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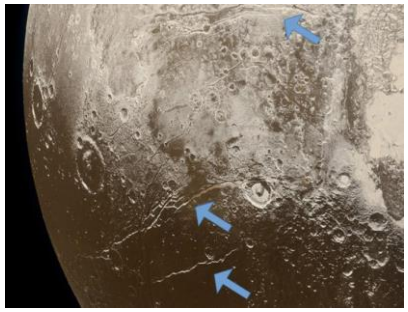
Evidence supports 'hot start' scenario and early ocean formation on Pluto

A new study suggests that Pluto and other large Kuiper belt objects started out with liquid oceans which have been slowly freezing over time



Extensional faults (arrows) on the surface of Pluto indicate expansion of the dwarf planet's icy crust, attributed to freezing of a subsurface ocean.
NASA/Johns Hopkins University Applied Physics Laboratory/Southwest Research Institute/Alex Parker

The accretion of new material during Pluto's formation may have generated enough heat to create a liquid ocean that has persisted beneath an icy crust to the present day, despite the dwarf planet's orbit far from the sun in the cold outer reaches of the solar system.

This "hot start" scenario, presented in a paper published June 22 in *Nature Geoscience*, contrasts with the traditional view of Pluto's origins as a ball of frozen ice and rock in which radioactive decay could have eventually generated enough heat to melt the ice and form a subsurface ocean.

"For a long time people have thought about the thermal evolution of Pluto and the ability of an ocean to survive to the present day," said coauthor Francis Nimmo, professor of Earth and planetary sciences at UC Santa Cruz. "Now that we have images of Pluto's surface from NASA's New Horizons mission, we can compare what we see with the predictions of different thermal evolution models."

Because water expands when it freezes and contracts when it melts, the hot-start and cold-start scenarios have different implications for the tectonics and resulting surface features of Pluto, explained first author and UCSC graduate student Carver Bierson.

"If it started cold and the ice melted internally, Pluto would have contracted and we should see compression features on its surface, whereas if it started hot it should have expanded as the ocean froze and we should see extension features on the surface," Bierson said. "We see lots of evidence of expansion, but we don't see any evidence of compression, so the observations are more consistent with Pluto starting with a liquid ocean."

The thermal and tectonic evolution of a cold-start Pluto is actually a bit complicated, because after an initial period of gradual melting the subsurface ocean would begin to refreeze. So compression of the surface would occur early on, followed by more recent extension. With a hot start, extension would occur throughout Pluto's history.

"The oldest surface features on Pluto are harder to figure out, but it looks like there was both ancient and modern extension of the surface," Nimmo said.

The next question was whether enough energy was available to give Pluto a hot start. The two main energy sources would be heat released by the decay of radioactive elements in the rock and gravitational energy released as new material bombarded the surface of the growing protoplanet.

Bierson's calculations showed that if all of the gravitational energy was retained as heat, it would inevitably create an initial liquid ocean. In practice, however, much of that energy would radiate away from the surface, especially if the accretion of new material occurred slowly.

"How Pluto was put together in the first place matters a lot for its thermal evolution," Nimmo said. "If it builds up too slowly, the hot material at the surface radiates energy into space, but if it builds up fast enough the heat gets trapped inside."

The researchers calculated that if Pluto formed over a period of less that 30,000 years, then it would have started out hot. If, instead,

accretion took place over a few million years, a hot start would only be possible if large impactors buried their energy deep beneath the surface.

The new findings imply that other large Kuiper belt objects probably also started out hot and could have had early oceans. These oceans could persist to the present day in the largest objects, such as the dwarf planets Eris and Makemake.

"Even in this cold environment so far from the sun, all these worlds might have formed fast and hot, with liquid oceans," Bierson said.

In addition to Bierson and Nimmo, the paper was coauthored by Alan Stern at the Southwest Research Institute, the principal investigator of the New Horizons mission.

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New class of precision medicine strips cancer of its DNA defenses

A new precision medicine targeting cancer's ability to repair its DNA has shown promising results in the first clinical trial of the drug class.

The new study, designed to test the drug's safety, found that half of patients given the new drug either alone or with platinum chemotherapy saw their cancer stop growing, and two patients saw their tumours shrink or disappear completely. Damage to the DNA in cells is the root cause of cancer - but it is also a fundamental weakness in tumours, and cancer cells can be killed by further damaging their DNA or attacking their ability to repair it.

The new phase I trial tested the first in a new family of drugs blocking a key DNA repair protein called ATR. Phase I trials are designed to assess the safety of new treatments, and it's unusual to see a clinical response at this stage.

A team at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, led a trial of the benefit of an ATR inhibitor called berzosertib either on its own or with chemotherapy in 40 patients with very advanced tumours, treated in hospitals around the world. The researchers established the doses at which the drug was safe for use in further clinical trials, and found berzosertib on its own caused only mild side effects.

Surprisingly for a phase I trial, the researchers also found that berzosertib stopped tumours growing in over half of patients given the drug either on its own or with chemotherapy - 20 out of 38 patients whose treatment response could be measured.

The drug's benefit in blocking DNA repair was even more marked in patients also given chemotherapy, which works by causing DNA damage. In these patients, 15 of 21, or 71 per cent saw their disease stabilise - suggesting that chemotherapy boosted sensitivity to berzosertib.

One patient with advanced bowel cancer whose tumour contained faults in key DNA repair genes including CHEK1 and ARID1A responded remarkably well to berzosertib on its own, seeing his tumours disappear and staying cancer free for more than two years.

Another woman with advanced ovarian cancer whose disease had come back after treatment with a drug blocking PARP, another key DNA repair protein, received the combination treatment and saw her tumours shrink.

This patient's response suggests that berzosertib could be explored as a strategy to overcome resistance to the PARP inhibitor family of targeted treatments. The drug is now moving forward in further trials, and the hope is that it could be developed into a new targeted treatment for patients, and help overcome resistance to other precision medicines such as PARP inhibitors that target DNA repair.

The new results are published in the *Journal of Clinical Oncology* today (Monday), and the trial was funded by Merck KGaA, Darmstadt, Germany, the manufacturer of the drug.

Drug resistance - as cancers evolve in response to treatment - is one of the biggest challenges facing cancer research and treatment today.

The Institute of Cancer Research (ICR), a charity and research institute, will be focusing on how to overcome cancer evolution and drug resistance in its new Centre for Cancer Drug Discovery, for which it still needs to raise the final £2 million.

The ICR discovered how to genetically target the first approved precision medicine attacking cancer's ability to repair DNA, the PARP inhibitor olaparib.

Professor Johann de Bono, Head of Drug Development at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, said: "Our new clinical trial is the first to test the safety of a brand new family of targeted cancer drugs in people, and it's encouraging to see some clinical responses even in at this early stage. Now, we and others are planning further clinical trials of berzosertib and other drugs blocking the ATR protein.

"In future, this new class of ATR inhibiting drugs could boost the effect of treatments like chemotherapy that target cancer DNA, expand our range of treatment options and overcome resistance to other targeted treatments.

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said: "Targeting a cancer's ability to repair its DNA is a fundamentally important avenue of cancer research which has delivered some of the most important advances against the disease in recent years.

"It's exciting to see the first clinical trial of a drug targeting a key player in the DNA repair process have such promising results, and I look forward to the results of further studies testing the benefit of this new family of targeted treatments.

"I'm keen to explore the potential for these ATR inhibitors to overcome resistance to other targeted drugs and to form effective treatment combinations. That's exactly the kind of approach we will be taking in our new Centre for Cancer Drug Discovery as we look to block off cancer's escape routes by creating a new generation of anti-evolution treatments."

Notes to editors

Berzosertib is also known under the names VX 970 and M6620.

https://bit.ly/37ZSbmr

COVID-19 Can Cause Loss of Smell, And Scientists Finally Discovered Why

The part of the nose that does the smelling, the olfactory cleft, is blocked with swollen soft tissue and mucus – known as a cleft syndrome.

Simon Gane & Jane Parker

From the first reports coming out of Wuhan, Iran and later Italy, we knew that losing your sense of smell (anosmia) was a significant symptom of the disease. Now, after months of reports, both anecdotal and more rigorous clinical findings, we think we have a model for how this virus may cause smell loss.

One of the most common causes of smell loss is a viral infection, such as the common cold, sinus or other upper respiratory tract infections. Those coronaviruses that don't cause deadly diseases, such as COVID-19, SARS and MERS, are one of the causes of the common cold and have been known to cause smell loss.

In most of these cases, sense of smell returns when symptoms clear, as smell loss is simply the result of a blocked nose, which prevents aroma molecules reaching olfactory receptors in the nose. In some cases, smell loss can persist for months and years.

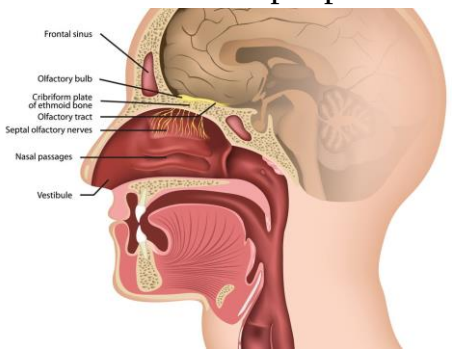
For the novel coronavirus (SARS-CoV-2), however, the pattern of smell loss is different. Many people with COVID-19 reported a sudden loss of sense of smell and then a sudden and full return to a normal sense of smell in a week or two.

Interestingly, many of these people said their nose was clear, so smell loss cannot be attributed to a blocked nose. For others, smell loss was prolonged and several weeks later they still had no sense

of smell. Any theory of anosmia in COVID-19 has to account for both of these patterns.

This sudden return of a normal sense of smell suggests an obstructive smell loss in which the aroma molecules cannot reach the receptors in the nose (the same type of loss one gets with a clothes peg on the nose).

Now that we have CT scans of the noses and sinuses of people with COVID-19 smell loss, we can see that the part of the nose that does the smelling, the olfactory cleft, is blocked with swollen soft tissue and mucus – known as a cleft syndrome. The rest of the nose and sinuses look normal and patients have no problem breathing through their nose.



Location of the olfactory bulb. **(medicalstocks/iStock/Getty Images Plus)**

We know that the way SARS-CoV-2 infects the body is by attaching to ACE2 receptors on the surface of cells that line the upper respiratory tract. A protein called TMPRSS2 then helps the virus invade the cell.

Once inside the cell, the virus can replicate, triggering the immune system's inflammatory response. This is the starting point for the havoc and destruction that this virus causes once in the body.

Initially, we thought that the virus might be infecting and destroying the olfactory neurons. These are the cells that transmit the signal from the aroma molecule in your nose to the area in the brain where these signals get interpreted as "smell".

However, an international collaboration showed recently that the ACE2 proteins the virus needs to invade the cells were not found on the olfactory neurons. But they were found on cells called "sustentacular cells", which support the olfactory neurons.

We expect that these support cells are likely to be the ones that are damaged by the virus, and the immune response would cause swelling of the area but leave the olfactory neurons intact. When the immune system has dealt with the virus, the swelling subsides and the aroma molecules have a clear route to their undamaged receptors and the sense of smell returns to normal.

So why does smell not return in some cases? This is more theoretical but follows from what we know about inflammation in other systems. Inflammation is the body's response to damage and results in the release of chemicals that destroy the tissues involved.

When this inflammation is severe, other nearby cells start to be damaged or destroyed by this "splash damage". We believe that accounts for the second stage, where the olfactory neurons are damaged.

Recovery of smell is much slower because the olfactory neurons need time to regenerate from the supply of stem cells within the lining of the nose.

Initial recovery is often associated with distortion of the sense of smell known as parosmia, where things don't smell like they used to. For many parosmics, for instance, the smell of coffee is often described as burnt, chemical, dirty and reminiscent of sewage.

Physiotherapy for the nose

Olfaction has been called the Cinderella of the senses because of its neglect by scientific research. But it has come to the forefront in this pandemic. The silver lining is that we will learn a lot about how viruses are involved in smell loss from this. But what hope is there for people with a loss of smell now?

The good news is that the olfactory neurons can regenerate. They're regrowing in almost all of us, all of the time. We can harness that regeneration and guide it with "physiotherapy for the nose": smell training.

There is solid evidence that many forms of smell loss are helped by this repeated, mindful exposure to a fixed set of odorants every day and no reason to think it won't work in COVID-19 smell loss.

Simon Gane, Consultant Rhinologist and ENT surgeon, City, University of London and Jane Parker, Associate Professor, Flavour Chemistry, University of Reading.

https://bit.ly/3dAOG7c

Initial COVID-19 infection rate may be 80 times greater than originally reported

Number of early COVID-19 cases in the U.S. may have been more than 80 times greater and doubled nearly twice as fast as originally believed

University Park, Pa. - Many epidemiologists believe that the initial COVID-19 infection rate was undercounted due to testing issues, asymptomatic and alternatively symptomatic individuals, and a failure to identify early cases.

Now, a new study from Penn State estimates that the number of early COVID-19 cases in the U.S. may have been more than 80 times greater and doubled nearly twice as fast as originally believed. In a paper published today (June 22) in the journal *Science Translational Medicine*, researchers estimated the detection rate of symptomatic COVID-19 cases using the Centers for Disease Control and Prevention's influenza-like illnesses (ILI) surveillance data over a three week period in March 2020.

"We analyzed each state's ILI cases to estimate the number that could not be attributed to influenza and were in excess of seasonal baseline levels," said Justin Silverman, assistant professor in Penn State's College of Information Sciences and Technology and Department of Medicine. "When you subtract these out, you're left with what we're calling excess ILI - cases that can't be explained by either influenza or the typical seasonal variation of respiratory pathogens."

The researchers found that the excess ILI showed a nearly perfect correlation with the spread of COVID-19 around the country. Said Silverman, "This suggests that ILI data is capturing COVID cases, and there appears to be a much greater undiagnosed population than originally thought."

Remarkably, the size of the observed surge of excess ILI corresponds to more than 8.7 million new cases during the last three weeks of March, compared to the roughly 100,000 cases that were officially reported during the same time period.

"At first I couldn't believe our estimates were correct," said Silverman. "But we realized that deaths across the U.S. had been doubling every three days and that our estimate of the infection rate was consistent with three-day doubling since the first observed case was reported in Washington state on January 15."

The researchers also used this process to estimate infection rates for each state, noting that states showing higher per capita rates of infection also had higher per capita rates of a surge in excess ILI. Their estimates showed rates much higher than initially reported but closer to those found once states began completing antibody testing.

In New York, for example, the researchers' model suggested that at least 9% of the state's entire population was infected by the end of March. After the state conducted antibody testing on 3,000 residents, they found a 13.9% infection rate, or 2.7 million New Yorkers.

Excess ILI appears to have peaked in mid-March as, the researchers suggest, fewer patients with mild symptoms sought care and states implemented interventions which led to lower transmission rates. Nearly half of U.S. states were under stay-at-home orders by March 28.

The findings suggest an alternative way of thinking about the COVID-19 pandemic.

"Our results suggest that the overwhelming effects of COVID-19 may have less to do with the virus' lethality and more to do with how quickly it was able to spread through communities initially," Silverman explained. "A lower fatality rate coupled with a higher prevalence of disease and rapid growth of regional epidemics provides an alternative explanation of the large number of deaths and overcrowding of hospitals we have seen in certain areas of the world."

Other collaborators on the project included Nathaniel Hupert of Cornell University and the New York-Presbyterian Hospital, and Alex Washburne of Montana State University.

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Doctors Describe Bizarre Brain Injury Case of a Man Who Can't 'See' Numbers

What comes first – the squiggle or the inability to see numbers?

Jacinta Bowler

That's what scientists have had to investigate in the unusual case of an engineering geologist who suffered a neurological injury, and suddenly couldn't perceive the numbers 2-9. But here's the thing – he could still understand letters, symbols, and even the numbers 0 and 1.

Number Shown to RFS RFS's Drawing of What He Saw

(Schubert, Rothlein, et al., PNAS, 2020)

"When he looks at a digit, his brain has to 'see' that it is a digit before he can not see it - it's a real paradox," said senior author, Johns Hopkins University cognitive scientist Michael McCloskey.

"In this paper what we did was to try to investigate what processing went on outside his awareness."

The patient - anonymously referred to in the case study as RFS - was diagnosed with a rare degenerative brain disease called corticobasal syndrome caused by significant damage to two areas of the brain: the cortex and basal ganglia.

Most people who have this disease suffer symptoms such as memory issues, muscle spasms, and difficulty walking. But as well as those normal symptoms, RFS also lost his ability to perceive, describe, or even copy most regular old Arabic numerals.

In a video released by the researchers, RFS tries to copy an orange '8', but instead, he draws what he describes as spaghetti, with an orange background.

In another experiment, the team tried to put pictures or words in or near large block numbers. The patient could easily see the pictures in equivalent letters, but couldn't see the pictures placed inside the numbers.

While this sounds unbelievable, the medical team carefully weighed up a range of possibilities, concluding the man was genuinely experiencing the strange perceptual anomaly.

"Given the rare form of RFS' metamorphopsia, how can we be sure that his deficit is genuine? With any unusual deficit, there is the possibility that the underlying dysfunction is psychiatric, psychogenic, or 'functional', rather than an impairment of basic perceptual/cognitive processes," the team writes in their paper.

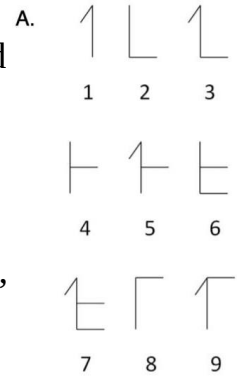
"We believe this unlikely in the present case for multiple reasons … At the time of our study RFS was seeing a psychiatrist for help in adjusting to his condition, and the psychiatrist had no suspicion that any of his perceptual, cognitive, or physical symptoms reflected a functional disorder. In addition, RFS' performance in two-choice discrimination was not below chance, as is often found in cases of malingered deficits."

The team worked with the man for nearly eight years – even creating a surrogate number system that RFS was able to use to continue his job until his retirement a few years later.

But the researchers really only understood what was actually happening when they studied RFS's brain using electroencephalography (EEG).

When RFS looked at a number with a face or a word inside of it, he couldn't tell there was something in there, but the researchers think his *brain* could.

"He was completely unaware that a word was there, yet his brain was not only detecting the presence of a word, but identifying which particular word it was, such as 'tuba'," said Harvard University cognitive scientist Teresa Schubert.



Surrogate system of numbers for RFS. **(Schubert, Rothlein et al., PNAS, 2020)**

In neurology, it's normally assumed that the neural activity the research team was seeing on the EEG is what causes the visual awareness, but this research suggests that additional processing is required – and it's only this last step that RFS doesn't seem to have any more.

"His brain detected the faces in the digits without his having any awareness of them," said VA Boston Healthcare's David Rothlein.

"These results show that RFS's brain is performing complex processing in the absence of awareness."

The research has been published in *PNAS*.

https://wb.md/3dvbhSz

Five Healthy Lifestyle Choices Tied to Dramatic Cut in Dementia Risk

Combining four of five healthy lifestyle choices has been linked to up to a 60% reduced risk for Alzheimer dementia

Megan Brooks

Combining four of five healthy lifestyle choices has been linked to up to a 60% reduced risk for Alzheimer dementia in new research that strengthens ties between healthy behaviors and lower dementia risk.

"I hope this study will motivate people to engage in a healthy lifestyle by not smoking, being physically and cognitively active, and having a high-quality diet," lead investigator Klodian Dhana, MD, PhD, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois, told *Medscape Medical News*.

The study was published online June 17 in *Neurology*.

Risk-Modifying Behaviors

To help quantify the impact of a healthy life on risk for Alzheimer dementia, Dhana and colleagues reviewed data from two longitudinal study populations: the Chicago Health and Aging Project (CHAP), with 1845 participants; and the Memory and Aging Project (MAP), with 920 participants.

They defined a healthy lifestyle score on the basis of the following factors: not smoking; engaging in ≥150 min/wk of physical exercise of moderate to vigorous intensity; light to moderate alcohol consumption (between 1 and <15 g/day for women and between 1 and <30 g/day for men); consuming a high-quality Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet (upper 40%); and engaging in late-life cognitive activities (upper 40%). The overall score ranged from 0 to 5.

At baseline, the mean age of participants was 73.2 years in the CHAP study and 81.1 years in the MAP study; 62.4% of the CHAP participants and 75.2% of the MAP participants were women.

During a median follow-up of 5.8 years in CHAP and 6.0 years in MAP, a total of 379 and 229 participants, respectively, developed Alzheimer dementia. Rates of dementia decreased with an increasing number of healthy lifestyle behaviors.

In multivariable-adjusted models across the two cohorts, the risk for Alzheimer dementia was 27% lower with each additional healthy lifestyle factor (pooled hazard ratio [HR], 0.73; 95% confidence interval [CI] 0.66 – 0.80).

Compared to individuals with a healthy lifestyle score of 0 to 1, the risk was 37% lower (pooled HR, 0.63; 95% CI, 0.47 – 0.84) for those with two or three healthy lifestyle factors and 60% lower (pooled HR, 0.40; 95% CI, 0.28 – 0.56) for those with four or five healthy lifestyle factors.

"From these findings and the fact that the lifestyle factors we studied are modifiable and in direct control of the individual, it is imperative to promote them concurrently among older adults as a strategy to delay or prevent Alzheimer dementia," Dhana and colleagues conclude in their article.

In a statement, Dallas Anderson, PhD, program director, Division of Neuroscience, National Institute on Aging, said the findings help "paint the picture of how multiple factors are likely playing parts in Alzheimer's disease risk."

"It's not a clear cause-and-effect result, but a strong finding because of the dual data sets and combination of modifiable lifestyle factors that appear to lead to risk reduction," Anderson added.

Essential Questions Remain

Commenting on the new study for *Medscape Medical News*, Luca Giliberto, MD, PhD, neurologist with the Litwin-Zucker Research Center for Alzheimer's Disease and Memory Disorders at the Feinstein Institutes for Medical Research in Manhasset, New York, said this analysis is "further demonstration that a healthy lifestyle is essential to overcome or curb" the risk for Alzheimer disease.

"What needs to be determined is how early should we start 'behaving.' We should all aim to score four to five factors across our entire lifespan, but this is not always feasible. So, when is the time to behave? Also, what is the relative weight of each of these factors?" said Giliberto.

Of note, he added, although addressing vascular risk factors such as hypertension, hyperlipidemia, and diabetes "may require an extensive mindful and logistic effort, leading a healthy diet is effortlessly achieved in some countries, where both the DASH and MIND diets do not need to be 'prescribed' but are rather culturally engraved in the population.

"This is, in part, related to the wide availability of high-quality food in these countries, which is not the same in the US. This work is one more demonstration of the need to revisit our take on quality of food in the US," said Giliberto.

Numerous clinical trials testing lifestyle interventions for dementia prevention are currently underway. The MIND Diet Intervention to Prevent Alzheimer's Disease, for example, is an interventional clinical trial comparing parallel groups with two different diets. MIND has enrolled more than 600 participants and is ongoing. The anticipated completion date is 2021.

Another is the US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER), a multisite randomized clinical trial evaluating whether lifestyle interventions — including exercise, cognitively stimulating activities, and the MIND diet — may protect cognitive function in older adults who are at increased risk for cognitive decline.

Funding for the current study was provided by the National Institutes of Health and the National Institute on Aging. Dhana and Giliberto have disclosed no relevant financial relationships.

Neurology. Published online June 17, 2020. Abstract

https://bit.ly/3i7iWdq

Coronavirus and sex hormones — baldness may be a risk factor and anti-androgens a treatment

Androgens seem to play an important role in the entry of SARS-CoV-2

Jenny Graves *

Two small studies published recently suggested most men hospitalised with COVID-19 are bald, generating headlines around the world. While this may sound strange, science does offer a plausible explanation.

Male pattern baldness is associated with high levels of male sex hormones called androgens. And androgens seem to play an important role in the entry of SARS-CoV-2, the coronavirus that causes COVID-19, into cells.

So it's possible high levels of androgens might increase the risk of severe infection and death from COVID-19.

This hypothesis is important to identify people at risk and raises the possibility of new treatment strategies for COVID-19.

Men suffer more than women from COVID-19

It's been obvious from early in the pandemic. Men are at greater risk of severe infection and death from COVID-19 than women.

There are several possible factors at play here. For one, men are more likely to suffer from chronic conditions known to pose a higher risk of serious illness from COVID-19. These include heart disease and diabetes.

Another is that men's immune systems are not as good as women's at warding off the severe effects of viral infections.

These factors are indirectly influenced by sex hormones. Now it seems sex hormones might also have a direct effect on SARS-CoV-2's ability to enter our cells and establish infection.

Baldness and COVID-19

In one study of 122 male COVID-19 patients admitted to hospitals in Madrid, 79% were bald — about double the population frequency.

Another small study in Spain observed a similar overrepresentaton of baldness among men hospitalised with COVID-19.

Male pattern baldness is strongly associated with a higher level of dihydrotestosterone (DHT), a more active derivative of testosterone, and one of the androgen family of male sex hormones.

Confirming this correlation between baldness and susceptibility to COVID-19 with larger samples, controlling for age and other conditions, would be significant. It would suggest a higher DHT level could be a risk factor for severe COVID-19.

How does this link make biological sense?

SARS-CoV-2 enters human lung cells when a protein on the virus' surface (the spike protein) latches onto protein receptors (ACE2 receptors) embedded in the cells' surfaces.

How does this work? Recently scientists discovered that an enzyme called TMPRSS2 cleaves the SARS-CoV-2's spike protein, enabling it to bind to the ACE2 receptor. This allows the virus to enter the cell.

The gene that encodes TMPRSS2 is activated when male hormones, particularly DHT, bind to the androgen receptor (a protein on the surface of cells, including hair cells and lung cells).

So the more male hormone, the more androgen receptor binding, the more TMPRSS2 is present, and the easier it is for virus to get in.

A preliminary, non-peer-reviewed study which correlated the androgen levels of hundreds of people in the UK with COVID-19 severity supports this theory. Higher androen level was associated with susceptibility to and severity of COVID-19 in men (but not women, who have much lower androgen levels in their blood).

The same researchers showed that inhibiting androgen receptors reduced the ability of SARS-CoV-2's spike protein to bind to ACE2 receptors on stem cells in culture.

Androgen disruptions are linked to different diseases

Over- or underproduction of androgens in the body causes a variety of conditions in both men and women.

For instance, men with benign prostate enlargement overproduce androgen, as do women with polycystic ovary syndrome.

Many such conditions are treated with androgen deprivation therapy (ADT), which inhibits the production or effect of androgens. For instance, prostate cancer, in which cancer cell growth is fuelled by androgens, is routinely treated with ADT.

Conversely, some people have low androgen production, or mutations that affect the binding and action of androgens — such as women with androgen insensitivity syndrome caused by mutations of the androgen receptor.

It will be important to find out whether, as the androgen hypothesis predicts, patients with over- or under-production of male hormones are at greater — or lesser — risk of COVID-19.

A potential treatment option?

If the androgen link holds up, this would encourage exploration of anti-androgens as a way to prevent and treat COVID-19.

Many anti-androgens are already approved for the treatment of other conditions. Some, like baldness treatments, have been used safely for years or decades. Some, like cancer treatments, can be tolerated for months.

A study which looked at men hospitalised with COVID-19 in Italy showed the rate of infection was four times lower in prostate cancer patients on ADT than in untreated cancer patients.

Perhaps a single dose given to someone who tests positive to SARS-CoV-2, or has just been exposed, would suffice to lower the chance of the virus taking hold.

But we need research to confirm this. Several androgen-suppressing drugs are now undergoing clinical trials to determine whether they reduce complications among men with COVID-19.

It will be important to verify that anti-androgen treatment works in the lungs as well as the prostate, and is effective in cancer-free patients. We'd also need to find out what dose is effective, and when it should be administered.

Anti-androgen treatments have several side effects in men, including breast enlargement and sexual dysfunction, so medical oversight is a must.

A promising new direction in COVID-19 research

The androgen link could go a long way to explaining why men are more susceptible to COVID-19 than women. It also may explain why children younger than ten seem very resistant to COVID-19 because, until puberty, boys as well as girls make little androgen.

The more we know about who is at heightened risk from COVID-19, the better we can target information.

The androgen link also opens up an avenue for the discovery of drugs which might mitigate some of the impact of COVID-19 as it continues to sweep the globe.

* *Jenny Graves is a Friend of The Conversation.*
Distinguished Professor of Genetics and Vice Chancellor's Fellow, La Trobe University

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https://bit.ly/3ibBIR9

A Gene May Help Discern Language Tone Differences: Is It Shí or Shì?

Subtle variations in our DNA may have led to the modulation of pitch to convey word meaning

By Rachel Nuwer on June 23, 2020

More than 7,000 languages exist today, a wealth of diversity that continues to puzzle researchers. Languages vary in a number of ways: Parts of speech, for instance, may be ordered differently. And a change in tone can signify a distinct word meaning. One lingering question that has perplexed linguists is whether genes predispose the use of tones or other linguistic features.

A study published last month in *Science Advances* suggests subtle DNA differences influence a person's ability to perceive tones. It provides the first tangible evidence for the potential impact of genes in the evolution of language.

"For the first time, we found direct evidence that a genetic variant is actually tied to a linguistic feature," says Patrick Wong, a cognitive

neuroscientist at the Chinese University of Hong Kong and lead author of the paper. This insight, he adds, carries important practical implications for those with language impairments.

Wong and his colleagues are not the first to hypothesize that genetic diversity may drive the evolution of language. In 2007 researchers compared two dozen linguistic features to nearly 1,000 gene variants in 49 populations around the world. They found a significant correlation between the presence of separate variants in the genes *ASPM* and *MCPH1* and an increased likelihood that a group speaks a language that uses pitch to change words' meaning. Such tonal languages —spoken in China, Southeast Asia and Central Africa, among other regions—make up at least half of the world's languages. The 2007 investigation did not test whether genetics exerted any real-world effect on tone perception, however. "That study generated a hypothesis, but many people were pretty skeptical," Wong says. "We really needed direct evidence."

In the new study, Wong and his colleagues performed listening tests on more than 400 native Cantonese speakers to determine each participant's proficiency at distinguishing the language's six tones. They administered additional tests to measure the volunteers' IQ, memory, and musical pitch and rhythm. The team genetically analyzed participants' saliva for nine variants of three genes hypothesized to be connected to tone perception, as well as 13 variants of seven genes thought to play a role in general language processing.

The researchers' analysis revealed that only a single variant of the *ASPM* gene known as TT—one of the two variants identified in the 2007 paper—predicted how well participants could perceive tone. They also found that the majority of the people they tested, about 70 percent, had the TT variant (which consists of two copies of the base thymine), confirming its prominence in the Cantonese-speaking population.

The gene's overall effect, however, was still small: it ranked behind IQ and musical background in terms of predicting tonal proficiency. But applied over many years, subtle genetic differences can exert significant influence, Wong says. "It reveals a potential underlying mechanism of how language evolves."

Damián Blasi, a language scientist at Harvard University, who was not involved in the study, agrees that small genetic effects could potentially drive language change. But he emphasizes that researchers still have much to learn. "I would not expect any single study to be a definitive demonstration of a causal effect in a language change," Blasi says. "And this study is no exception."

Wong's paper, however, is still "a big step in the field because it uses a more suitable experimental design than previous work and a considerably larger sample size," says Balthasar Bickel, a linguist at the University of Zurich, who also was not involved in the research. The study also highlights the need for "far tighter collaboration between biologists and linguists than what happens traditionally," he says.

Wong hopes to carry out follow-up studies with speakers of other tonal languages in Southeast Asia, China and Africa. He also plans to explore the practical implications of the findings.

Speech disorders, for example, often cause problems with pitch perception for speakers of tonal languages, so clinicians could potentially use *ASPM*, along with other genes, in early genetic screenings to identify children at risk of such disorders. The fact that *ASPM* seems to be tied to tonal perception also implies that any genetic test used to screen for speech impairments should be tailored to specific populations, depending on the language spoken. "There's no one-size-fits-all solution," Wong says.

The new study also hints at possible interventions for certain speech and language disorders. Unexpectedly, Wong and his colleagues' analysis reveals that musical training of any kind—including

something as simple as childhood piano lessons—increased tonal perception in participants who did not carry *ASPM*'s TT variant. Violin or voice lessons could be an early intervention for those who speak a tonal language and are at risk for a language impairment, Wong says. They may include autistic tonal language speakers, who sometimes struggle with pitch perception.

"Genetic testing is not just about testing. It's about planning for interventions," Wong says. "To me, the possibility of interventions for helping at-risk groups is the most exciting aspect of this."

https://bit.ly/2BcpBCv

Scientists Used Dopamine to Seamlessly Merge Artificial and Biological Neurons

It's possible to get an artificial neuron to communicate directly with a biological one using not just electricity, but dopamine

By Shelly Fan

In just half a decade, neuromorphic devices—or brain-inspired computing—already seem quaint. The current darling? Artificial-biological hybrid computing, uniting both man-made computer chips and biological neurons seamlessly into semi-living circuits.

It sounds crazy, but a new study in *Nature Materials* shows that it's possible to get an artificial neuron to communicate directly with a biological one using not just electricity, but dopamine—a chemical the brain naturally uses to change how neural circuits behave, most known for signaling reward.

Because these chemicals, known as "neurotransmitters," are how biological neurons functionally link up in the brain, the study is a dramatic demonstration that it's possible to connect artificial components with biological brain cells into a functional circuit.

The team isn't the first to pursue hybrid neural circuits. Previously, a different team hooked up two silicon-based artificial neurons with a biological one into a circuit using electrical protocols alone. Although a powerful demonstration of hybrid computing, the study relied on only one-half of the brain's computational ability: electrical computing.

The new study now tackles the other half: chemical computing. It adds a layer of compatibility that lays the groundwork not just for brain-inspired computers, but also for brain-machine interfaces and—perhaps—a sort of "cyborg" future. After all, if your brain can't tell the difference between an artificial neuron and your own, could you? And even if you did, would you care?

Of course, that scenario is far in the future—if ever. For now, the team, led by Dr. Alberto Salleo, professor of materials science and engineering at Stanford University, collectively breathed a sigh of relief that the hybrid circuit worked.

"It's a demonstration that this communication melding chemistry and electricity is possible," said Salleo. "You could say it's a first step toward a brain-machine interface, but it's a tiny, tiny very first step."

Neuromorphic Computing

The study grew from years of work into neuromorphic computing, or data processing inspired by the brain.

The blue-sky idea was inspired by the brain's massive parallel computing capabilities, along with vast energy savings. By mimicking these properties, scientists reasoned, we could potentially turbo-charge computing. Neuromorphic devices basically embody artificial neural networks in physical form—wouldn't hardware that mimics how the brain processes information be even more efficient and powerful?

These explorations led to novel neuromorphic chips, or artificial neurons that "fire" like biological ones. Additional work found that it's possible to link these chips up into powerful circuits that run deep learning with ease, with bioengineered communication nodes called artificial synapses.

As a potential computing hardware replacement, these systems have proven to be incredibly promising. Yet scientists soon wondered: given their similarity to biological brains, can we use them as "replacement parts" for brains that suffer from traumatic injuries, aging, or degeneration? Can we hook up neuromorphic components to the brain to restore its capabilities?

Buzz & Chemistry

Theoretically, the answer's yes.

But there's a huge problem: current brain-machine interfaces only use electrical signals to mimic neural computation. The brain, in contrast, has two tricks up its sleeve: electricity and chemicals, or electrochemical.

Within a neuron, electricity travels up its incoming branches, through the bulbous body, then down the output branches. When electrical signals reach the neuron's outgoing "piers," dotted along the output branch, however, they hit a snag. A small gap exists between neurons, so to get to the other side, the electrical signals generally need to be converted into little bubble ships, packed with chemicals, and set sail to the other neuronal shore.

In other words, without chemical signals, the brain can't function normally. These neurotransmitters don't just passively carry information. Dopamine, for example, can dramatically change how a neural circuit functions. For an artificial-biological hybrid neural system, the absence of chemistry is like nixing international cargo vessels and only sticking with land-based trains and highways.

"To emulate biological synaptic behavior, the connectivity of the neuromorphic device must be dynamically regulated by the local neurotransmitter activity," the team said.

Let's Get Electro-Chemical

The new study started with two neurons: the upstream, an immortalized biological cell that releases dopamine; and the downstream, an artificial neuron that the team previously introduced in 2017, made of a mix of biocompatible and electrical-conducting materials.

Rather than the classic neuron shape, picture more of a sandwich with a chunk bitten out in the middle (yup, I'm totally serious). Each of the remaining parts of the sandwich is a soft electrode, made of biological polymers. The "bitten out" part has a conductive solution that can pass on electrical signals.

The biological cell sits close to the first electrode. When activated, it dumps out boats of dopamine, which drift to the electrode and chemically react with it—mimicking the process of dopamine docking onto a biological neuron. This, in turn, generates a current that's passed on to the second electrode through the conductive solution channel. When this current reaches the second electrode, it changes the electrode's conductance—that is, how well it can pass on electrical information. This second step is analogous to docked dopamine "ships" changing how likely it is that a biological neuron will fire in the future.

In other words, dopamine release from the biological neuron interacts with the artificial one, so that the chemicals change how the downstream neuron behaves in a somewhat lasting way—a loose mimic of what happens inside the brain during learning.

But that's not all. Chemical signaling is especially powerful in the brain because it's flexible. Dopamine, for example, only grabs onto the downstream neurons for a bit before it returns back to its upstream neuron—that is, recycled or destroyed. This means that its effect is temporary, giving the neural circuit breathing room to readjust its activity.

The Stanford team also tried reconstructing this quirk in their hybrid circuit. They crafted a microfluidic channel that shuttles both dopamine and its byproduct away from the artificial neurons after they've done their job for recycling.

Putting It All Together

After confirming that biological cells can survive happily on top of the artificial one, the team performed a few tests to see if the hybrid circuit could "learn."

They used electrical methods to first activate the biological dopamine neuron, and watched the artificial one. Before the experiment, the team wasn't quite sure what to expect. Theoretically, it made sense that dopamine would change the artificial neuron's conductance, similar to learning. But "it was hard to know whether we'd achieve the outcome we predicted on paper until we saw it happen in the lab," said study author Scott Keene.

On the first try, however, the team found that the burst of chemical signaling was able to change the artificial neuron's conductance long-term, similar to the neuroscience dogma "neurons that fire together, wire together." Activating the upstream biological neuron with chemicals also changed the artificial neuron's conductance in a way that mimicked learning.

"That's when we realized the potential this has for emulating the long-term learning process of a synapse," said Keene.

Visualizing under an electron microscope, the team found that, similar to its biological counterpart, the hybrid synapse was able to efficiently recycle dopamine with timescales similar to the brain after some calibration. By playing with how much dopamine accumulates at the artificial neuron, the team found that they loosely mimic a learning rule called spike learning—a darling of machine learning inspired by the brain's computation.

A Hybrid Future?

Unfortunately for cyborg enthusiasts, the work is still in its infancy.

For one, the artificial neurons are still rather bulky compared to biological ones. This means that they can't capture and translate information from a single "boat" of dopamine. It's also unclear if, and how, a hybrid synapse can work inside a living brain. Given the billions of synapses firing away in our heads, it'll be a challenge to find-and-replace those that need replacement, and be able to control our memories and behaviors similar to natural ones.

That said, we're inching ever closer to full-capability artificial-biological hybrid circuits.

"The neurotransmitter-mediated neuromorphic device presented in this work constitutes a fundamental building block for artificial neural networks that can be directly modulated based on biological feedback from live neurons," the authors concluded. "[It] is a crucial first step in realizing next-generation adaptive biohybrid interfaces."

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Humans navigate with stereo olfaction

"If in doubt, always follow your nose," said Gandalf in The Lord of the Rings.

Despite Gandalf's advice, humans tend to regard themselves as "microsmatic" - having a poor sense of smell. Human navigation is thought to rely primarily on vision and audition. Specifically, subtle differences between the inputs to the paired eyes and ears are exploited by the brain to construct three-dimensional experiences that guide navigation.

Although humans also have two separate nasal passages that simultaneously sample from nonoverlapping regions in space, it is widely held that inter-nostril differences in odor concentration do not provide directional information in humans unless that odor also stimulates the trigeminal nerve (i.e., elicits hot, cold, spicy, tingling, or electric feelings), in which case it is really the trigeminal system that generates a directional cue.

However, a new study conducted by graduate student WU Yuli and his colleagues at the Institute of Psychology of the Chinese Academy of Sciences (CAS) argues otherwise.

WU and his colleagues introduced various levels of binaral concentration disparity to a heading judgment paradigm based on

optic flow - a unique type of visual stimulus that captures the pattern of apparent motion of surface elements in a visual scene and induces the illusory feeling of self-movement in stationary observers.

The odorants they used were phenylethyl alcohol and vanillin, which smell like rose and vanilla, respectively, and are known to activate only the olfactory nerve.

Results from stringent psychophysical testing in four experiments involving a total of 180 participants consistently showed that a moderate binaral disparity biases recipients' perceived direction of self-motion toward the higher-concentration side in manners reminiscent of stereo vision (i.e., binocular stereopsis), despite not being able to verbalize which nostril smells a stronger odor.

In addition, the effect depends on the inter-nostril ratio of odor concentrations as opposed to the numeric difference in concentration between the two nostrils.

"Our work presents clear behavioral evidence that humans have a stereo sense of smell that subconsciously guides navigation," said Dr. ZHOU Wen, senior author of the study. "The findings underscore the multisensory nature of heading perception and could provide guidance for the design and development of olfactory virtual-reality systems for humans."

The study, entitled "Humans navigate with stereo olfaction," was published online on *PNAS* on June 22.

It was funded by the Key Research Program of Frontier Sciences and the Strategic Priority Research Program of the Chinese Academy of Sciences, the National Natural Science Foundation of China, and the Beijing Municipal Science and Technology Commission.

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Study confirms "classic" symptoms of COVID-19

A persistent cough and fever have been confirmed as the most prevalent symptoms associated with COVID-19, according to a major review of the scientific literature.

Other major symptoms include fatigue, losing the ability to smell and difficulty in breathing.

The study ratifies the list of symptoms listed by the World Health Organisation at the start of the pandemic.

The researchers - from five universities including the University of Leeds in the UK - combined data from 148 separate studies to identify the common symptoms experienced by more than 24,000 patients from nine countries, including the UK, China and the US.

The study - published in the online journal *PLoS ONE* - is one of the biggest reviews ever conducted into COVID-19 symptoms. The researchers also acknowledge there is likely to be a large proportion of people who had the virus but did not display symptoms .

Of the 24,410 cases, the study found:

- ***78 percent had a fever. Although this tended to vary across countries: with 72 percent of fever reported by patients in Singapore and 32 percent in Korea.***
- ***57 percent reported a cough. Again, this varied across countries, with 76 percent of patients reporting a cough in the Netherlands compared to 18 percent in Korea.***
- ***31 percent said they had suffered fatigue.***
- ***25 percent lost the ability to smell.***
- ***23 percent reported difficulty breathing.***

The researchers believe the variation in the prevalence of symptoms between countries is due, in part, to the way data was collected.

Of those patients who needed hospital treatment, 17 percent needed non-invasive help with their breathing; 19 percent had to be looked after in an intensive care unit, nine percent required invasive ventilation and two percent needed extra-corporeal membrane oxygenation, an artificial lung.

Ryckie Wade, a surgeon and Clinical Research Fellow at the Leeds Institute of Medical Research, supervised the research. He said:

"This analysis confirms that a cough and fever were the most common symptoms in people who tested positive with COVID-19."

"This is important because it ensures that people who are symptomatic can be quarantined, so they are not infecting others.

"The study gives confidence to the fact that we have been right in identifying the main symptoms and it can help determine who should get tested."

The study involved academics from the University of Leeds with colleagues from the University of Sheffield, University of Bristol, Imperial College, London, and the Belgium Cancer Centre. The research was funded by the UK's National Institute for Health Research and VALCOR, in Belgium.

https://wb.md/2VieRcr

Flu-COVID 'Collision' Expected This Fall, Health Experts Warn

U.S. must increase its influenza vaccination rate substantially this fall to mitigate a potentially deadly confluence of seasonal influenza with an anticipated second wave of COVID-19.

Kenneth J. Terry, MA

Public health and infectious disease experts warn that the United States needs to increase its influenza vaccination rate substantially this fall to mitigate a potentially deadly confluence of seasonal influenza with an anticipated second wave of COVID-19.

"When you have a collision of these two things happening at the same time, I think we're going to be in real trouble," Rochelle Walensky, MD, chief of the infectious diseases division at Massachusetts General Hospital, Boston, told *Medscape Medical News*.

Walensky noted that about 45% to 50% of people get a flu vaccine in any given flu season. While a COVID vaccine is also needed, she said, increased uptake of the flu vaccine is sorely needed. "We need to do a massive vaccine campaign because that's something we can do something about in terms of prevention," she noted.

"High vaccine coverage would reduce influenza-related mortality, while also helping to preserve the capacity and function of the health system during circulation of influenza viruses and severe acute respiratory syndrome coronavirus 2," writes Lawrence O. Gostin, JD, a professor at Georgetown University's O'Neill Institute for National and Global Health Law, Washington, DC, and Daniel A. Salmon, MD, of the Institute for Vaccine Safety at Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, in a recent *JAMA* Viewpoint.

Gostin told *Medscape Medical News* that a bad flu outbreak this year "would be really ruinous for the healthcare system. If we continue to have those COVID spikes as a second wave, there would probably be 50% or 100% more hospitalizations on top of those from the flu."

In an editorial in *Science Magazine*, Edward A. Belongia, MD, director of the Center for Clinical Epidemiology and Population Health at the Marshfield Clinic Research Institute, Wisconsin, and Michael T. Osterholm, PhD, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, Minneapolis, write: "The stress on hospitals will be greatest if the COVID-19 and influenza epidemics overlap and peak around the same time."

"We do not yet have a COVID-19 vaccine, but safe and moderately effective influenza vaccines are available. Their widespread use is more important now than ever, and we encourage health care providers, employers, and community leaders to promote vaccination," they add.

William Schaffner, MD, professor of preventive medicine and infectious diseases at Vanderbilt University, Nashville, Tennessee, agreed with his colleagues that seasonal flu vaccination is especially important this year.

He told *Medscape Medical News* that the Centers for Disease Control and Prevention (CDC) has informed the influenza vaccine workgroup of its Advisory Committee on Immunization Practices (ACIP), of which he is a member, that the agency is planning a major public awareness campaign this year to raise the percentage of people who get flu shots.

The CDC confirmed it is planning such a campaign.

"This season, getting a flu vaccine is more important than ever as it will not only protect against flu, but it also will help preserve scarce medical resources for healthcare providers and COVID-19 patients," agency spokesperson Kristen Nordlund told *Medscape Medical News.*

"CDC is developing and will roll out new communications materials to increase awareness about the importance of flu vaccination this season, especially among people who are at higher risk for flu and COVID-19," she added.

The CDC usually begins its annual flu vaccine campaign activities in a joint press conference with the National Foundation for Infectious Diseases. That news conference is scheduled for October 1, around the time flu vaccinations for the 2020-2021 season are expected to begin.

A successful campaign to raise vaccination rates would require the involvement of state and local public health departments, Gostin noted. These agencies need federal support in the form of a framework for an effective health communications strategy and funding to carry that strategy out, he said. The CDC didn't respond to *Medscape Medical News'* question about how it plans to support state and local health departments.

Effect of Flu Vaccination

Although not as lethal as COVID-19, seasonal influenza causes a lot of deaths, especially among the elderly. In 2018-2019, the United States had 35.5 million influenza cases, with nearly 500,000 hospitalizations and 34,200 deaths attributed to the virus, Gostin and Salmon noted in their *JAMA* article. The year before, a particularly nasty flu caused 79,400 US deaths.

The CDC recommends that every person 6 months and older get vaccinated for seasonal influenza. Despite adult vaccination coverage of only 45% in 2018-2019, Gostin and Salmon observed, the vaccine prevented approximately 4.4 million influenza cases, 58,000 hospitalizations, and 3500 deaths. Besides preventing flu infections, vaccines also reduce intensive care admissions and duration of hospitalizations.

The editorialists attribute the relatively low vaccination rate to "public perceptions of low effectiveness, along with safety concerns. While effectiveness is low compared with other vaccines, influenza immunization is very safe and cannot cause influenza."

National Effort

Gostin and Salmon are calling for a national effort to attain high influenza vaccine coverage, including near-universal coverage among healthcare personnel and other groups at high risk for COVID-19. This effort should include a mass communication campaign, tailoring messages to specific populations, they say.

Gostin and Salmon also note that adequate flu vaccine supplies must be produced to meet the demand if immunization coverage is increased. Vaccine shortages have occurred in the past, and some drug companies have stopped manufacturing vaccines because of low profits and high financial risks.

They propose in their *JAMA* commentary that the federal government absorb this risk through "advance purchase commitments" for flu vaccines.

Schaffner said he is confident there will be enough flu vaccine supplies to meet the demand this year, even if a government campaign persuades more people to get inoculated. Additional manufacturers have recently entered the flu vaccine field, he said,

and these companies have assured the ACIP's influenza vaccine workgroup that they are prepared for a surge.

"If there's an increasing demand for the vaccine, the manufacturers have told us that they can gin up their production capacity," he said.

Overcoming Vaccine Hesitancy

Vaccine uptake will be limited unless more patients make routine clinical visits, the *JAMA* article noted. Consequently, physician offices must use best practices to protect their patients from COVID-19 infection and encourage them to get vaccinated.

Pharmacies can also provide flu shots, as many do now, and many pharmacy chains are already preparing for a big push for flu vaccines this fall; schools and universities can also mount flu vaccination campaigns if they reopen. Businesses can take advantage of federal regulations that allow them to require influenza vaccination as a condition of employment.

Schaffner concurred. "Part of the message that has to go out is that you can be inoculated safely, and it's important to do this now. This is especially important because elderly people and vulnerable people with underlying conditions are those who are sheltering at home the most. They're being the most cautious about getting out there."

Gostin and Salmon emphasize that as many healthcare workers as possible should be immunized against the seasonal flu. In 2018-2019, they point out, the flu vaccination rate among healthcare personnel was 81%. This year, they say, "higher vaccine coverage should be a national priority."

State laws, they note, require workers at healthcare facilities to receive flu shots, but only if they consent. Many hospitals, however, have made influenza vaccination mandatory over the past decade, Schaffner said, adding that big institutions like Vanderbilt University Medical Center have vaccination rates in the 95% range. Flu vaccine coverage is considerably lower in outpatient clinics, he added. Even if ambulatory care physicians do hospital rounds, they may not ensure their office staffs are inoculated, he noted.

Social Media Misinformation

In their *Science* op-ed, Belongia and Osterholm warn that social media is spreading misinformation about flu shots, such as the claim that they increase the risk of SARS-CoV-2 infection.

"Scientists, health care providers, and public health leaders must counter these claims with clear, evidence-based information on the importance of influenza vaccination during the COVID-19 pandemic," they say.

Belongia and Osterholm emphasize the importance of social distancing and other measures at vaccination sites to minimize the risk of SARS-CoV-2 infection, "particularly because many influenza vaccine recipients are at high risk for both influenza and COVID-19 complications."

It's unclear when COVID-19 patients should receive flu shots, they add, "but it may be prudent to delay vaccine administration until after the acute illness has been resolved."

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Invasive fire ants limiting spread of meat allergy -- but pose their own dangers

Invasive fire ants common in the Gulf Coast and Texas likely are limiting a tick-acquired meat allergy in these areas, scientists report.

Invasive fire ants with a nasty bite are limiting the spread of a dangerous meat allergy, new research suggests. But it's not all good news, as the ants themselves can also cause severe allergic reactions. School of Medicine researchers and their collaborators made the discovery while seeking to understand the scope of the "alpha-gal" meat allergy in the United States. Spread by the bite of the lone star

tick, the allergy causes people to develop potentially severe allergic reactions to mammalian meat, including beef and pork.

The allergy is commonly seen throughout the Southeast, the Mid-Atlantic and the Midwest, but rarely in the Gulf Coast and Texas. That is likely caused by the steady expansion of fire ants accidentally imported from South America in the 1930s, the researchers conclude.

But the ants are no heroes, as their bites can be very painful and cause severe allergic reactions. In some cases, the bites can cause life-threatening anaphylaxis. That's in addition to the dangers the ants pose to animals and crops. And the strong-jawed insects are marching relentlessly northward.

"We did not set out to study fire ants, but when the number of alpha-gal cases in the Gulf Coast was consistently lower than we expected, the fire ant emerged as an interesting explanation," said UVA researcher Behnam Keshavarz, PhD, a co-first author of a new scientific paper outlining the discovery.

Mapping the Meat Allergy

The meat allergy was first identified more than a decade ago by UVA's Thomas Platts-Mills, MD, PhD, an internationally renowned allergist. Since then, he and his colleagues have shed light on how and why the tick's bite causes people to develop allergic reactions to a particular sugar, alpha-gal, present in meat and other mammalian products. The symptoms can include itchy rashes, nausea and difficulty breathing. Severe reactions can progress to anaphylaxis if untreated.

Until now, there has been little examination of the geographic scope of the allergy in the United States. The UVA researchers set out to change that. They surveyed allergists across the country to map out cases of the meat allergy. They also tested blood samples from two different geographic areas where it was particularly prevalent. The latter was important to show that the allergy is "immunologically similar" across the country.

The researchers found the meat allergy was common in significant portions of at least 14 states. Eleven states had at least one allergist report more than 100 case in their practice: Alabama, Arkansas, Georgia, Kentucky, Maryland, Missouri, New York, North Carolina, Oklahoma, Tennessee and Virginia.

In contrast, six of 10 allergy practices in Eastern Texas - the domain of the invasive fire ant - reported no cases of the meat allergy at all.

Weirdness in Minnesota

Oddly, there were an unexpectedly high number of cases in an area of Minnesota where the lone star tick is not thought common. Three separate providers in the northern portion of the state reported at least five cases of the meat allergy, with one reporting more than 40. That, the UVA researchers note, may suggest there are more lone star ticks in the area than thought - or perhaps that another tick or even other parasite is spreading the meat allergy. Other species of ticks are known to cause the allergy outside North America.

"The best evidence is that lone stars are the dominant cause of the alpha-gal meat allergy in North America," said co-first author Jeffrey Wilson, MD, PhD. "That said, we wouldn't be surprised if other ticks, chiggers or even other kinds of parasitic organisms can occasionally contribute to allergic sensitization to alpha-gal."

Fire Ants Marching

After collecting reports of the meat allergy from 44 states the researchers were surprised to see few cases in the Gulf Coast or Texas. This was unexpected because the lone star tick is usually reported on CDC maps in the area. After considering potential explanations, the researchers again surveyed many of the same allergists about allergic reactions caused by the fire ant. They overlaid their results, and the results showed a striking, inverse

relationship: Areas with the most fire ant cases had the lowest presence of the meat allergy.

That suggests that the fire ants are either preying on or somehow competing with the ticks, limiting the spread of the meat allergy, the researchers say. They also identified an increasing number of allergy cases caused by the fire ants. This likely will continue as the fire ants spread north, they report.

The spread should help control the number of meat allergy cases in the Southeast and Mid-Atlantic, they predict. But it also likely will lead to an increase in allergic reactions caused by the fire ant.

"These are two arthropod-related allergic diseases that are connected with each other," Platts-Mills concludes. "The situation is unique because we think we can predict how both will change over time."

Read a patient's experiences with the meat allergy.

Meat Allergy Findings

The researchers have published their findings in the Journal of Allergy and Clinical Immunology. The research team consisted of Wilson, Keshavarz, Maya Retterer, Lisa J. Workman, Alexander J. Schuyler, Emily C. McGowan, Charles Lane, Alaaddin Kandeel, Jane Purser, Eva Ronmark, Joseph LaRussa, Scott P. Commins, Tina Merritt and Platts-Mills. Platts-Mills and Merritt have a patent on a test for the meat allergy, while Wilson has received funding from Thermo Fisher/Phadia. A full list of disclosures is included in the paper.

The research was supported by the National Institutes of Health, grant R37 AI-20565.

https://bit.ly/2Z4ROTy

New DNA Analysis Reveals Ancient Scythian Warrior Was a 13-Year-Old Girl

The warrior women who may have inspired myths really did exist.

Tessa Koumoundouros

In a time of ancient gods, warriors and kings, the tale of a tribe of warrior women was established in Greek mythology. Said to be daughters of the gods, these fierce female fighters from Asia Minor have caught people's imaginations for centuries and still permeate through popular culture today as legendary Amazon warriors.

For a long time these warrior women were assumed to be figments of ancient imaginations, but archaeological evidence has since revealed that the warrior women, who may have inspired these myths, really did exist.

Late last year, an archaeological discovery of two women thought to be nomadic Scythians from around 2,500 years ago (4th century BCE) was revealed. They were buried in what's now the western Russian village of Devitsa, with parts of a horse-riding harness and weapons, including iron knives and 30 arrowheads.

Remains of the young ancient Scythian warrior. **(Vladimir Semyonov)**

"We can certainly say that these two women were horse warriors," said archaeologist Valerii Guliaev of the Russian Academy of Sciences' Institute of Archaeology at the time.

They were found in a burial mound with two other women - one aged between 40-50 years old, who wore a golden headdress with decorative floral ornaments. The other, aged 30-35, was buried alongside two spears and positioned like she was riding a horse.

"During the last decade our expedition has discovered approximately 11 burials of young armed women. Separate barrows were filled for them and all burial rites which were usually made for men were done for them," explained Guliaev.

Now, another team from Russia has mapped the genome of 2,600-year-old Scythian remains that had been discovered in a wooden sarcophagus with an array of weapons back in 1988.

"This child was initially considered to be male because with him were found characteristics [usually attributed to male] archaeological finds: an axe, a bow, arrows," archaeologist Varvara Busova from the Russian Academy of Sciences told ScienceAlert.

But the child's DNA revealed the remains were actually female. "That means we can say with some probability that [Scythian] girls have also participated in hunting or military campaigns," Busova added.

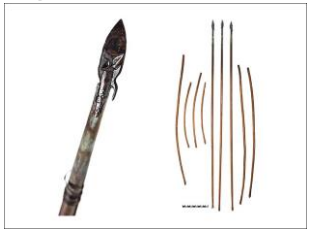
The warrior girl was buried in Siberia's modern-day Tuva republic, with an axe, a birch bow and a quiver with ten arrows - some wood, bone or bronze tipped. Due to the larch coffin sealing tightly against fresh air, her remains were partially mummified.

The Scythian girl's battle axe. **(A. Yu. Makeeva/Kilunovskaya et al., Stratum Plus, 2020)**

"This young 'Amazon' had not yet reached the age of 14 years," said lead author of the new research, archaeologist Marina Kilunovskaya from the Institute for the History of Material Culture, Russian Academy of Sciences.

The girl was clothed in a long fur coat, a shirt, and trousers or a skirt. Using a scanning electron microscope ,the researchers found her coat was composed of a patchwork of skins from a rodent related to Jerboa. And carbon dating of other grave items placed the burial complex from 7th-5th centuries BCE, which is early Scythian times.

Busova said the research team would now like to get more accurate dating of the young warrior girl's remains, investigate the composition of the metal grave objects, and work to restore and conserve what they have found. They're also hoping CT scans of the remains may give them clues on how the young female warrior died.



The young warrior's arrows. **(A. Yu. Makeeva/Kilunovskaya et al., Stratum Plus, 2020)**

The finding "unwittingly brings us back to the myth about the Amazons that have survived to this day thanks to Herodotus (Herod. IV: 110-118)," the team wrote in their paper.

The ancient Greek historian Herodotus claimed Amazons fought the Scythians, but it seems they could actually be the Scythian women who trained, hunted and fought alongside their male counterparts.

"About one-third of all Scythian women are buried with weapons and have war injuries just like the men," historian Adrienne Mayor told *National Geographic* in 2014.

"They lived in small tribes, so it makes sense that everyone in the tribe is a stakeholder. They all have to contribute to defence and to war efforts and hunting."

Through the centuries, myths of the Amazons have been embellished with outrageous claims, from cutting off their own breasts to improve their archery, to murdering their male children.

But we now have the opportunity to learn more about the true female warriors behind the myths thanks to modern archaeological studies and DNA techniques.

https://bit.ly/3dzF4JZ

Far-UVC light safely kills airborne coronaviruses

99.9% of coronaviruses in airborne droplets killed when exposed to a wavelength of ultraviolet light that is safe to use around humans

New York, NY -- More than 99.9% of seasonal coronaviruses present in airborne droplets were killed when exposed to a particular wavelength of ultraviolet light that is safe to use around humans, a new study at Columbia University Irving Medical Center has found. "Based on our results, continuous airborne disinfection with far-UVC light at the current regulatory limit could greatly reduce the level of airborne virus in indoor environments occupied by people," says the study's lead author David Brenner, PhD, Higgins Professor

of Radiation Biophysics at Columbia University Vagelos College of Physicians and Surgeons and director of the Center for Radiological Research at Columbia University Irving Medical Center.

The research was published today in *Scientific Reports*.

Background

Conventional germicidal UVC light (254 nm wavelength) can be used to disinfect unoccupied spaces such as empty hospital rooms or empty subway cars, but direct exposure to these conventional UV lamps is not possible in occupied public spaces, as this could be a health hazard.

To continuously and safely disinfect occupied indoor areas, researchers at Columbia University Irving Medical Center have been investigating far-UVC light (222 nm wavelength). Far-UVC light cannot penetrate the tear layer of the eye or the outer dead-cell layer of skin so it cannot reach or damage living cells in the body.

The researchers had previously shown that far-UVC light can safely kill airborne influenza viruses.

The new paper extends their research to seasonal coronaviruses, which are structurally similar to the SARS-CoV-2 virus that causes COVID-19.

Study details

In the study, the researchers used a misting device to aerosolize two common coronaviruses. The aerosols containing coronavirus were then flowed through the air in front of a far-UVC lamp. After exposure to far-UVC light, the researchers tested to see how many of the viruses were still alive.

The researchers found that more than 99.9% of the exposed virus had been killed by a very low exposure to far-UVC light.

Based on their results, the researchers estimate that continuous exposure to far-UVC light at the current regulatory limit would kill 90% of airborne viruses in about 8 minutes, 95% in about 11 minutes, 99% in about 16 minutes, and 99.9% in about 25 minutes.

Using far-UVC light in occupied indoor spaces

The sensitivity of the coronaviruses to far-UVC light suggests that it may be feasible and safe to use overhead far-UVC lamps in occupied indoor public places to markedly reduce the risk of person-to-person transmission of coronaviruses, as well as other viruses such as influenza.

Ongoing studies in SARS-CoV-2

In a separate ongoing study, the researchers are testing the efficacy of far-UVC light against airborne SARS-CoV-2. Preliminary data suggest that far-UVC light is just as effective at killing SARS-CoV-2.

"Far-UVC light doesn't really discriminate between coronavirus types, so we expected that it would kill SARS-CoV-2 in just the same way," Brenner says. "Since SARS-CoV-2 is largely spread via droplets and aerosols that are coughed and sneezed into the air it's important to have a tool that can safely inactivate the virus while it's in the air, particularly while people are around."

Brenner continues, "Because it's safe to use in occupied spaces like hospitals, buses, planes, trains, train stations, schools, restaurants, offices, theaters, gyms, and anywhere that people gather indoors, far-UVC light could be used in combination with other measures, like wearing face masks and washing hands, to limit the transmission of SARS-CoV-2 and other viruses."

More information

The paper is titled, "Far-UVC light (222-nm) efficiently and safely inactivates airborne coronaviruses."

The other authors (all CUIMC) are Manuela Buonnano, David Welch, and Igor Shuryak.

The study was funded by the Shostack Foundation and the NIH (grant R42-AI125006-03).

The authors declare that the Trustees of Columbia University in the City of New York have a pending patent on the technology: "Apparatus, method and system for selectively affecting and/or killing a virus."

The authors declare no additional financial or other conflicts of interest.

https://wb.md/3eGGeF2

Many People Lack Protective Antibodies After COVID-19 Infection

Attempting to answer the question of just how protective coronavirus antibodies are. At first blush, the news isn't great.

F. Perry Wilson, MD, MSCE

This transcript has been edited for clarity.

Welcome to Impact Factor, your weekly dose of commentary on a new medical study. I'm Dr. F. Perry Wilson.

In what seems like 10 years ago but was actually just 6 weeks ago, on this very website, I said this:

"This is the COVID that allows us to open up more quickly, assuming that antibodies are protective, which — let's be honest — if they aren't, we're sort of screwed no matter what."

Cut to a couple of days ago, when I came across this article in *Nature* — the first deep dive attempting to answer the question of just how protective those coronavirus antibodies are.

And, at first blush at least, the news isn't great.

Researchers recruited patients who had recovered from COVID-19 from the Rockefeller University Hospital in New York. The 111 individuals enrolled had to have been asymptomatic for at least 14 days. They also recruited 46 asymptomatic household contacts and some controls who had never had COVID-19.

Now, a brief refresher on antibodies. There are several different types, but we broadly think about immunoglobulin M as the acute antibody, generated in the throes of the illness, and immunoglobulin G as the long-term antibody. But here's the thing: The mere *presence* of antibodies does not mean that those

They zeroed in on two types of anti-coronavirus antibodies: a group that binds to the spike protein (that's the crown part of the corona), and more specifically, antibodies that bind to the receptor binding domain of the spike protein. This is the key, if you will, that opens the door of your cells (a receptor called ACE2) to infection. It's a good bet that if there is an antibody that will shut down the virus, it's one that will block the receptor binding domain.

Should we start with the good news?

Compared with controls, IgG and IgM levels were higher among those who had recovered from COVID-19. As expected in this convalescent group, a bigger difference was seen in IgG compared with IgM. You can see in this graph that IgM levels seem to go down a bit over time.

And, I'll note, about 20%-30% of people didn't have antibody titers significantly above controls. But broadly, okay — the majority of people made antibodies. But that's not the key thing here. Were these neutralizing antibodies? Do they stop viral replication?

To figure this out, the researchers genetically engineered a SARS-CoV-2 pseudovirus which expressed the spike protein and let it run amok infecting ACE2-expressing cells in culture.

They then added varying dilutions of patient plasma to the petri dishes to determine how much plasma you would need to shut the virus down by 50%, the so-called "neutralizing titer" 50 (NT50).

The results here were not so encouraging.

Thirty-three percent of the individuals tested had an NT50 of less than 50, which implies essentially no immunity to repeat infection; 79% had an NT50 less than 1000 — they may have partial immunity. Only two people tested had an NT50 greater than 5000.

Higher overall antibody titers were associated with neutralizing ability, as might be expected.

Individuals who had been hospitalized for COVID-19 were more likely to have neutralizing antibodies than those who hadn't been hospitalized, suggesting that those with more severe illness are more likely to be immune in the future.

Overall, this is fairly concerning. Without neutralizing antibodies, an end to coronavirus transmission seems unlikely. But let's also

remember the empiric data: We don't yet have any significant numbers of individuals who have been documented to have cleared COVID-19 and then become reinfected. And even without high levels of neutralizing antibodies, a second infection is likely not to be as bad as the first.

There's another nugget of hope in this study. The researchers didn't stop by simply measuring how many people had neutralizing antibodies. They actually sequenced 89 different anti-COVID antibodies to determine which specific antibodies were highly neutralizing. They identified 52 that had neutralizing ability and several that had potent neutralizing ability, targeted to specific amino acids on the receptor binding domain.

And here's the thing: Most of the people in the study *had* those highly neutralizing antibodies; they just weren't the main antibodies they were producing. Why is this good news? Because it suggests a pathway for a successful vaccine. We *can* make these potent neutralizing antibodies; it's just that many of us don't. But a vaccine designed to promote that particular antibody response could be highly successful. All in all, this was a study that suggested that the tunnel we are in now may be a bit longer than we had hoped, but it also shows a light at the end.

F. Perry Wilson, MD, MSCE, is an associate professor of medicine and director of Yale's Program of Applied Translational Research. His science communication work can be found in the Huffington Post, on NPR, and here on Medscape. He tweets @methodsmanmd and hosts a repository of his communication work at www.methodsman.com.

https://bit.ly/2Zi9ICG

Sledge dogs are closely related to 9,500-year-old 'ancient dog'

The sledge dog is both older and has adapted to the Arctic much earlier than thought.

Dogs play an important role in human life all over the world - whether as a family member or as a working animal. But where the dog comes from and how old various groups of dogs are is still a bit of a mystery.

Now, light has been shed on the origin of the sledge dog. In a new study published in *SCIENCE*, researchers from the Faculty of Health and Medical Sciences, University of Copenhagen, show that the sledge dog is both older and has adapted to the Arctic much earlier than thought. The research was conducted in collaboration with the University of Greenland and the Institute of Evolutionary Biology, Barcelona.

'We have extracted DNA from a 9,500-year-old dog from the Siberian island of Zhokhov, which the dog is named after. Based on that DNA we have sequenced the oldest complete dog genome to date, and the results show an extremely early diversification of dogs into types of sledge dogs', says one of the two first authors of the study, PhD student Mikkel Sinding, the Globe Institute.

Until now, it has been the common belief that the 9,500-year-old Siberian dog, Zhokhov, was a kind of ancient dog - one of the earliest domesticated dogs and a version of the common origin of all dogs. But according to the new study, modern sledge dogs such as the Siberian Husky, the Alaskan Malamute and the Greenland sledge dog share the major part of their genome with Zhokhov.

'This means that modern sledge dogs and Zhokhov had the same common origin in Siberia more than 9,500 years ago. Until now, we have thought that sledge dogs were only 2-3,000 years old', says the other first author, Associate Professor Shyam Gopalakrishnan, Globe Institute.

The Original Sledge Dog

To learn more about the origins of the sledge dog, researchers have further sequenced genomes of a 33,000-year-old Siberian wolf and ten modern Greenlandic sledge dogs. They have compared these genomes to genomes of dogs and wolves from around the world.

'We can see that the modern sledge dogs have most of their genomes in common with Zhokhov. So, they are more closely related to this ancient dog than to other dogs and wolves. But not just that - we can see traces of crossbreeding with wolves such as the 33,000-year-old Siberian wolf - but not with modern wolves. It further emphasises that the origin of the modern sledge dog goes back much further than we had thought', says Mikkel Sinding.

The modern sledge dogs have more genetic overlap with other modern dog breeds than Zhokhov has, but the studies do not show us where or when this occurred. Nevertheless, among modern sledge dogs, the Greenland sledge dogs stands out and has the least overlap with other dogs, meaning that the Greenland sledge dog is probably the most original sledge dog in the world.

Common Features with Inuit and Polar Bears

In addition to advancing the common understanding of the origin of sledge dogs, the new study also teaches the researchers more about the differences between sledge dogs and other dogs. Sledge dogs do not have the same genetic adaptations to a sugar and starch rich diet that other dogs have. On the other hand, they have adaptations to high-fat diets, with mechanisms that are similar to those described for polar bears and Arctic people.

'This emphasises that sledge dogs and Arctic people have worked and adapted together for more than 9,500 years. We can also see that they have adaptations that are probably linked to improved oxygen uptake, which makes sense in relation to sledding and give the sledding tradition ancient roots', says Shyam Gopalakrishnan.

https://bit.ly/2NDed5p

Life-emulating molecules show basic metabolism

Findings, bring artificial life one step closer

In a system with self-replicating molecules -previously shown to have the capability to grow, divide and evolve - chemists from the University of Groningen have now discovered catalytic capabilities that result in a basic metabolism. Furthermore, they linked a light-sensitive dye to the molecules, which enabled them to use light energy to power growth. These findings, which bring artificial life one step closer, were published simultaneously in the journals *Nature Chemistry* and *Nature Catalysis* on 26 June.

Ten years ago, Sijbren Otto, Professor of Systems Chemistry at the University of Groningen's Stratingh Institute for Chemistry, discovered a new mechanism for self-replication: small peptide-containing molecules in solution form rings that subsequently form growing stacks. When a stack breaks, both halves start to grow again. Furthermore, the growth of stacks depletes the number of rings in solution and this, in turn, stimulates the formation of new rings from the building blocks. The system could also 'mutate' when different building blocks were added.

Stunning discovery

This system, which arose spontaneously, is a form of artificial proto-life. 'The definition of life is complex but in general, life should have three basic properties,' explains Otto. 'The first is replication, and this happens in our system. The second is metabolism, which should create building blocks from materials in the environment. And the third is compartmentalization, which separates the living organism from its surroundings.' Finally, such organisms should develop a fourth, more advanced property, which is the ability to evolve and invent.

Otto and his team set out to make changes to their molecules in order to add catalytic capabilities. 'However, when we started the project, we made a stunning discovery. Without requiring any changes, the system already showed catalysis; we just hadn't noticed this before.' The stacks grow from rings made up of six building blocks. These rings are formed by combining the building blocks of smaller rings that are made up of three or four building blocks.

Evolution

'It turned out that the stacks of rings catalyse the formation of the smaller rings,' says Otto. Further analysis showed that catalysis of this reaction requires the presence of two specific amino acid residues (two lysine residues). 'Neither the building blocks nor the separate rings have catalytic abilities but the stacks do. So, we assume that in these stacks, a 3D configuration of these lysine residues arises that acts as the catalytic centre, just like proteins shape active sites by placing amino acid residues in highly specific arrangements,' explains Otto. Thus, in the structures that emerge as a result of their ability to self-replicate, amino acids become organized in such a way that they can act as catalysts.

The stacks are also capable of retro-aldol catalysis, a well-known reaction that is often used to benchmark catalyst design efforts. 'Interestingly, our stacks, which were not designed to have catalytic capabilities, were as efficient as the best-designed catalysts we know.' Finding out that the same stacks can catalyse two very different reactions is interesting. Many enzymes have this ability, which gives evolution a chance to develop something new.

Metabolism

In a second study, a photosensitive dye was added. 'Guille Monreal, one of my PhD students, read that such a dye could stimulate the formation of reactive singlet oxygen in amyloid peptides. As reactive oxygen drives important steps in ring formation, he wanted to see if this would speed up the formation of rings.' Two different dyes were found that indeed speed up ring formation when exposed to light, but only when they were bound to the stacks. 'The dyes appeared to act as cofactors for the stacks, just like modern-day proteins use cofactors for their catalysis,' says Otto. When bound to the replicating fibres, the dye can use energy from light to create reactive singlet oxygen and thereby increase the formation of new rings.

Both the spontaneous catalysis by the stacks and the catalysis mediated by the cofactor result in a kind of metabolism that is linked to replication. 'It is not yet the kind of metabolism you see in living organisms,' explains Otto. 'In our system, catalysis merely speeds up reactions that would occur slowly without help. In life, metabolism also drives reactions that would otherwise not occur.'

Artificial life

However, Otto's artificial system shows both replication and a primitive form of metabolism. 'Furthermore, from this point, compartmentalization is a relatively small step.' So, is he close to seeing artificial life evolve in his test tubes? 'Not quite,' admits Otto. 'That would require the system to be capable of open-ended evolution, which means it can evolve capabilities that are not present in the system. And we have as yet no clear idea how to accomplish that. But our system appears to be a sound basis from which we may get there.'

Simple Science Summary

Ten years ago, Sijbren Otto, Professor of Chemistry at the University of Groningen, discovered self-replicating molecules that spontaneously formed rings, which then organized into stacks. These growing stacks were able to divide by breaking in half after which each half continues to grow. This system looks like a primitive form of life. Otto and scientists from his research team now discovered that the stacks act as catalysts, which speed up the formation of new rings from simple building blocks. Furthermore, when a light-sensitive dye is added and binds to the stacks, it will use the energy from light to produce reactive oxygen, which also speeds up the formation of new rings. Both reactions are a simple kind of metabolism. This means that these molecules do not just grow and multiply, they can also stimulate the production of their own building blocks. This brings them one step closer to a man-made system that would qualify as 'artificial life'.

A video on this research project can be seen here: https://youtu.be/gKM1Dda7u_4

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https://nyti.ms/3iafGhr

Decades-Old Soviet Studies Hint at Coronavirus Strategy

A married pair of virologists in Moscow tested a vaccine on their own children in the 1950s. Now, a side effect they found is sparking new hope for a defense against the coronavirus.

By Andrew E. Kramer

MOSCOW — To the boys, it was just a sugary treat. To their parents, prominent medical researchers, what happened in their Moscow apartment that day in 1959 was a vital experiment with countless lives at stake — and their own children as guinea pigs.

"We formed a kind of line," Dr. Peter Chumakov, who was 7 at the time, recalled in an interview. Into each waiting mouth, a parent popped a sugar cube laced with weakened poliovirus — an early vaccine against a dreaded disease. "I was eating it from the hands of my mother."

Today, that same vaccine is gaining renewed attention from researchers — including those brothers, who all grew up to be virologists — as a possible weapon against the new coronavirus, based in part on research done by their mother, Dr. Marina Voroshilova.

Dr. Voroshilova established that the live polio vaccine had an unexpected benefit that, it turns out, could be relevant to the current pandemic: People who got the vaccine did not become sick with other viral illnesses for a month or so afterward. She took to giving the boys polio vaccine each fall, as protection against flu.

Now, some scientists in several countries are taking a keen interest in the idea of repurposing existing vaccines, like the one with live poliovirus and another for tuberculosis, to see if they can provide at least temporary resistance to the coronavirus. Russians are among them, drawing on a long history of vaccine research — and of researchers, unconcerned about being scoffed at as mad scientists, experimenting on themselves.

Children in Blackburn, Britain, receiving doses of the oral polio vaccine in 1965. **Credit...Associated Newspapers, via Shutterstock**

Experts advise that the idea — like many other proposed ways of attacking the pandemic — must be approached with great caution.

"We are much better off with a vaccine that induces specific immunity," Dr. Paul A. Offit, a co-inventor of a vaccine against the rotavirus and professor at the Perelman School of Medicine at the University of Pennsylvania, said in a telephone interview. Any benefits from a repurposed vaccine, he said, are "much shorter lived and incomplete," compared with a tailored vaccine.

Still, Dr. Robert Gallo, a leading advocate of testing the polio vaccine against coronavirus, said that repurposing vaccines is "one of the hottest areas of immunology." Dr. Gallo, director of the Institute of Human Virology at the University of Maryland School of Medicine, said that even if the weakened poliovirus confers immunity for only a month or so, "it gets you over the hump, and it would save a lot of lives."

But there are risks.

Billions of people have taken live poliovirus vaccine, nearly eradicating the disease. However, in extremely rare cases, the weakened virus used in the vaccine can mutate into a more dangerous form, cause polio and infect other people. The risk of paralysis is estimated at one in 2.7 million vaccinations.

For those reasons, public health organizations say that once a region eliminates naturally occurring polio, it must stop routine use of oral vaccine, as the United States did 20 years ago.

And this month, the National Institute of Allergy and Infectious Diseases delayed a study designed by Dr. Gallo's institute, the Cleveland Clinic, the University at Buffalo and Roswell Park Comprehensive Cancer Center to test the effectiveness of live polio vaccine against coronavirus, using health care workers as subjects. The agency raised safety concerns, including the chance of live poliovirus making its way into water supplies and infecting others, according to researchers familiar with the study application. The press office of the N.I.A.I.D. declined to comment.

But other countries are moving ahead. Trials with the polio vaccine have begun in Russia, and are planned in Iran and Guinea-Bissau.

A specific vaccine for the coronavirus would be one that trains the immune system to target that virus specifically, and more than 125 vaccine candidates are under development around the world.

Repurposed vaccines, in contrast, use live but weakened viruses or bacteria to stimulate the innate immune system more broadly to fight pathogens, at least temporarily.

The first polio vaccine, developed by Dr. Jonas Salk, an American, used "inactivated" virus — particles of killed virus. It had to be injected, an obstacle to immunization campaigns in poorer countries.

When that vaccine was widely introduced in 1955, Dr. Albert Sabin was testing a vaccine using live but attenuated poliovirus, which could be taken orally. But in the United States, with the Salk vaccine already in use, the authorities were reluctant to take the perceived risk of conducting live-virus trials.

Dr. Sabin gave his three strains of attenuated virus to a married pair of virologists in the Soviet Union, Dr. Mikhail Chumakov, the founder of a polio research institute that now bears his name, and Dr. Voroshilova. Dr. Chumakov vaccinated himself, but a medicine intended primarily for children needed child test subjects, so he and Dr. Voroshilova gave it to their three sons and several nieces and nephews.

Their experiment enabled Dr. Chumakov to persuade a senior Soviet official, Anastas Mikoyan, to proceed with wider trials, eventually leading to the mass production of an oral polio vaccine used around the world. The United States began oral polio vaccinations in 1961 after it was proved safe in the Soviet Union.

"Somebody has to be the first," Dr. Peter Chumakov said in an interview. "I was never angry. I think it was very good to have such a father, who is confident enough that what he is doing is right and is sure he will not harm his children."

His mother was, if anything, even more enthusiastic about running the tests on the boys, he said.

"She was absolutely sure there was nothing to be scared of," he said.

Something Dr. Voroshilova noticed decades ago has renewed interest in the oral vaccine.

A typical healthy child is host to a dozen or so respiratory viruses that cause little or no illness. But Dr. Voroshilova could not find any of them in children soon after they were immunized against polio.

A huge study in the Soviet Union of 320,000 people, from 1968 to 1975, overseen by Dr. Voroshilova, found reduced mortality from flu in people immunized with other vaccines, including the oral polio vaccine.

She won recognition in the Soviet Union for demonstrating a link between vaccinations and broad protection against viral diseases, likely by stimulating the immune system.

Dr. Voroshilova's and Dr. Chumakov's work clearly influenced their sons' minds as well as their health — not only did all of them become virologists, they embraced self-testing as well.

Dr. Peter Chumakov today is the chief scientist at the Engelhardt Institute of Molecular Biology at the Russian Academy of Sciences and co-founder of a company in Cleveland that treats cancer with viruses. He has developed about 25 viruses for use against tumors — all of which, he said, he has tested on himself.

He is also now taking polio vaccine, which he grows in his own laboratory, as possible protection against coronavirus.

Dr. Ilia Chumakov, a molecular biologist, helped sequence the human genome in France.

Dr. Alexei Chumakov, who was not yet born when his parents experimented on his brothers, worked as a cancer researcher at Cedars-Sinai in Los Angeles for much of his career. While working in Moscow, he developed a vaccine against hepatitis E, which he tested first on himself.

"It's an old tradition," he said. "The engineer should stand under the bridge when the first heavy load goes over."

Dr. Konstantin Chumakov is an associate director of the U.S. Food and Drug Administration's Office of Vaccine Research and Review, which would be involved in approving any coronavirus vaccines for use in Americans. He is also a co-author, with Dr. Gallo and others, of a recent article in the journal Science that promotes research into repurposing existing vaccines.

In an interview, Dr. Konstantin Chumakov said he cannot remember eating the sugar cube back in 1959 — he was 5 years old — but approved of his parents' experiment as a step toward saving untold numbers of children from paralysis.

"It was the right thing to do," he said. "Now, there would be questions, like 'Did you get permission from the ethics committee?'"

Oleg Matsnev contributed reporting from Moscow.

Andrew E. Kramer is a reporter based in the Moscow bureau. He was part of a team that won the 2017 Pulitzer Prize in International Reporting for a series on Russia's covert projection of power. @AndrewKramerNYT

https://nyti.ms/2BkfonB

In Norway, Gymgoers Avoid Infections as Virus Recedes

In an unusual experiment, researchers found no coronavirus infections among thousands of people allowed to return to their gyms.

By Gina Kolata

Like many countries, Norway ordered all gyms to close in March to prevent the spread of the coronavirus. But unlike any other nation, Norway also funded a rigorous study to determine whether the closings were really necessary.

It is apparently the first and only randomized trial to test whether people who work out at gyms with modest restrictions are at greater risk of infection from the coronavirus than those who do not. The tentative answer after two weeks: no.

So this week, responding to the study it funded, Norway reopened all of its gyms, with the same safeguards in place that were used in the study.

Is there hope for gymgoers in other parts of the world?

"I personally think this is generalizable, with one caveat," said Dr. Michael Bretthauer, a cancer screening expert at the University of Oslo who led the study with Dr. Mette Kalager. "There may be places where there is a lot of Covid, or where people are less inclined to follow restrictions."

Norway is bringing its epidemic under control, and the number of new infections has fallen. But the incidence of the infection in Oslo, where the study was conducted, resembles that in such cities as Boston, Oklahoma City and Trenton, N.J.

The trial, begun on May 22, included five gyms in Oslo with 3,764 members, ages 18 to 64, who did not have underlying medical conditions. Half of the members — 1,896 people — were invited to go back to their gyms and work out.

They were required to wash their hands and to maintain social distancing: three feet apart for floor exercises, and six feet apart in high-intensity classes. The subjects could use the lockers, but not the saunas or the showers. They were not asked to wear masks.

Another 1,868 gym members served as a comparison group; they were not permitted to return to their gyms.

During the two weeks of the study, 79.5 percent of the members invited to use their gyms went at least once, while 38.4 percent went more than six times. Some were overjoyed to restart their routines.

Goril Bjerkan, a 53-year-old economist who lives in Baerum, just outside Oslo, went to the gym three to four times a week during the study, using the treadmill, taking classes and doing strength training. "It was fantastic to get back to the gym again after almost 11 weeks of closure," she said. "I suspect it was more risky to visit the shopping center than to visit the gym."

Heide Tjom, a 57-year-old architect who bicycles into Oslo, leapt at the opportunity to return to the gym four times a week, where she works with a personal trainer and takes group cardio classes.

"Keeping fit is very important to me," Ms. Tjom said. "I feel it is important to my existence."

Over the study period, there were 207 new coronavirus cases in Oslo. Study participants and gym staff members were tested for the infection on June 8. (Antibody tests of participants are now being conducted.)

Dr. Bretthauer and Dr. Kalager also examined Norway's extensive electronic health records database for outpatient visits and hospitalizations among the participants.

The results? The researchers found only one coronavirus case, in a person who had not used the gym before he was tested; it was traced to his workplace. Some participants visited hospitals, but for diseases other than Covid-19, the illness caused by the coronavirus. There was no difference in hospital visits between the groups, and there were no outpatient visits or hospitalizations because of the coronavirus. The findings were posted online on Thursday, but had not been peer-reviewed nor published. Some experts felt the results demonstrated that returning to the gym was relatively safe — but only in places where there were few infections.

"This shows us that low-prevalence environments are safe for gyms and probably just about everything else," said Dr. Gordon Guyatt, a professor of medicine at McMaster University in Canada. "It is very unlikely you will get infected." "If you were in a different environment where there is a substantially higher prevalence, we don't know what will happen," he added.

But Jon Zelner, an epidemiologist at the University of Michigan, did not find the study to be fully convincing: "These findings don't tell me that going to the gym isn't riskier than not going to the gym, even in Oslo," he said.

A larger study is needed in places with a relatively low prevalence to determine whether the virus is more easily transmitted in gyms, Dr. Zelner added. Alternatively, a study with fewer people, but in a community with a high prevalence of infection, could answer the question. Such a study may raise ethical concerns, since it may not be safe to send people to gyms in high-prevalence communities — "kind of a Catch-22," Dr. Zelner said.

Still, how low does risk have to be before it is acceptable to reopen gyms and fitness centers? Dr. Guyatt said the risks of infection in a community where the prevalence is low are outweighed by the advantages to society. "You can't stay locked down forever," he said. "We are never going to be completely free of this thing. And in a low-prevalence environment, the risk is low wherever you go — gyms or grocery stores or even restaurants."

Now, Dr. Bretthauer and Dr. Kalager want to see whether the social-distancing measures they used in the study were necessary.

They hope to randomly assign 150 gyms to operate without restrictions or to maintain those in place now, then compare infection rates among gymgoers. The study is only in its planning stages.

https://wb.md/3ieyVpZ

Doomsday Scene: COVID-19, Flu, Measles, & Winter. Here's Our Plan

Here are 10 important areas we need to think about.

Arthur L. Caplan, PhD

Despite flare-ups of COVID-19 in the US and other nations, there is a lot of optimism floating around that we are going to get out of this pandemic with the discovery and distribution of a vaccine by late this year or early 2021. But I highly doubt that a vaccine "magic bullet" will appear that quickly, because of the need for careful, large-scale clinical research; manufacturing and distribution challenges; and uncertainty about the efficacy and durability of a vaccine.

Further, COVID-19 is not the sole challenge we face. Flu and measles are likely to make our lives very miserable by the end of the year as kids miss their shots and people resist getting flu vaccinations. We need more debate about how to get ready for a perfect storm of infectious disease.

I asked my colleagues at NYU Grossman School of Medicine in pediatrics, infectious disease, public health, and bioethics for their ideas about managing a "doomsday" scenario — which I hope never to see but nonetheless think needs to be discussed and debated. Here are 10 important areas we need to think about.

1. Data Monitoring and Surveillance — Get the Numbers

Monitoring of infection rates and data surveillance must be ongoing and transparent. Data should include:

- ***Syndromic sentinel surveillance for the area (number of patients presenting to emergency departments with influenza-like symptoms, which could be COVID-19 or flu)***
- ***Tests on sewage and residual blood from emergency departments***
- ***Number tested for COVID-19 and number positive***
- ***Number tested for flu and number positive***
- ***Number of nursing home outbreaks detected by area (COVID-19 and flu)***
- ***Number of measles cases***

2. Contact Tracing

- ***Local health authorities should establish and implement strategy***
- ***Must be mandatory, with fines for noncompliance***
- ***Not GPS-based, to help protect privacy and gain public support***
- ***Essential it is separate from police/ICE to enable outreach to undocumented citizens and those with legal residency status concerns.***

3. Establishing Policies

Institute policies for housing and protecting the vulnerable, including those who are homeless, cognitively impaired, and technology dependent (including those who resist masks).

Formulate policies for distributing flu shots and any emerging COVID-19 vaccine effectively. Policies to cover the cost of testing, treatment, and counseling must be established, along with financial allotments for lost income, etc.

4. Quarantine and Isolation

Some parts of the country have seen little to no COVID-19 presence, and thus should not be subject to quarantine/social isolation. A national policy, based on public metrics, must be established for exempting those areas.

Areas that see high infection and hospitalization rates need to be prepared to return rapidly to strict quarantine/social isolation practices, according to national metrics.

Some areas may institute quarantine only for high risk, nonessential workers. This would permit low-risk populations, such as children

and young adults, to leave their homes if they are properly protected with masks and flu vaccination; staggered school and recreation hours to minimize crowding would be implemented to further reduce risk. The lower-risk populations must protect older and other at-risk people they live with by isolating, distancing, using masks, and practicing good hygiene.

In addition to stay-at-home orders, winter in many parts of the country means more time indoors, which can increase risk for domestic conflicts. Initiate and publicize broadly an extensive education campaign about resources for those who experience, or are at risk of experiencing, abuse or intimate partner violence.

5. Sharing Information

The National Academies of Medicine should establish a forum of trustworthy, independent science and medical experts to provide daily briefings online about what is currently happening and what is known/not known. The forum should serve as a trusted source for the media. Numbers of infected, hospitalized, and deceased should be published nationally and state-by-state, with accuracy of demographic information certified by the CDC.

Promulgate expert advice about pregnancy and breastfeeding, and how to both protect kids who are too young to wear masks and prevent them from spreading a virus to others. Distribute clear, expert advice about what to do if you're at home or work and feel ill.

6. Planning Ahead for States and Hospitals/Hospital Systems

States must prepare a large stockpile of high-quality PPE, as well as therapies including ventilators, dialysis equipment, etc. This should be predeposited regionally to permit rapid deployment based on urgency and need, without regard to state boundaries, cost, or unexplained federal seizure.

States must create nursing home/long-term care/home care strategies that plan for patient transfers; PPE for staff; resident prophylaxis; special isolation; equipment for televised visits and protective gear for permitting in-person family visits; and rapid, frequent seropositive testing. Policies must be established for discharging to homes patients with COVID-19, flu, measles, and other conditions.

States must establish and publicize criteria for school closures, including daycare/afterschool programs.

Establish nationwide consensus on how to fill out death certificates to accurately reflect COVID-19 deaths, including "probable" cases.

Hospitals must create clear, transparent plans in place for what to do if a case of infectious disease is detected in staff or residents.

Formulate clear policies about non-COVID-19 health services. Which will continue, and where? Consider establishing flu- and COVID-19-only medical units/facilities.

Encourage crash-funding of research to determine which techniques are most effective at getting people to follow guidelines (wearing masks, distancing) and get vaccinations.

Maximize the use of telemedicine as well as other virtual interaction (online banking, online shopping, etc).

7. Daily Life

Masks must be worn in public and in close proximity to others; protective shields should be used at workplaces, in buildings, etc.

Ensure that water in public housing, on reservations, in public toilets, and in shelters is in good repair and widely available so that people can frequently wash their hands and maintain other recommended hygiene.

Grocery stores and pharmacies should continue to reserve/implement special hours for seniors and those with health-related reasons to minimize social contact.

Program or physically monitor elevators to control the number of people who can enter.

HEPA air filtration systems should be installed in buildings, schools, daycare centers, etc. Negative-pressure systems should be

also be considered, especially for public gathering places such as community centers and libraries.

8. Schools

Formulate daycare/afterschool policies to allow both their operation and to protect older/vulnerable teachers and support personnel, as well as older relatives of children. Colleges and universities should be transparent about plans to maintain student safety when they open, and promulgate criteria for closures.

9. Public Transportation

Continue/implement efforts to clean and maintain public transportation. Provide hazardous duty pay for drivers, cleaners, other frontline essential employees. Set maximum occupancy and require physical distancing.

10. Travel

No cruises or train excursions, and close smoking stations in airports. The CDC should issue and publicize guidance on "safe" vacationing and other nonessential travel.

COVID-19 in combination with flu and measles would incapacitate our healthcare system and break our economy. Perhaps that will not happen. We ought to be planning as if it will.

Dr Caplan co-directs an advisory group on sports and recreation for the US Conference of Mayors. He helped develop an ethical framework for distributing drugs and vaccines for J&J and is a member of the WHO advisory committee on COVID-19, ethics, and experimental drugs/vaccines. All of the above are unpaid.

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https://wb.md/3igOEVU

Higher Rate of Alzheimer's in Women Explained?

Loss of estrogen related to menopause may explain why women are much more likely than men to develop Alzheimer disease (AD), new research suggests.

Pauline Anderson

In a study of more than 120 participants, menopausal status was the main factor contributing to higher beta amyloid (Aβ) levels, lower glucose metabolism, and lower gray matter volume (GMV) and white matter volume (WMV) in women.

"Our findings suggest that hormonal factors may predict who will have changes in the brain," study author Lisa Mosconi, PhD, associate professor of neuroscience in neurology, director of the Women's Brain Initiative, and associate director of the Alzheimer's Prevention Clinic, Weill Cornell Medicine, New York City, said in a press release.

"The results show changes in brain imaging features, or biomarkers in the brain, suggesting menopausal status may be the best predictor of Alzheimer's-related brain changes in women," Mosconi added.

Hormone therapy, hysterectomy status, and thyroid disease were other factors linked to sex differences in brain biomarkers.

The findings were published online June 24 in *Neurology*.

Emerging Evidence

After advanced age, female sex is the major risk factor for late-onset AD, the most common form of dementia. Women compose about two thirds of AD dementia patients; postmenopausal women account for more than 60% of affected individuals.

Previously, the higher proportion of women affected by AD was attributed to their longer life expectancy relative to men, but several emerging lines of evidence point to sex- and gender-specific AD risk factors.

Such factors that might more severely affect women include genetic risks, such as family history and *APOE* genotype; medical conditions, such as depression, stroke, and diabetes mellitus; hormone-related risks, such as menopause and thyroid disease; and factors related to lifestyle, such as smoking, diet, exercise, and intellectual activity.

The new study included 121 cognitively normal middle-aged participants aged 40 to 65 years (70% women) who had more than 12 years of education.

All participants received neuropsychological evaluations of memory function, attention, and language. They provided information on family history of late-onset AD and on personal lifestyle factors, such as smoking, diet, exercise, and intellectual activity.

Researchers examined several measures related to vascular risks, including abdominal obesity, hypertension, hyperlipidemia, insulin resistance, and type 2 diabetes status. They also collected information on thyroid function and depression.

In female patients, the investigators determined menopausal status (premenopausal, perimenopausal, and postmenopausal) through information on symptoms, such as hot flashes, mood swings, insomnia, appetite changes, loss of libido, and cognitive problems.

A number of well-established AD biomarkers were also examined, including Aβ on C-Pittsburgh compound B (PiB) positron-emission tomography (PET), neurodegeneration via glucose metabolism on 18F-fluorodeoxyglucose (FDG) PET, and GMV and WMV on MRI.

"Sensitive" Biomarkers

Men and women were comparable with regard to clinical and cognitive measures. That there were no differences in cognitive performance between the two groups "is not surprising," inasmuch as the effects of estrogen loss on cognition have been difficult to pinpoint with neuropsychological testing, the investigators note.

"It is well documented that across the adult lifespan, women perform better than men across several cognitive domains, especially verbal memory, and that this advantage may persist even into early AD," they add.

After adjusting for relevant confounders, PiB Aβ deposition was about 30% greater in the female group than in the male group, and FDG glucose metabolism was about 22% lower.

GMV was also about 11% lower in women than men (0.73 cm^3 vs 0.8 cm^3). About the same difference was seen in WMV (0.74 cm^3 vs had 0.82 cm^3). The differences were found in several brain regions. *P* values were < .001 for age-matched women in comparison with men with regard to GMV and WMV, as well as PiB uptake and FDG uptake.

The new findings support the hypothesis that "brain biomarkers are more sensitive than cognitive tests for the detection of AD risk in asymptomatic individuals," the investigators note.

After female sex, menopausal status was the predictor most consistently and strongly associated with brain biomarker differences between women and men.

The authors note that menopause is accompanied by neurologic symptoms, such as disturbed sleep, depression, and changes in multiple cognitive domains, especially memory. Many of these symptoms are known AD risk factors.

Estrogen Network

Although all sex hormones are likely involved, the findings support the view that a decrease in estrogen level is involved in the AD biomarker abnormalities in women, the researchers write.

"The pattern of gray matter loss in particular shows anatomic overlap with the brain estrogen network, which includes estrogen receptors widely found in, among other regions, the prefrontal cortex, hippocampus, amygdala, and posterior cingulate cortex," they add.

The findings suggest that middle-aged women may be more at risk for AD, "perhaps because of lower levels of the hormone estrogen during and after menopause," said Mosconi.

After menopausal status, hormone therapy and hysterectomy status were the factors most strongly linked to brain biomarker differences between women and men.

Results showed higher FDG uptake and generally more favorable biomarker outcomes in participants who had received hormone replacement therapy compared with those who had not. Similar trends were noted in women who had undergone hysterectomy in comparison with those who hadn't.

AD biomarkers were also influenced by thyroid disease, a hormone-related risk factor for AD that is more prevalent in women. Thyroid disease predicted reduced MRI volume in women compared with men.

The authors note that there are known links between thyroid disease and an increased risk for cognitive impairment.

They add that a potential limitation of the study is that it included only healthy, middle-aged participants who did not have severe brain or cardiovascular disease. The authors emphasize that these new data preclude assessment of causality. Larger studies that follow participants over time are needed, said Mosconi.

Drilling Down

Commenting on the study for *Medscape Medical News*, Thomas Vidic, MD, who manages AD patients at his clinic in Elkhart, Indiana, and is a fellow of the American Academy of Neurology, said the investigators "drilled down" and looked closely at sex differences in brain biomarkers.

"We have seen for years that more women than men have Alzheimer's disease, and we have sort of tap danced around that," said Vidic, who was not involved with the research.

"Instead of talking about it and being anecdotal, we now have some serious biomarkers that indicate this is a phenomenon we need to understand," he said. It's "too simplistic" to say that women should take hormone replacements to reduce dementia risk, Vidic added.

At one time, such therapy was "relatively common," but it has lost some appeal because of potential side effects, including heart-related effects, he said.

Researchers now need "to drill down even further" to determine the exact mechanism, which "is probably a lot more complicated than we ever imagined," Vidic said. "We need to invest resources into figuring out this phenomenon."

To understand the hormonal environment that influences AD and to identify the mechanism by which this occurs would be "an important step in developing new treatments," he added.

The study was supported by the National Institutes of Health, the National Institute on Aging, the Cure Alzheimer's Fund, and the Women's Alzheimer's Movement. The investigators and Vidic report no relevant financial relationships.

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https://bit.ly/3dI4eWQ

CRISPR Gene Editing Prompts Chaos in DNA of Human Embryos

Three studies identify unintended consequences of gene editing in human embryos, including large deletions and reshuffling of DNA.

Amanda Heidt

The ability of CRISPR gene-editing technology to safely modify human embryos has been cast into doubt after several recent papers described massive disruptions to DNA in embryos subjected to editing.

Each of the three papers, published this month without peer review on the preprint server *bioRxiv*, intended to edit only a single gene. But results showed large-scale, unintended DNA deletions and rearrangements in the areas surrounding the targeted sequence. While past research has shown that gene editing can lead to mutations far away from the targeted region, these studies instead draw attention to more localized damage involving larger sequences

of DNA that could be overlooked by traditional safety screenings, *Nature* reports.

These studies were intended only for research purposes, meaning the embryos were destroyed after the experiment ended. But in response to their findings, many researchers are voicing their objections to further editing. The field itself is still grappling with the fallout from the birth of twin girls as a result of highly controversial CRISPR experiments carried out by He Jiankui at the Southern University of Science and Technology in China in 2018.

"There's no sugarcoating this," Fyodor Urnov, a geneticist and CRISPR researcher at the University of California, Berkeley, who was not involved with the research, tells *OneZero*. "This is a restraining order for all genome editors to stay the living daylights away from embryo editing."

In the first study, published June 5, researchers at the Francis Crick Institute used CRISPR to remove the *POU5F1* gene—an important contributor to embryonic development and stem cell pluripotency—in 18 embryos. When they analyzed the effect of the deletion on the genome, they unexpectedly found that eight of these embryos contained additional abnormalities, four of which involved substantial DNA rearrangements and deletions of several thousand base pairs.

A second group from Columbia University attempted to modify embryos with a blindness-causing mutation in the *EYS* gene, the most common gene implicated in the onset of a degenerative eye condition called retinitis pigmentosa. But in addition to the expected changes, they reported on June 18 that almost half of the 23 embryos also lost large chunks of the chromosome on which *EYS* is located. In the most extreme cases, the chromosome disappeared entirely.

Lastly, a study published June 20 by researchers at Oregon Health & Science University similarly focused on correcting a mutation in the *MYBPC3* gene that is known to cause a heart condition. While they were successful in repairing the damage in close to half of the 86 embryos—a complement to their pioneering work in 2017—the authors also reported large disruptions in the chromosome containing the gene.

Taken together, these three studies highlight the contrast between off-target effects, which happen when the CRISPR tools edit someplace unintended, and on-target edits, in which the changes are properly localized but have some unintended consequence. In each case, the on-target effects were unexpected.

"What that means is that you're not just changing the gene you want to change, but you're affecting so much of the DNA around the gene you're trying to edit that you could be inadvertently affecting other genes and causing problems," Kiran Musunuru, a cardiologist at the University of Pennsylvania who was not involved in any of the studies, tells *OneZero*.

These problems also show just how little is known about the ways in which the body naturally repairs molecular cuts to the genome made by CRISPR technology, *Nature* reports. Rather than neatly heal the newly cleaved ends of DNA subjected to editing, the mechanism can sometimes be faulty, leading to degraded or broken DNA.

Speaking to *Nature*, Urnov says these on-target effects warrant the attention of researchers moving forward. "This is something that all of us in the scientific community will, starting immediately, take more seriously than we already have. This is not a one-time fluke."

https://bit.ly/3icaxFI

A Nobel Winner Explains Why The Way You Breathe Is So Important During The Pandemic

Inhale through your nose and exhale through your mouth.

Louis Ignarro

It's not just something you do in yoga class – breathing this way actually provides a powerful medical benefit that can help the body fight viral infections.

The reason is that your nasal cavities produce the molecule nitric oxide, which chemists abbreviate NO, that increases blood flow through the lungs and boosts oxygen levels in the blood.

Breathing in through the nose delivers NO directly into the lungs, where it helps fight coronavirus infection by blocking the replication of the coronavirus in the lungs.

But many people who exercise or engage in yoga also receive the benefits of inhaling through the nose instead of the mouth. The higher oxygen saturation of the blood can make one feel more refreshed and provides greater endurance. I am one of three pharmacologists who won the Nobel Prize in 1998 for discovering how nitric oxide is produced in the body and how it works.

The role of nitric oxide in the body

Nitric oxide is a widespread signaling molecule that triggers many different physiological effects. It is also used clinically as a gas to selectively dilate the pulmonary arteries in newborns with pulmonary hypertension. Unlike most signaling molecules, NO is a gas in its natural state.

NO is produced continuously by the 1 trillion cells that form the inner lining, or endothelium, of the 100,000 miles of arteries and veins in our bodies, especially the lungs. Endothelium-derived NO acts to relax the smooth muscle of the arteries to prevent high blood pressure and to promote blood flow to all organs. Another vital role of NO is to prevent blood clots in normal arteries.

In addition to relaxing vascular smooth muscle, NO also relaxes smooth muscle in the airways – trachea and bronchioles – making it easier to breathe. Another type of NO-mediated smooth muscle relaxation occurs in the erectile tissue (corpus cavernosum), which results in penile erection. In fact, NO is the principal mediator of penile erection and sexual arousal.

This discovery led to the development and marketing of sildenafil, trade name Viagra, which works by enhancing the action of NO.

Other types of cells in the body, including circulating white blood cells and tissue macrophages, produce nitric oxide for antimicrobial purposes.

The NO in these cells reacts with other molecules, also produced by the same cells, to form antimicrobial agents to destroy invading microorganisms including bacteria, parasites and viruses. As you can see, NO is quite an amazing molecule.

Nitric oxide gas as an inhaled therapy

Since NO is a gas, it can be administered with the aid of specialized devices as a therapy to patients by inhalation. Inhaled NO is used to treat infants born with persistent pulmonary hypertension, a condition in which constricted pulmonary arteries limit blood flow and oxygen harvesting.

Inhaled NO dilates the constricted pulmonary arteries and increases blood flow in the lungs. As a result, the red blood cell hemoglobin can extract more lifesaving oxygen and move it into the general circulation.

Inhaled NO has literally turned blue babies pink and allowed them to be cured and to go home with mom and dad. Before the advent of inhaled NO, most of these babies died.

Inhaled NO is currently in clinical trials for the treatment of patients with COVID-19. Researchers are hoping that three principal actions of NO may help fight covid: dilating the pulmonary arteries and increasing blood flow through the lungs, dilating the airways and increasing oxygen delivery to the lungs and blood, and directly killing and inhibiting the growth and spread of the coronavirus in the lungs.

How nitric oxide kills viruses

In an in vitro study done in 2004 during the last SARS outbreak, experimental compounds that release NO increased the survival rate of nucleus-containing mammalian cells infected with SARS-CoV.

This suggested that NO had a direct antiviral effect. In this study, NO significantly inhibited the replication cycle of SARS-CoV by blocking production of viral proteins and its genetic material, RNA.

In a small clinical study in 2004, inhaled NO was effective against SARS-CoV in severely ill patients with pneumonia.

The SARS CoV, which caused the 2003/2004 outbreak, shares most of its genome with SARS CoV-2, the virus responsible for COVID-19. This suggests that inhaled NO therapy may be effective for treating patients with COVID-19.

Indeed, several clinical trials of inhaled NO in patients with moderate to severe COVID-19, who require ventilators, are currently ongoing in several institutions. The hope is that inhaled NO will prove to be an effective therapy and lessen the need for ventilators and beds in the ICU.

The sinuses in the nasal cavity, but not the mouth, continuously produce NO. The NO produced in the nasal cavity is chemically identical to the NO that is used clinically by inhalation.

So by inhaling through the nose, you are delivering NO directly into your lungs, where it increases both airflow and blood flow and keeps microorganisms and virus particles in check.

While anxiously awaiting the results of the clinical trials with inhaled NO, and the development of an effective vaccine against COVID-19, we should be on guard and practice breathing properly to maximize the inhalation of nitric oxide into our lungs. Remember to inhale through your nose; exhale through your mouth.

Louis J. Ignarro, Distinguished Professor Emeritus of Molecular & Medical Pharmacology, School of Medicine, University of California, Los Angeles.

https://bit.ly/2YFeJWC

Declining eyesight improved by looking at deep red light

Staring at a deep red light for three minutes a day can significantly improve declining eyesight, finds a new UCL-led study, the first of its kind in humans.

Scientists believe the discovery, published in the *Journals of Gerontology*, could signal the dawn of new affordable home-based eye therapies, helping the millions of people globally with naturally declining vision.

This is an example of hand held LED torch used in study. **Credit: UCL**

In the UK there are currently around 12 million people aged over 65: in 50 years this will increase to around 20 million and all will have some degree of visual decline because of retinal ageing.

Lead author, Professor Glen Jeffery (UCL Institute of Ophthalmology) said: "As you age your visual system declines significantly, particularly once over 40.

"Your retinal sensitivity and your colour vision are both gradually undermined, and with an ageing population, this is an increasingly important issue.

"To try to stem or reverse this decline, we sought to reboot the retina's ageing cells with short bursts of longwave light."

In humans around 40 years-old, cells in the eye's retina begin to age, and the pace of this ageing is caused, in part, when the cell's mitochondria, whose role is to produce energy (known as ATP) and boost cell function, also start to decline.

Mitochondrial density is greatest in the retina's photoreceptor cells, which have high energy demands. As a result, the retina ages faster than other organs, with a 70% ATP reduction over life, causing a significant decline in photoreceptor function as they lack the energy to perform their normal role.

Researchers built on their previous findings in mice, bumblebees and fruit flies, which all found significant improvements in the function of the retina's photoreceptors when their eyes were exposed to 670 nanometre (long wavelength) deep red light.

"Mitochondria have specific light absorbance characteristics influencing their performance: longer wavelengths spanning 650 to 1000nm are absorbed and improve mitochondrial performance to increase energy production," said Professor Jeffery.

The retina's photoreceptor population is formed of cones, which mediate colour vision and rods, which provide peripheral vision and adapt vision in low/dim light.

For the study, 24 people (12 male, 12 female), aged between 28 and 72, who had no ocular disease, were recruited. All participants' eyes were tested for the sensitivity of their rods and cones at the start of the study. Rod sensitivity was measured in dark adapted eyes (with pupils dilated) by asking participants to detect dim light signals in the dark, and cone function was tested by subjects identifying coloured letters that had very low contrast and appeared increasingly blurred, a process called colour contrast.

All participants were then given a small LED torch to take home and were asked to look into* its deep red 670nm light beam for three minutes a day for two weeks. They were then re-tested for their rod and cone sensitivity

Results

Researchers found the 670nm light had no impact in younger individuals, but in those around 40 years and over, significant improvements were obtained.

Cone colour contrast sensitivity (the ability to detect colours) improved by up to 20% in some people aged around 40 and over. Improvements were more significant in the blue part of the colour spectrum that is more vulnerable in ageing.

Rod sensitivity (the ability to see in low light) also improved significantly in those aged around 40 and over, though less than colour contrast.

Professor Jeffery said: "Our study shows that it is possible to significantly improve vision that has declined in aged individuals using simple brief exposures to light wavelengths that recharge the energy system that has declined in the retina cells, rather like re-charging a battery.

"The technology is simple and very safe, using a deep red light of a specific wavelength, that is absorbed by mitochondria in the retina that supply energy for cellular function.

"Our devices cost about £12 to make, so the technology is highly accessible to members of the public."

This research was funded by the Biotechnology and Biological Sciences Research Council.