'What an extraordinarily odd virus that it's not leading to robust immunity,' but they're totally wrong,'" Dr. Mina said. "It doesn't get more textbook than this."

Antibodies are not the only form of protection against pathogens. The coronavirus also provokes a vigorous defense from immune cells that can kill the virus and quickly rouse reinforcements for future battles. Less is known about how long these so-called memory T cells persist — those that recognize other coronaviruses may linger for life — but they can buttress defenses against the new coronavirus.

"If those are maintained, and especially if they're maintained within the lung and the respiratory tract, then I think they can do a pretty good job of stopping an infection from spreading," said Akiko Iwasaki, an immunologist at Yale University.

Megan Kent, 37, a medical speech pathologist who lives just outside Boston, first tested positive for the virus on March 30, after her boyfriend became ill. She couldn't smell or taste anything, she recalled, but otherwise felt fine. After a 14-day quarantine, she went back to work at Melrose Wakefield Hospital and also helped out at a nursing home.

On May 8, Ms. Kent suddenly felt ill. "I felt like a Mack truck hit me," she said. She slept the whole weekend and went to the hospital on Monday, convinced she had mononucleosis. The next day she tested positive for the coronavirus — again. She was unwell for nearly a month, and has since learned she has antibodies.

"This time around was a hundred times worse," she said. "Was I reinfected?"

There are other, more plausible explanations for what Ms. Kent experienced, experts said. "I'm not saying it can't happen. But from what I've seen so far, that would be an uncommon phenomenon," said Dr. Peter Hotez, the dean of the National School of Tropical Medicine at Baylor College of Medicine.

Ms. Kent may not have fully recovered, even though she felt better, for example. The virus may have secreted itself into certain parts of the body — as the Ebola virus is known to do — and then resurfaced. She did not get tested between the two positives, but even if she had, faulty tests and low viral levels can produce a false negative.

Given these more likely scenarios, Dr. Mina had choice words for the physicians who caused the panic over reports of reinfections. "This is so bad, people have lost their minds," he said. "It's just sensationalist click bait."

In the early weeks of the pandemic, some people in China, Japan and South Korea tested positive twice, sparking similar fears.

South Korea's Centers for Disease Control and Prevention investigated 285 of those cases, and found that several of the second positives came two months after the first, and in one case 82 days later. Nearly half of the people had symptoms at the second test. But the researchers were unable to grow live virus from any of the samples, and the infected people hadn't spread the virus to others.

"It was pretty solid epidemiological and virological evidence that reinfection was not happening, at least in those people," said Angela Rasmussen, a virologist at Columbia University in New York.

Most people who are exposed to the coronavirus make antibodies that can destroy the virus; the more severe the symptoms, the stronger the response. (A few people don't produce the antibodies, but that's true for any virus.) Worries about reinfection have been fueled by recent studies suggesting that these antibody levels plummet.

For example, a study published in June found that antibodies to one part of the virus fell to undetectable levels within three months in 40

percent of asymptomatic people. Last week, a study that has not yet been published in a peer-reviewed journal showed that neutralizing antibodies — the powerful subtype that can stop the virus from infecting cells — declined sharply within a month.

“It’s actually incredibly depressing,” said Michael Malim, a virologist at King’s College London. “It’s a huge drop.”

But other work suggests that the antibody levels decline — and then stabilize. In a study of nearly 20,000 people posted to the online server MedRxiv on July 17, the vast majority made plentiful antibodies, and half of those with low levels still had antibodies that could destroy the virus.

“None of this is really surprising from a biological point of view,” said Florian Krammer, an immunologist at the Icahn Mount Sinai School of Medicine who led that study.

Dr. Mina agreed. “This is a famous dynamic of how antibodies develop after infection: They go very, very high, and then they come back down," he said.

He elaborated: The first cells that secrete antibodies during an infection are called plasmablasts, which expand exponentially into a pool of millions. But the body can’t sustain those levels. Once the infection wanes, a small fraction of the cells enters the bone marrow and sets up shop to create long-term immunity memory, which can churn out antibodies when they’re needed again. The rest of the plasmablasts wither and die.

In children, each subsequent exposure to a virus — or to a vaccine — boosts immunity until, by adulthood, the antibody response is steady and strong.

What’s unusual in the current pandemic, Dr. Mina said, is to see how this dynamic plays out in adults, because they so rarely experience a virus for the first time.

Even after the first surge of immunity fades, there is likely to be some residual protection. And while antibodies have received all the attention because they are easier to study and detect, memory T cells and B cells are also powerful immune warriors in a fight against any pathogen.

A study published July 15, for example, looked at three different groups. In one, each of 36 people exposed to the new virus had T cells that recognize a protein that looks similar in all coronaviruses. In another, 23 people infected with the SARS virus in 2003 also had these T cells, as did 37 people in the third group who were never exposed to either pathogen.

“A level of pre-existing immunity against SARS-CoV2 appears to exist in the general population,” said Dr. Antonio Bertoletti, a virologist at Duke NUS Medical School in Singapore.

The immunity may have been stimulated by prior exposure to coronaviruses that cause common colds. These T cells may not thwart infection, but they would blunt the illness and may explain why some people with Covid-19 have mild to no symptoms. “I believe that cellular and antibody immunity will be equally important,” Dr. Bertoletti said.

Vaccine trials that closely track volunteers may deliver more information about the nature of immunity to the new coronavirus and the level needed to block reinfection. Research in monkeys offers hope: In a study of nine rhesus macaques, for example, exposure to the virus induced immunity that was strong enough to prevent a second infection.

Researchers are tracking infected monkeys to determine how long this protection lasts. “Durability studies by their nature take time,” said Dr. Dan Barouch, a virologist at Beth Israel Deaconess Medical Center in Boston who led the study.

Dr. Barouch and other experts rejected fears that herd immunity might never be reached.

“We achieve herd immunity all the time with less than perfect vaccines,” said Dr. Saad Omer, the director of the Yale Institute for Global Health. “It’s very rare in fact to have vaccines that are 100-percent effective.”

A vaccine that protects just half of the people who receive it is considered moderately effective, and one that covers more than 80 percent highly effective. Even a vaccine that only suppresses the levels of virus would deter its spread to others.

The experts said reinfection had occurred with other pathogens including influenza — but they emphasized that those cases were exceptions, and the new coronavirus was likely to be no different.

"I would say reinfection is possible, though not likely, and I'd think it would be rare," Dr. Rasmussen said. "But even rare occurrences might seem alarmingly frequent when a huge number of people have been infected."

***https://bit.ly/3f2dV3b***

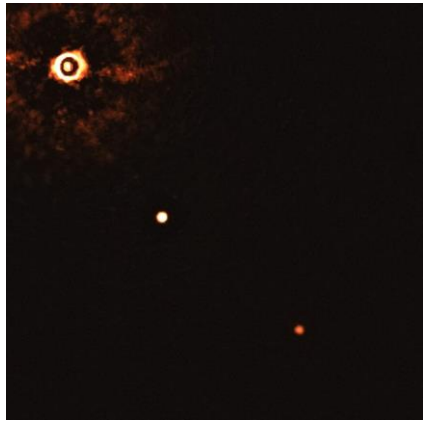
## A Faraway Solar System Is an Uncanny Reflection of Our Own

***Astronomers have captured a strangely comforting scene 300 light-years from Earth.***

**Marina Koren**

Astronomers have a saying about how difficult it is to see a distant planet outside of our own solar system: It's like spotting a firefly next to a lighthouse.

Stars are so luminous that they block our view of planets that might be orbiting nearby, so astronomers have to work around them. They use special instruments on telescopes to block the light coming from these celestial beacons. With the glare gone, they can detect something else: heat radiating off of planets. In the resulting observations, the worlds are easier to spot—glowing orbs in the darkness, like fireflies hovering in the heat of a summer night.



**ESO / Bohn et al**

This is how astronomers captured two planets around a star that resides about 300 light-years away from Earth. The portrait, released yesterday, is rare. Astronomers have directly taken images of individual exoplanets before. And they have previously captured cosmic family portraits: planets together with stars brighter and heavier than our sun. But this is the first time anyone has captured two exoplanets around a *sunlike star*.

In the photo at the top of this story, the star is at left. The planets are not rocky like Earth, but gaseous like Jupiter, and more massive than Jupiter too. They are also extremely hot, still cooling down from their fiery formation out of a stew of dust and gas. At 17 million years old, their star is a baby version of our sun. Matthew Kenworthy, an astronomy professor at Leiden University, in the Netherlands, who was involved with the research, told me that if our sun was his age, 46, this star would be just 12 weeks old.

This other solar system looks almost cozy, but these planets are a few hundred times farther from their star than Saturn and Jupiter are from our own. There might be rocky planets like Earth somewhere in this system, Kenworthy said, but they would be too small for even our most powerful telescopes to spot. As far as we can tell, this system is not like our home in the cosmos, and yet its landscape seems somehow familiar, like seeing a photograph of a famous skyline with a few skyscrapers missing. My first thought when I saw this image was, *Huh, I wonder how things are going there. Maybe they're having a better time of it than we are.*

This is, I realize, an absurd thought—a knee-jerk projection of pandemic stress at a time when the fight against the coronavirus in the United States feels more frustrating and helpless each day. Our world seems particularly exhausting right now, and these kinds of astronomical observations provide a strange sense of comfort. They present a different version of something recognizable, and an opportunity to imagine a calmer existence, in which the pandemic isn't always on our minds.

Maddalena Reggiani, a postdoctoral researcher at KU Leuven, in Belgium, and one of the researchers in this study, gets a similar feeling—not my desperate wishful thinking about an alternate reality, but the sense that she is looking at a cosmic doppelgänger. This image, after all, resembles how our own solar system appears in textbooks and on classroom posters: as a ball of fire suspended in the darkness, with a few glassy marbles circling it.

To produce the image, Kenworthy and his colleagues compared multiple observations of the solar system. In the first set, the star is surrounded by several blobs of glowing gas, any one of which could be a planet. In the second set, taken some time later, some of the orbs have moved, while others have stayed put, as unmoving as the star itself. The objects that shifted turned out to be other stars, somewhere in the background, moving along on their own journey through space. The objects that stuck around, the researchers concluded, were planets.

Astronomers seek out such cosmic doppelgängers to learn about our own history. By studying a baby version of the sun somewhere else, they can better understand how our own adult sun—all the planets around it—came to be. Studying images of similar solar systems is like looking at a childhood photo album. "We can't, during our lifetime, look at how a planetary system is born and how it evolves," Reggiani told me. "All we can do is look at stars at different ages so we can guess a little bit at the history of our solar system."

Cosmic analogues can also help scientists understand the kinds of circumstances that can lead to a planet sprouting life, even if all they see is gas planets capable of producing only swirling cloud tops instead of squirming organisms. Spotting a couple of gas planets in another solar system is not the triumphant discovery that detecting an Earthlike atmosphere on a rocky exoplanet would be, but it is an important bread crumb in the search for life in the universe.

That's because outer, Jupiter-like planets help protect inner, rocky planets. Research has shown that Jupiter might have spared Earth from collisions with small objects in the early solar system, when stuff was flying around all over the place. Without these big planets, rocky objects could have coalesced into a cloud in the inner solar system and showered Earth with enough collisions to strip away its atmosphere. With Saturn and Jupiter standing by, conditions near Earth remained stable enough for life to start stirring in the water. Even today, Jupiter often deflects comets and asteroids.

Emily Deibert, a doctoral student in astronomy and astrophysics at the University of Toronto who studies exoplanets, told me that this new research makes her think about of Earth's place in the universe. "Especially seeing something like this, an actual image of another planetary system, which is really rare, it makes me think about how unique our Earth is and how difficult it would be to find somewhere else suitable for us to live," said Deibert, who was not involved in the research.

Pictures like this can provide a dose of awe amid the doom-scrolling, a tiny break from a reality that itself feels like an alternate timeline for 2020, much in the same way that the sight of a fuzzy comet called NEOWISE has dazzled stargazers around the world in recent weeks. These are temporary delights. The comet will eventually fade from view, not to return for thousands of years, and the solar system in the new photograph is too far away to ever visit. But turning our attention to something otherworldly, even for a few moments, can distract us from pandemic despair.

Deibert wonders whether a planet like Earth is hidden in that other solar system hundreds of light-years away, and whether someone there is gazing back at us, trying to see past the glare of our sun. "Perhaps some other intelligent civilization out there might be looking at our system right now and only seeing our two biggest gas giants," she said. What might those inhabitants be thinking, as they look upon a home that is almost like theirs?

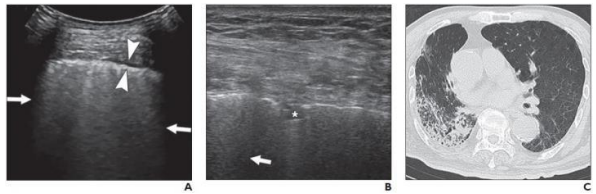
https://bit.ly/3jMmlzo

# Lung ultrasound shows duration, severity of coronavirus disease (COVID-19)

***Thickened pleural line more frequently observed in patients with longer time intervals after symptom onset; pulmonary consolidation more common in severe and critical cases***

Leesburg, VA, July 23, 2020--According to an open-access article published in ARRS' *American Journal of Roentgenology* (AJR), lung ultrasound (US) was highly sensitive for detecting abnormalities in patients with coronavirus disease (COVID-19), with B-lines, a thickened pleural line, and pulmonary consolidation the most commonly observed features.

"In addition," concluded Yao Zhang of at China's Beijing Ditan Hospital, "our results indicate that lung US findings can be used to reflect both the infection duration and disease severity."



***A and B, Lung ultrasound images obtained with convex (A) and linear (B) probes. Multiple confluent B-lines (arrows), patchy pulmonary consolidation (asterisk, B), and thickened pleural line (between arrowheads, A) are visualized. C, Chest CT image shows reticular and interlobular septal thickening and patchy, focal opacities associated with architectural distortion. This patient was classified in critical group and was assigned to severe group for statistical analysis.*** **American Journal of Roentgenology (AJR)**

From March 3 to March 30, 2020, Zhang and colleagues performed lung US on consecutive patients with positive reverse transcriptase polymerase chain reaction (RTPCR) test results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the Fisher exact test to compare the percentages of patients with each US finding between groups with different symptom durations and disease severity.

All 28 patients (14 men and 14 women; age range, 21-92 years) had positive findings on both lung US and chest CT. On US, B-lines were present in 100% of patients, and 19 (67.9%) patients had pulmonary consolidation. Thickened pleural lines were observed in 17 patients (60.7%), and only one patient (3.6%) showed a small amount of pleural effusion.

"A thickened pleural line was more frequently observed on US in patients with longer time intervals after the initial onset of symptoms," Zhang et al. noted, adding that pulmonary consolidations--visualized as tissuelike hypoechoic regions, reflecting highly reduced air flow and increased quantity of inflammatory cellular exudate--were more common in severe and critical cases.

Acknowledging that portable radiography could be just as useful in evaluating consolidation, "a bedside portable, handheld US system or even a robot-assisted tele-US system (a unique technique for physicians to remotely scan patients) further minimizes the number of health care workers and medical devices exposed to COVID-19," wrote Zhang and team.

The authors of this AJR article also proposed that severity scoring for lung US, similar to CT severity scores, should be developed to facilitate more accurate comparisons in future studies.

The latest AJR Podcast episode takes a closer look at "Lung US Findings in Coronavirus Disease-19 (COVID-19) Patients," noting that compared to CT, US is portable, less costly, and does not use radiation--making US a useful tool for triage, particularly in pre-hospital/outpatient settings, and severity stratification and monitoring, especially for critically ill patients who may be challenging to transport and require careful ventilation management:

*https://ajrpodcast.libsyn.com/lung-us-findings-in-coronavirus-disease-19-covid-19-patients*

https://bit.ly/2WYfo46

# Meet the 4 frontrunners in the COVID-19 vaccine race

***Safety and immune responses look good, but do these vaccines work?***

**Beth Mole - 7/23/2020, 10:43 PM**

Researchers have now reported data from early (and small) clinical trials of four candidate COVID-19 vaccines.

So far, the data is positive. The vaccines appear to be generally safe, and they spur immune responses against the novel coronavirus, SARS-CoV-2. But whether these immune responses are enough to protect people from infection and disease remains an important unknown.

The four candidates are now headed to larger trials—phase III trials—that will put them to the ultimate test: can they protect people from COVID-19 and end this pandemic?

**The challenge**

While early trials looking at safety and immune response required dozens or hundreds of volunteers, researchers will now have to recruit tens of thousands. Ideally, volunteers will be in places that still have high levels of SARS-CoV-2 circulating. The more likely it is that volunteers will encounter the virus in their communities, the easier it is to extrapolate if a vaccine is protective. As such, researchers are planning to do a significant amount of testing in the US and other parts of the Americas, which have largely failed at controlling the pandemic.

There has been much debate about the use of "human challenge trials," in which researchers would give young, healthy volunteers at low risk from COVID-19 an experimental vaccine and then intentionally expose them to SARS-CoV-2 in controlled settings. This could *potentially* provide a clearer, faster answer on vaccine efficacy. It's certainly an appealing idea given the catastrophic pandemic—and it's an idea that has gained traction in recent weeks. An advocacy group called 1Day Sooner has collected the names of more than 30,000 people willing to participate in such a trial, for instance.

But experts remain divided on the idea. The main concern is that there is no "rescue" treatment for COVID-19 that can fully protect a trial volunteer from severe disease and death if an experimental vaccine fails. Though young, healthy people have *less* risk than older people and those with underlying health conditions, some still suffer severe disease and death from COVID-19—and it's unclear why. Opponents also note that challenge trials may not be faster or necessary, given the high levels of disease spread in the US and elsewhere.

Though the debate on challenge trials is ongoing, it's unclear if researchers will end up needing or using them. Meanwhile, traditional phase III trials are now underway—and they have generated plenty of enthusiasm from the public. According to a report this week, more than 138,600 people have signed up through the National Institutes of Health to participate in vaccine testing. If all goes well, we could have data from these trials by the end of the year.

So how do the four top vaccine candidates work, and what do we know about them?

**mRNA-1273: Moderna, NIAID**

mRNA-1273 is a messenger RNA (mRNA) vaccine made by the biotechnology company Moderna, which was working with the NIH's National Institute of Allergy and Infectious Diseases (NIAID). The idea behind the mRNA vaccine platform is that it delivers snippets of a target virus's genetic code—in this case, code in the form of mRNA—into human cells. Those cells can then translate that code into viral protein. From there, the immune system can mount a response to the protein, which can be activated if the target virus ever tries to invade.

In the case of mRNA-1273, researchers used a fatty nanoparticle to package up mRNA that codes for the SARS-CoV-2 spike protein, which is usually found jutting out from SARS-CoV-2 viral particles.

Vaccines using genetic material—RNA or DNA—are new and untested. So far, there are no approved vaccines using this type of platform. It's unclear if they will be successful here or elsewhere and—if they are—how easy it will be to manufacture such a vaccine on a global scale. (For background on the different types of vaccine platforms, see our vaccine primer.)

On July 14, researchers published results from a phase 1 trial, which primarily looks at safety in a small group of people. The study, appearing in the New England Journal of Medicine, included 45

healthy volunteers between the ages of 18 and 55 and tested three dose levels of the vaccine. That is, there were three groups of 15 people, with each group getting either a low, medium, or high dose of the vaccine (25 micrograms, 100 micrograms, or 250 micrograms dose). Each participant got two shots of their dose, 28 days apart.

The vaccine was generally found to be safe. More than half of the participants had mild to moderate side effects, mainly including fatigue, chills, headache, myalgia, and pain at the injection site. Side effects were more common after the second dose, regardless of the strength, but those who received the two higher-dose vaccinations reported more side effects. Two people (one in the 100-microgram group and the other in the 250-microgram group) had severe skin redness at the site of the injection. Two people in the 250-microgram group experienced lightheadedness and fainted.

All participants produced antibodies against SARS-CoV-2, with antibody levels jumping up after the second shot. Those who got the higher doses had slightly higher levels of antibodies. The researchers compared participant antibody levels to those seen in 41 people who had recovered from a COVID-19 infection. Those vaccinated all had antibodies in the same range as the recovered people.

The researchers also tested specifically for neutralizing antibodies—that is, antibodies that don't just bind to a virus particle but can completely disable it. Researchers found that the vaccine prompted higher levels of neutralizing antibodies than was seen in most of the people who recovered. For instance, 57 days after the first dose, people in the 100-microgram group had neutralizing antibody titers ranging from 163 to 329, while the range was about 60 to 200 in the patients who had recovered from COVID-19.

Last, the researchers looked at responses from T-cells—which can attack cells infected with virus—and found that the vaccine did generate certain types of T-cell responses against SARS-CoV-2.

Overall, the results are encouraging but not conclusive. Researchers don't yet know what immune responses or levels of antibodies are necessary to prevent a SARS-CoV-2 infection and/or disease. And, being only six months into the pandemic, it's unclear how long any such protective immune responses would last.

According to a listing on the NIH's registry for clinical trials, Moderna plans to begin a phase III trial of mRNA-1273 on July 27. Moderna wants to enroll 30,000 people in the trial, looking at efficacy as well as further safety and immune response data.

**AZD1222 (ChAdOx1 nCoV-19): Oxford University, AstraZeneca**

On July 20, researchers published results from a phase I/II trial of AZD1222, a candidate vaccine made by researchers at the University of Oxford and the international pharmaceutical company AstraZeneca. AZD1222 (also called ChAdOx1 nCoV-19) is a viral vector-based vaccine. With this platform, researchers can package bits of a dangerous virus into a far less dangerous virus. The mostly harmless viral parcel then gets delivered to the immune system, which can learn to seek and destroy the dangerous virus based on the smuggled fragments.

In the case of AZD1222, genetic material of the SARS-CoV-2 spike protein is packaged into a weakened type of adenovirus that infects chimpanzees. Human-infecting adenoviruses normally cause mild infections, often considered common colds. The chimpanzee virus, which doesn't typically infect humans, is made even more harmless by engineering that prevents it from replicating in human cells. In early tests, AZD1222 protected monkeys from developing pneumonia after researchers exposed them to high doses of SARS-CoV-2.

The clinical trial results, published in The Lancet, show that AZD1222 is generally safe and spurred immune responses in humans. The trial involved 1,077 participants (aged 18 to 55), 543 of which were randomly assigned to get AZD1222, and the remaining 534 were given a meningococcal vaccine as a control. Researchers divided the participants into four groups and ran different types of tests on their immune responses. Ten of the participants who received AZD1222

were in a "boost" group that got a second vaccine shot after 28 days. The other participants who received AZD1222 only received one dose. Mild side effects from AZD1222 were common, including pain, feeling feverish, chills, muscle ache, headache, and malaise. Some participants were preemptively given paracetamol (acetaminophen/Tylenol) to lessen these effects. No serious side effects were reported.

In 127 participants vaccinated with AZD1222, all produced antibodies against SARS-CoV-2. The levels were within the range seen in people who had recovered from COVID-19. The researchers conducted two separate tests to look for neutralizing antibodies in 35 vaccinated participants. In one test, 32 (91 percent) were positive for neutralizing antibodies 28 days after vaccination and, in the other test, 100 percent were positive. The ten participants who got a booster shot all produced neutralizing antibodies, some which were at levels higher than those typically seen in the COVID-19 recovered patients. The researchers also reported that AZD1222 induced T-cell responses.

Researchers have already begun a phase III trial of AZD1222 at sites in Brazil, the UK, and South Africa. They also plan to test the vaccine in the US soon. AstraZeneca said it will use two doses in trials moving forward in order to maximize immune responses.

jump to endpage 1 of 2

**Ad5-vectored COVID-19: CanSino, Chinese military**

Alongside the AZD1222 results published July 20 in The Lancet, Chinese researchers published phase II trial results for their Ad5-vectored COVID-19 vaccine, made by biotechnology company CanSino Biologics and the Chinese military.

Like AZD1222, CanSino uses the viral vector-based vaccine based on a weakened adenovirus. However, the adenovirus in this vaccine—Ad5—is one that circulates in humans, not chimpanzees. This is problematic because past exposure to the human adenovirus appears to throw off immune responses to the bit of the vaccine that's derived from SARS-CoV-2. In earlier published phase I trial data—previously reported by Ars here—researchers noted that those who had already been exposed to the adenovirus did not produce immune responses as robust as those who had not been exposed.

Nevertheless, CanSino forged on with a randomized phase II trial, involving 508 volunteers (aged 18 to 83) who received either a placebo or a single injection of Ad5-vectored COVID-19 at one of two dosage levels.

Mild side effects including fever, fatigue, headache, or pain at the site of injection were common. Though 24 participants in the high dose group and one in the low dose group had side effects rated as severe, there were no serious reactions.

Researchers found that more than 96 percent of participants who received Ad5-vectored COVID-19 developed antibodies against SARS-CoV-2. But researchers detected SARS-CoV-2 neutralizing antibodies in only 59 percent of the high dose group (148 out of 253 participants) and 47 percent of the low dose group (61 out of 129 participants). For those who developed antibodies, the level of those antibodies was only compared with those from the placebo group, not with those found in people who recovered from COVID-19. Finally, around 89 percent developed T-cell responses.

The researchers note that 52 percent of participants showed high pre-existing immunity to the human adenovirus, Ad5, used to make the vaccine. They also note that in some populations, immunity to Ad5 is as high as 80 percent. Still, CanSino is now planning its phase III trial, and—as Ars reported previously—the vaccine has already been approved for use by the Chinese military.

**BNT162b1: BioNTech, Pfizer**

BNT162b1 is an mRNA-based vaccine made by German firm BioNTech and the pharmaceutical giant Pfizer. Like Moderna's vaccine, BNT162b1 uses a fatty nanoparticle wrapping to deliver a fragment of the genetic code for the SARS-CoV-2 spike protein into human cells.

On July 1, researchers released results of a phase I/II trial of BNT162b1 on a preprint server, where scientists can air their study data before it is published in a peer-reviewed journal. The study involved 45 participants (ages 19 to 54), with three groups of twelve. One group got two shots of a low dose (10 micrograms), spaced 20 days apart. A second group got two shots of a medium dose (30 micrograms), also spaced 20 days apart. And the third group got one shot of a high dose (100 micrograms). The remaining nine people in the trial got a placebo.

Most participants reported side effects, which were largely mild to moderate. Common side effects included pain at the injection site, fatigue, fever, headache, chills, and muscle pain. The occurrence of side effects increased with dose level and were stronger after the second dose. Researchers decided against giving the 100-microgram group a second injection for this reason. No serious side effects were reported.

All vaccinated participants developed antibodies and neutralizing antibodies against SARS-CoV-2. Researchers noted that after the second injection of the low and medium doses, participants developed higher levels of antibodies and neutralizing antibodies than those seen in blood samples from 38 people who had recovered from COVID-19. For example, those given the low dose had 1.8 times the mean level of neutralizing antibodies seen in people who have recovered from COVID-19. And those who received the medium dose had 2.8 times the level.

On July 20, the researchers released a second batch of data from 60 participants, again on a preprint server. The data echoed the earlier findings that the vaccine is generally safe and produces strong antibody responses. In addition, the researchers found that more than 80 percent of those vaccinated mounted strong T-cell responses to SARS-CoV-2.

Like the others, Pfizer and BioNtech are moving toward phase III trials for BNT162b1.

**That's not all**

While it's unclear how successful any of these vaccines will be in larger trials, there are plenty of other vaccine candidates following close behind in the pipeline. According to the latest vaccine tracking by the World Health Organization, 20 other COVID-19 vaccines are currently in some phase of clinical trials, with 142 others in preclinical development.

***https://bit.ly/2P0oCss***

## Some 'inert' drug ingredients may be biologically active

***Comprehensive laboratory study flags drug components in need of more rigorous review***

Some supposedly inert ingredients in common drugs -- such as dyes and preservatives -- may potentially be biologically active and could lead to unanticipated side effects, according to a preliminary new study by researchers from the UC San Francisco School of Pharmacy and the Novartis Institutes for BioMedical Research (NIBR).

Most medications include only a relatively small amount of their active pharmaceutical ingredient by mass (for instance, the acetaminophen in Tylenol and other medications). The rest of any given pill, liquid or injectable can be composed of ingredients including preservatives, dyes, antimicrobials and other compounds known as excipients. These ingredients play critical roles in making sure a drug's active ingredient is delivered safely and effectively, as well as conferring important qualities like shelf stability and the ability to quickly distinguish pills by color.

Excipients are generally accepted to be biologically inactive based on their long history of use, or because they don't produce any obvious toxicity in animal studies. But few studies have looked for more subtle effects of long-term exposure to these compounds or how they might interact in people who take multiple different medicines that include these ingredients.

Researchers Brian Shoichet, PhD, of the UCSF Department of Pharmaceutical Chemistry and Laszlo Urban, PhD, Global Head of

Preclinical Safety Profiling at NIBR, had begun to wonder about whether all of these substances were really inert, and joined forces to investigate them. They began the work in 2017 with a database documenting most readily accessible pure excipients, which the UCSF group had compiled in an easy-to-use excipients browser, itself drawing on a more specialized FDA inactive ingredients database (IID), with support from the FDA-funded UCSF-Stanford Center of Excellence in Regulatory Science and Innovation (CERSI).

As reported in their new study, published July 23, 2020 online in *Science*, the researchers have now systematically screened 3296 excipients contained in the inactive ingredient database, and identified 38 excipient molecules that interact with 134 important human enzymes and receptors.

The research team emphasizes that their study, which did not look for actual effects on human patients, is only intended to flag molecules with the potential to pose negative health effects, and the examples they list will need to be further studied to understand how they might contribute to side effects of drugs in which they are found.

"These data illustrate that while many excipient molecules are in fact inert, a good number may have previously unappreciated effects on human proteins known to play an important role in health and disease," Shoichet said. "We demonstrate an approach by which drug makers could in the future evaluate the excipients used in their formulations, and replace biologically active compounds with equivalent molecules that are truly inactive."

The team used a couple of different approaches. At UCSF, Shoichet's team computationally examined excipient molecules that physically resemble the known biological binding partners of 3117 different human proteins in the public ChEMBL database. The team then computationally pared down 2 million possible interactions of these excipients and human target proteins to 20,000 chemically plausible interactions. Based on visual inspection, the researchers identified a subset of 69 excipients with highest likelihood of interacting with human target proteins, and tested these interactions experimentally in laboratory dishes, in collaboration with the groups of Bryan Roth, PhD, a professor of pharmacology at the University of North Carolina, Chapel Hill, and Kathy Giacomini, PhD, a professor of bioengineering at UCSF and co-director of the UCSF-Stanford CERSI center.

These experiments identified 25 different biological interactions involving 19 excipient molecules and 12 pharmacologically important human proteins.

In a complementary set of experiments at NIBR, the researchers screened 73 commonly used excipients against a panel of human protein targets involved in drug-induced toxicity and regularly used to test drug candidates for safety. They identified an additional 109 interactions between 32 excipients and these human safety targets.

"Our study was meant to expand on anecdotal evidence that excipients may be the culprits of unexpected physiological effects seen in certain drug formulations," said study lead author Joshua Pottel, PhD, a former postdoctoral researcher in the Shoichet lab who is now President and CEO of Montreal-based Molecular Forecaster Inc. "It was not so surprising to find new properties of understudied compounds that have been grandfathered in as 'inactive' for decades, but it was surprising to see how potent some of these molecules are, especially considering the fairly high quantities sometimes used in typical drug formulations."

The biologically active excipients the study identified in laboratory dishes merit further study in animal models to establish whether any of them may in fact produce unwanted side effects in human patients, the authors said. Many should be readily interchangeable with truly inert excipients of similar function, they said, but for others, new replacement compounds may need to be developed.

"After decades with little innovation in how drugs are formulated, we see this as an opportunity for a public-private partnership between academic, regulatory, and pharmaceutical communities to seek new and better excipients, and we demonstrate an approach to doing so,"

Shoichet said. "Given the challenge this work presents to the pharmaceutical status quo, we are grateful for the forward-thinking support the project has received primarily from the FDA and through our collaboration with Novartis, in addition to the National Institutes of Health."

***Authors:*** *Joshua Pottel, formerly of UCSF, is the study's lead author. Brian Shoichet of UCSF and Laszlo Urban of NIBR are joint corresponding authors.*
*Other authors include Ling Zou, Hayarpi Torosyan, John J. Irwin, and Kathleen M. Giacomini of UCSF; Duncan Armstrong, Alexander Fekete, Dallas Bednarczyk, Steven Whitebread, Barun Bhhatarai, Guiqing Liang, Hong Jin and Nassir Ghaemi of NIBR; Xi-Ping Huang, Samuel Slocum and Bryan L. Roth of the University of North Carolina, Chapel Hill; Katalin V. Lukacs of the National Heart and Lung Institute at Imperial College, London; and Ellen L. Berg of Eurofins DiscoverX in South San Francisco.*

***Funding:*** *The research was supported by US National Institutes of Health (NIH) grants GM122481 and GM71896, the National Institute of Mental Health (NIMH) Psychoactive Drug Screening Program, and FDA grants U01FD004979 and U01FD005978 which support the UCSF-Stanford Center of Excellence in Regulatory Sciences and Innovation. The study's contents are solely the responsibility of the authors and do not necessarily represent the official views of the US Department of Health and Human Services or FDA.*
***Disclosures:*** *The authors declare no relevant conflicts of interest.*

***https://wb.md/2X1w76G***

## Cancer Drug Counterfeiters Plead Guilty in US

### *Perpetrators Ran an Online Supplements Company*

**Nick Mulcahy**

Two Ukrainian nationals pleaded guilty last week to conspiring to smuggle and distribute counterfeit versions of cancer drugs pembrolizumab (Keytruda) and nab-paclitaxel (Abraxane) as well as hepatitis C drug sofosbuvir/velpatasvir (Epclusa) into the United States, according to the US Department of Justice.

Maksym Nienadov, 36, owner of Healthy Nation, an online nutritional supplements company, and employee Volodymyr Nikolaienko, 33, admitted to conspiracy, trafficking in counterfeit drugs, and smuggling goods into the United States.

Neither of the arrested pair is a doctor, pharmacist, or licensed pharmaceutical wholesaler in the United States; they did not have authorization to sell the drugs, according to authorities.

In 2018, undercover federal agents purchased via the mail purported pembrolizumab and nab-paclitaxel from Nienadov and, later, fake sofosbuvir/velpatasvir from both men. Merck, Celgene, and Gilead (the manufacturers of these drugs) performed analyses and confirmed that the packaging and drugs were counterfeit.

The Ukrainian pair were arrested in April 2019 when they arrived in the United States to discuss future shipments of counterfeit pharmaceuticals and have been in custody since then. US Magistrate Judge Christina Bryan took their guilty pleas on July 17.

The Ukrainians sold two boxes of 50 mg fake pembrolizumab and two boxes of fake nab-paclitaxel 5 mg/ml to undercover agents for a total of $3400. They also sold two boxes of fake sofosbuvir/velpatasvir tablets for $6000.

The counterfeit prices were drastically lower than retail prices. For example, in the US at a retail pharmacy, a single box (quantity 8 vials) of 50 mg pembrolizumab is about $17,000; thus, two boxes would be more than $30,000.

Healthy Nation, the mail-order supplements company owned by Nienadov, still has a functioning website (healthynation.com.ua) and apparently sells company-branded supplements, including omega-3, pumpkin seed oil, flax seed oil, fish oil, and hemp seed oil. Their products are also available on at least one other website, Rozetka.ua, a large consumer goods portal that additionally sells well-known health supplement brands such as Solgar.

Healthy Nation says it was looking to grow: “We are always evolving and looking for new scenarios for partnership.”

**The Problem of Drug Counterfeiting**

The World Health Organization claims that 10% of all drugs in low- and middle- income countries are substandard or falsified and that the global market for these agents is worth around $200 billion.

The US Food and Drug Administration in 2003 initiated an internal task force to address drug counterfeiting. In 2012, a spate of counterfeit versions of bevacizumab (Avastin) that did not contain the

active ingredient circulated in the United States, as reported by *Medscape Medical News*. In 2014, a Kentucky oncology practice pleaded guilty to charges that it purchased and sold unapproved and improperly labeled chemotherapeutic agents, including counterfeit bevacizumab.

Last year, the European Union implemented a new system to fight counterfeit drugs, which was 4 years in the making, according to Euronews.

***https://nyti.ms/2D7rGAf***

## Viking Age Smallpox Complicates Story of Viral Evolution

***An extinct version of the smallpox virus dating to 1,400 years ago prompts speculation about viruses becoming more lethal over time.***

**By James Gorman**

The evolution of the deadliest virus in human history — smallpox — is only partly understood. Like the novel coronavirus and many other disease-causing viruses, smallpox seems to have originated in animals, probably rodents, and spilled over to humans, probably thousands of years ago. In the 20th century alone it killed hundreds of millions of people.

Until now, the earliest confirmed case of smallpox had been found in the mummified remains of a Lithuanian child from the 17th century. On Thursday, an international team of researchers pushed that date back 1,000 years, reporting in the Science journal that they had recovered smallpox DNA from the remains of people in Northern Europe in the Viking Age.

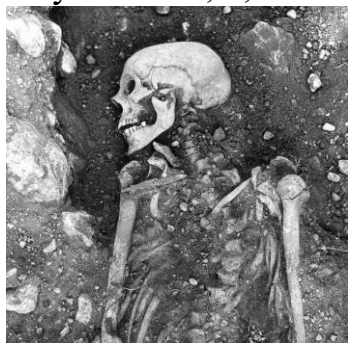
The virus they found is now extinct and has not been found in other, more recent skeletal remains. It is not an ancestor of the modern smallpox virus, but an evolutionary dead end. It has more genes than the modern virus, and scientists have observed that among the many different pox viruses in nature, fewer genes tend to mean a more deadly virus. Putting those facts together caused one prominent smallpox specialist to suggest that the modern virus might have become more deadly as it evolved. Most viruses become less deadly over time.

Pox viruses are not closely related to coronaviruses, and the research has no direct application to the current spread of the novel coronavirus. But in the midst of a pandemic, even the thought of some viruses evolving to be more deadly is decidedly uncomfortable.

The early date of the new smallpox virus, experts say, is significant but not surprising. Like other pox virus experts, the authors think that although DNA evidence is so far lacking, smallpox almost certainly goes much farther back in time.

Terry C. Jones, who studies the evolution of disease-causing organisms at the University of Cambridge and was one of the senior authors, said that judging by historical sources, “it seems quite likely that the virus was around in, let’s say, India, or maybe China, 1,000 or 1,500 years before the Common Era.”

What was most intriguing about the find, Dr. Jones said, was the genetic makeup of the smallpox virus recovered from the bones of 11 people who lived between 600 and 1050, and the fact that the old viral strain is now extinct. The modern version, as the authors call it, was eradicated from the human population by 1980.



***A 1,200-year-old smallpox-infected Viking skeleton found in Öland, Sweden.*** **Credit...The Swedish National Heritage Board**

The Latin name of the smallpox virus is Variola, and other strains of Variola are known. Variola minor, which was eradicated along with smallpox (Variola major), caused a mild illness with less than a 1 percent death rate, whereas smallpox killed about 30 percent of those it infected. Why it was less lethal is not known.

The differences in the Viking variant are significant enough for the virus to make up a new group, or clade, of Variola. It is not an earlier version of the modern virus. Both modern smallpox and the newly discovered variant descended from a common ancestor, but diverged

at least 1,700 years ago. Dr. Jones said: “The Viking viruses were on a different evolutionary path that could not have led to the modern viruses.”

Klaus Osterrieder, a pox virus specialist at the City University of Hong Kong and who was not part of the research, said that the analysis of the Viking virus, and the establishment of a new clade, was quite convincing.

The genetic details of the Viking virus are what prompted speculation that perhaps the smallpox virus may have become more deadly. Barbara Mühlemann**,** also a virologist at Cambridge and the first author on the paper, said that the general understanding of pox viruses is that the ones with fewer genes directed at deceiving the immune system of a host are actually more deadly. The reason is not clear, although with viral infections, a very strong immune reaction is often what kills the victim.

“The pattern that we’ve seen in the paper,” she said, “ is that there has been a loss of genes over time” in the modern smallpox virus compared to the Viking virus, which had more active genes than the modern virus. But, she cautioned, she and her colleagues have no direct evidence that the Viking version of the virus was less deadly.

Antonio Alcami, a smallpox specialist at the Autonomous University of Madrid, wrote a commentary in the same issue of Science raising the hypothesis that smallpox actually evolved to become more deadly. He said that the standard view of viral evolution, in which viruses become less virulent, might not always be true. Variola virus evolved in humans over time. “Maybe it was a mild disease for a while,” he said.

That idea has been suggested before, Dr. Jones said, by historians who proposed that smallpox may once have been a relatively benign illness.

The way this kind of evolution might have happened is “counterintuitive,” Dr. Alcami said. The genes that are inactivated in modern smallpox and other deadly pox viruses are ones that help weaken or evade immune responses of the infected host. But why lose those genes, since they should help a virus?

Somehow, loss of those genes seems to help the virus, Dr. Alcami said. Perhaps with fewer active genes the virus may replicate faster and therefore improve its chances of transmission to another person, even though it is provoking an out of control immune reaction, which, in the end is what kills the host. He emphasized that he was raising the idea only as a hypothesis to promote discussion and further investigation.

Dr. Osterrieder said that even though the idea was still speculative, he thought it made sense. “I think it’s a very compelling hypothesis,” he said.

***https://bbc.in/30NisBv***

## UK and US say Russia fired a satellite weapon in space

***The US and UK have accused Russia of testing a weapon-like projectile in space that could be used to target satellites in orbit.***

The US State Department described the recent use of "what would appear to be actual in-orbit anti-satellite weaponry" as concerning.

Russia's defence ministry earlier said it was using new technology to perform checks on Russian space equipment. The US has previously raised concerns about new Russian satellite activity.

But it is the first time the UK has made accusations about Russian test-firing in space. They come just days after an inquiry said the UK government "badly underestimated" the threat posed by Russia.

In a statement on Thursday, US Assistant Secretary of State for International Security and Non-proliferation, Christopher Ford, accused Moscow of hypocrisy after it said it wanted arms control to be extended to space.

"Moscow aims to restrict the capabilities of the United States while clearly having no intention of halting its own counter-space programme," he said.

The head of the UK's space directorate, Air Vice Marshal Harvey Smyth, said he was also concerned about the latest Russian satellite test, which he said had the "characteristics of a weapon".

"Actions like this threaten the peaceful use of space and risk causing debris that could pose a threat to satellites and the space systems on which the world depends," he said. He urged Russia to be "responsible" and to "avoid any further such testing".

Russia, the UK, the US and China are among more than 100 nations to have committed to a space treaty that stipulates that outer space is to be explored by all and purely for peaceful purposes.

The treaty adds that weapons should not be placed in orbit or in space.

The US said the Russian satellite system was the same one it raised concerns about in 2018 and earlier this year when the US accused it of manoeuvring close to an American satellite.

In this latest incident, Gen Jay Raymond, who heads US space command, said there was evidence Russia "conducted a test of a space-based anti-satellite weapon".

Gen Raymond added: "This is further evidence of Russia's continuing efforts to develop and test space-based systems and [is] consistent with the Kremlin's published military doctrine to employ weapons that hold US and allied space assets at risk."

**Analysis By Jonathan Marcus Defence Correspondent**

***This Russian test of what the Americans say is an anti-satellite weapon is part of a pattern of recent Russian space activity. In February, the US military said that two Russian satellites manoeuvred close to an American one, and in April Moscow test-fired a ground-based satellite interceptor.***

***Only four countries - Russia, the US, China and India - have demonstrated an anti-satellite capability over the past decades. Anti-satellite warheads have been carried aloft by aircraft or rockets, and satellites have also been illuminated by lasers.***

***But Moscow is also clearly looking at using one satellite to kill another. Interest in such weapons is growing given our reliance upon satellites for a variety of purposes such as intelligence gathering, communications, navigation and early-warning.***

***There is no treaty banning or limiting such wens though a number of countries have argued for some kind of agreement to do just this.***

***But in military terms, space has already become the new frontier with several countries organising specific commands in their armed forces to deal with both the defensive and offensive aspects of protecting their essential space-based systems.***

A test of a new Russian satellite took place on 15 July with the aim of performing checks on the country's space equipment, Russia's defence ministry said at the time.

"During testing of the latest space technology, one of the domestic satellites was examined close up using the specialised equipment of small space craft," the ministry said, according to Interfax news agency. It added that "valuable information about the technical condition of the object under investigation" had been recorded.

***https://bit.ly/2P0LlEM***

## In cell studies, seaweed extract outperforms remdesivir in blocking COVID-19 virus

***Heparin, a common anticoagulant, could also form basis of a viral trap for SARS-CoV-2***

TROY, N.Y. -- In a test of antiviral effectiveness against the virus that causes COVID-19, an extract from edible seaweeds substantially outperformed remdesivir, the current standard antiviral used to combat the disease. Heparin, a common blood thinner, and a heparin variant stripped of its anticoagulant properties, performed on par with remdesivir in inhibiting SARS-CoV-2 infection in mammalian cells.

Published online today in *Cell Discovery*, the research is the latest example of a decoy strategy researchers from the Center for Biotechnology and Interdisciplinary Studies (CBIS) at Rensselear Polytechnic Institute are developing against viruses like the novel coronavirus that spawned the current global health crisis.

The spike protein on the surface of SARS-CoV-2 latches onto the ACE-2 receptor, a molecule on the surface of human cells. Once secured, the virus inserts its own genetic material into the cell, hijacking the cellular machinery to produce replica viruses. But the virus could just as easily be persuaded to lock onto a decoy molecule that offers a similar fit. The neutralized virus would be trapped and eventually degrade naturally.

Previous research has shown this decoy technique works in trapping other viruses, including dengue, Zika, and influenza A. To hear the researchers discuss their findings, watch this video.

"We're learning how to block viral infection, and that is knowledge we are going to need if we want to rapidly confront pandemics," said Jonathan Dordick, the lead researcher and a professor of chemical and biological engineering at Rensselaer Polytechnic Institute. "The reality is that we don't have great antivirals. To protect ourselves against future pandemics, we are going to need an arsenal of approaches that we can quickly adapt to emerging viruses."

The *Cell Discovery* paper tests antiviral activity in three variants of heparin (heparin, trisulfated heparin, and a non-anticoagulant low molecular weight heparin) and two fucoidans (RPI-27 and RPI-28) extracted from seaweed. All five compounds are long chains of sugar molecules known as sulfated polysaccharides, a structural conformation that the results of a binding study published earlier this month in Antiviral Research suggested as an effective decoy.

The researchers performed a dose response study known as an EC50 -- shorthand for the effective concentration of the compound that inhibits 50% of viral infectivity -- with each of the five compounds on mammalian cells. For the results of an EC50, which are given in a molar concentration, a lower value signals a more potent compound.

RPI-27 yielded an EC50 value of approximately 83 nanomolar, while a similar previously published and independent in vitro test of remdesivir on the same mammalian cells yielded an EC50 of 770 nanomolar. Heparin yielded an EC50 of 2.1 micromolar, or about one-third as active as remdesivir, and a non-anticoagulant analog of heparin yielded an EC50 of 5.0 micromolar, about one-fifth as active as remdesivir.

A separate test found no cellular toxicity in any of the compounds, even at the highest concentrations tested.

"What interests us is a new way of getting at infection," said Robert Linhardt, a Rensselaer professor of chemistry and chemical biology who is collaborating with Dordick to develop the decoy strategy. "The current thinking is that the COVID-19 infection starts in the nose, and either of these substances could be the basis for a nasal spray. If you could simply treat the infection early, or even treat before you have the infection, you would have a way of blocking it before it enters the body."

Dordick added that compounds from seaweed "could serve as a basis for an oral delivery approach to address potential gastrointestinal infection."

In studying SARS-CoV-2 sequencing data, Dordick and Linhardt recognized several motifs on the structure of the spike protein that promised a fit compatible with heparin, a result borne out in the binding study. The spike protein is heavily encrusted in glycans, an adaptation that protects it from human enzymes which could degrade it, and prepares it to bind with a specific receptor on the cell surface.

"It's a very complicated mechanism that we quite frankly don't know all the details about, but we're getting more information," said Dordick. "One thing that's become clear with this study is that the larger the molecule, the better the fit. The more successful compounds are the larger sulfated polysaccharides that offer a greater number of sites on the molecules to trap the virus."

Molecular modeling based on the binding study revealed sites on the spike protein where the heparin was able to interact, raising the prospects for similar sulfated polysaccharides.

"This exciting research by Professors Dordick and Linhardt is among several ongoing research efforts at CBIS, as well as elsewhere at

Rensselaer, to tackle the challenges of the COVID-19 pandemic through novel therapeutic approaches and the repurposing of existing drugs," said CBIS Director Deepak Vashishth.

*"Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro" was published in Cell Discovery with the support of the National Research Foundation of Korea. At Rensselaer, Dordick and Linhardt were joined in the research by Paul S. Kwon, Seok-Joon Kwon, Weihua Jin, Fuming Zhang, and Keith Fraser, and by researchers at the Korea Research Institute of Bioscience and Biotechnology in Cheongju, Republic of Korea, and Zhejiang University of Technology in Hangzhou, China.*

***https://bit.ly/32ZwmTS***

## How COVID-19 causes smell loss

### *Olfactory support cells, not neurons, are vulnerable to novel coronavirus infection*

***At a glance:***

- ***Loss of smell is the main neurological symptom of COVID-19, but the underlying mechanism has been unclear***
- ***New study shows infection of nonneuronal supporting cells in the nose and forebrain may be responsible for loss of smell in patients with COVID-19***
- ***Findings suggest olfactory sensory neurons are not vulnerable to SARS-CoV-2 infection because they do not express ACE2, a key protein that the virus uses to enter human cells***
- ***Results inform efforts to better understand COVID-19-related loss of smell***

Temporary loss of smell, or anosmia, is the main neurological symptom and one of the earliest and most commonly reported indicators of COVID-19. Studies suggest it better predicts the disease than other well-known symptoms such as fever and cough, but the underlying mechanisms for loss of smell in patients with COVID-19 have been unclear.

Now, an international team of researchers led by neuroscientists at Harvard Medical School has identified the olfactory cell types most vulnerable to infection by SARS-CoV-2, the virus that causes COVID-19.

Surprisingly, sensory neurons that detect and transmit the sense of smell to the brain are not among the vulnerable cell types.

Reporting in *Science Advances* on July 24, the research team found that olfactory sensory neurons do not express the gene that encodes the ACE2 receptor protein, which SARS-CoV-2 uses to enter human cells. Instead, ACE2 is expressed in cells that provide metabolic and structural support to olfactory sensory neurons, as well as certain populations of stem cells and blood vessel cells.

The findings suggest that infection of nonneuronal cell types may be responsible for anosmia in COVID-19 patients and help inform efforts to better understand the progression of the disease.

"Our findings indicate that the novel coronavirus changes the sense of smell in patients not by directly infecting neurons but by affecting the function of supporting cells," said senior study author Sandeep Robert Datta, associate professor of neurobiology in the Blavatnik Institute at HMS.

This implies that in most cases, SARS-CoV-2 infection is unlikely to permanently damage olfactory neural circuits and lead to persistent anosmia, Datta added, a condition that is associated with a variety of mental and social health issues, particularly depression and anxiety.

"I think it's good news, because once the infection clears, olfactory neurons don't appear to need to be replaced or rebuilt from scratch," he said. "But we need more data and a better understanding of the underlying mechanisms to confirm this conclusion."

A majority of COVID-19 patients experience some level of anosmia, most often temporary, according to emerging data. Analyses of electronic health records indicate that COVID-19 patients are 27 times more likely to have smell loss but are only around 2.2 to 2.6 times more likely to have fever, cough or respiratory difficulty, compared to patients without COVID-19.

Some studies have hinted that anosmia in COVID-19 differs from anosmia caused by other viral infections, including by other coronaviruses.

For example, COVID-19 patients typically recover their sense of smell over the course of weeks--much faster than the months it can take to recover from anosmia caused by a subset of viral infections known to directly damage olfactory sensory neurons. In addition, many viruses cause temporary loss of smell by triggering upper respiratory issues such as stuffy nose. Some COVID-19 patients, however, experience anosmia without any nasal obstruction.

**Pinpointing vulnerability**

In the current study, Datta and colleagues set out to better understand how sense of smell is altered in COVID-19 patients by pinpointing cell types most vulnerable to SARS-CoV-2 infection.

They began by analyzing existing single-cell sequencing datasets that in total catalogued the genes expressed by hundreds of thousands of individual cells in the upper nasal cavities of humans, mice and nonhuman primates.

The team focused on the gene ACE2, widely found in cells of the human respiratory tract, which encodes the main receptor protein that SARS-CoV-2 targets to gain entry into human cells. They also looked at another gene, TMPRSS2, which encodes an enzyme thought to be important for SARS-CoV-2 entry into the cell.

The analyses revealed that both ACE2 and TMPRSS2 are expressed by cells in the olfactory epithelium--a specialized tissue in the roof of the nasal cavity responsible for odor detection that houses olfactory sensory neurons and a variety of supporting cells.

Neither gene, however, was expressed by olfactory sensory neurons. By contrast, these neurons did express genes associated with the ability of other coronaviruses to enter cells.

The researchers found that two specific cell types in the olfactory epithelium expressed ACE2 at similar levels to what has been observed in cells of the lower respiratory tract, the most common targets of SARS-CoV-2, suggesting a vulnerability to infection.

These included sustentacular cells, which wrap around sensory neurons and are thought to provide structural and metabolic support, and basal cells, which act as stem cells that regenerate the olfactory epithelium after damage. The presence of proteins encoded by both genes in these cells was confirmed by immunostaining.

In additional experiments, the researchers found that olfactory epithelium stem cells expressed ACE2 protein at higher levels after artificially induced damage, compared with resting stem cells. This may suggest additional SARS-CoV-2 vulnerability, but it remains unclear whether or how this is important to the clinical course of anosmia in patients with COVID-19, the authors said.

Datta and colleagues also analyzed gene expression in nearly 50,000 individual cells in the mouse olfactory bulb, the structure in the forebrain that receives signals from olfactory sensory neurons and is responsible for initial odor processing.

Neurons in the olfactory bulb did not express ACE2. The gene and associated protein were present only in blood vessel cells, particularly pericytes, which are involved in blood pressure regulation, blood-brain barrier maintenance and inflammatory responses. No cell types in the olfactory bulb expressed the TMPRSS2 gene.

**Smell loss clue**

Together, these data suggest that COVID-19-related anosmia may arise from a temporary loss of function of supporting cells in the olfactory epithelium, which indirectly causes changes to olfactory sensory neurons, the authors said.

"We don't fully understand what those changes are yet, however," Datta said. "Sustentacular cells have largely been ignored, and it looks like we need to pay attention to them, similar to how we have a growing appreciation of the critical role that glial cells play in the brain."

The findings also offer intriguing clues into COVID-19-associated neurological issues. The observations are consistent with hypotheses that SARS-CoV-2 does not directly infect neurons but may instead interfere with brain function by affecting vascular cells in the nervous

system, the authors said. This requires further investigation to verify, they added.

The study results now help accelerate efforts to better understand smell loss in patients with COVID-19, which could in turn lead to treatments for anosmia and the development of improved smell-based diagnostics for the disease.

"Anosmia seems like a curious phenomenon, but it can be devastating for the small fraction of people in whom it's persistent," Datta said. "It can have serious psychological consequences and could be a major public health problem if we have a growing population with permanent loss of smell."

The team also hope the data can help pave inroads for questions on disease progression such as whether the nose acts as a reservoir for SARS-CoV-2. Such efforts will require studies in facilities that allow experiments with live coronavirus and analyses of human autopsy data, the authors said, which are still difficult to come by. However, the collaborative spirit of pandemic-era scientific research calls for optimism.

"We initiated this work because my lab had a couple of datasets ready to analyze when the pandemic hit, and we published an initial preprint," Datta said. "What happened after that was amazing, researchers across the globe offered to share and merge their data with us in a kind of impromptu global consortium. This was a real collaborative achievement."

*Co-first authors on the study are David Brann, Tatsuya Tsukahara and Caleb Weinreb. Additional authors include Marcela Lipovsek, Koen Van den Berge, Boying Gong, Rebecca Chance, Iain Macaulay, Hsin-jung Chou, Russell Fletcher, Diya Das, Kelly Street, Hector Roux de Bezieux, Yoon-Gi Choi, Davide Risso, Sandrine Dudoit, Elizabeth Purdom, Jonathan Mill, Ralph Abi Hachem, Hiroaki Matsunami, Darren Logan, Bradley Goldstein, Matthew Grubb and John Ngai.*

*The study was supported by grants from the National Institutes of Health (grants RO11DC016222 and U19 NS112953) and the Simons Collaboration on the Global Brain. Additional funding information can be found in the full text of the paper.*

*DOI: 10.1126/sciadv.abc1564.*