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Scant Risk for SARS-CoV-2 From Hospital Air

Viable viruses typically are found only close to patients

Laird Harrison

Everywhere they look within hospitals, researchers find RNA from SARS-CoV-2 in the air. But viable viruses typically are found only close to patients, according to a review of published studies.

The finding supports recommendations to use surgical masks in most parts of the hospital, reserving respirators (such as N95 or FFP2) for aerosol-generating procedures on patients' respiratory tracts, said Gabriel Birgand, PhD, an infectious disease researcher at Imperial College London, United Kingdom.

"When the virus is spreading a lot in the community, it's probably more likely for you to be contaminated in your friends' areas or in your building than in your work area, where you are well equipped and compliant with all the measures," he told *Medscape Medical News*. "So it's pretty good news." The systematic review by Birgand and colleagues was published in *JAMA Network Open*.

Recommended precautions to protect healthcare workers from SARS-CoV-2 infections remain controversial. Most authorities believe droplets are the primary route of transmission, which would mean surgical masks may be sufficient protection. But some research has suggested transmission by aerosols as well, making N95 respirators seem necessary. There is even disagreement about the definitions of the words "aerosol" and "droplet."

To better understand where traces of the virus can be found in the air in hospitals, Birgand and his colleagues analyzed all the studies they could find on the subject in English.

They identified 24 articles with original data. All of the studies used reverse transcription–polymerase chain reaction (PCR) tests to identify SARS-CoV-2 RNA. In five studies, attempts were also made to culture viable viruses. Three studies assessed the particle size relative to RNA concentration or viral titer. Of 893 air samples across the 24 studies, 52.7% were taken from areas close to patients; 26.5% were taken in clinical areas; 13.7%, in staff areas; 4.7%, in public areas; and 2.4%, in toilets or bathrooms.

Table. Air Sampled for SARS-CoV-2 RNA

Location	Air samples, n	Positive (%)
ICU rooms	107	25.2
Non-ICU patient rooms	64	10.7
Toilets/bathrooms	21	23.8
Clinical areas	237	8.4
Staff areas	122	12.3
Hallways	16	56.3
Outdoor public areas	8	37.5

Among those studies that quantified RNA, the median interquartile range of concentrations varied from 1.0 x 10^3 copies/m^3 in clinical areas to 9.7 x 10^3 copies/m^3 in toilets or bathrooms. One study found an RNA concentration of 2.0 × 10^3 copies for particle sizes >4 μm and 1.3 × 10^3 copies/m^3 for particle sizes ≤4 μm, both in patients' rooms.

Three studies included viral cultures; of those, two resulted in positive cultures, both in a non-ICU setting. In one study, 3 of 39 samples were positive, and in the other, 4 of 4 were positive. Viral cultures in toilets, clinical areas, staff areas, and public areas were negative.

One of these studies assessed viral concentration and found that the median interquartile range was 4.8 tissue culture infectious dose (TCID50)/m^3 for particles <1 μm, 4.27 TCID50/m^3 for particles 1 – 4 μm, and 1.82 TCID50/m^3 for particles >4 μm.

Although viable viruses weren't found in staff areas, the presence of viral RNA in places such as dining rooms and meeting rooms raises a concern, Birgand said. "All of these staff areas are probably playing an important role in contamination," he said. "It's pretty easy to see when you are dining, you are not wearing a face mask, and it's associated with a strong risk when there is a strong dissemination of the virus in the community."

Studies on contact tracing among healthcare workers have also identified meeting rooms and dining rooms as the second most common source of infection after community contact, he said.

In general, the findings of the review correspond to epidemiologic studies, said Angela Rasmussen, PhD, a virologist with the Georgetown University Center for Global Health Science and Security, Washington, DC, who was not involved in the review. "Absent aerosol-generating procedures, healthcare workers are largely not getting infected when they take droplet precautions," she said.

One reason may be that patients shed the most infectious viruses a couple of days before and after symptoms begin. By the time they're hospitalized, they're less likely to be contagious but may continue to shed viral RNA. "We don't really know the basis for the persistence of RNA being produced long after people have been infected and have recovered from the acute infection," she said, "but it has been observed quite frequently."

Although the virus cannot remain viable for very long in the air, remnants may still be detected in the form of RNA, Rasmussen said. In addition, hospitals often do a good job of ventilation.

She pointed out that it can be difficult to cultivate viruses in air samples because of contaminants such as bacteria and fungi. "That's one of the limitations of a study like this. You're not really sure if it's because there's no viable virus there or because you just aren't able to collect samples that would allow you to determine that."

Birgand and colleagues acknowledged other limitations to their. The studies they reviewed used different approaches to sampling. Different procedures may have been underway in the rooms being sampled, and factors such as temperature and humidity could have affected the results. In addition, the studies used different cycle thresholds for PCR positivity, they write.

JAMA Netw Open. Published online December 23, 2020. Full text

http://bit.ly/3aXfIYK

$3.9M project on self-deleting genes takes aim at mosquito-borne diseases

Texas A&M AgriLife researchers' work to aid mosquito control efforts

To control mosquito populations and prevent them from transmitting diseases such as malaria, many researchers are pursuing strategies in mosquito genetic engineering. A new Texas A&M AgriLife Research project aims to enable temporary "test runs" of proposed genetic changes in mosquitoes, after which the changes remove themselves from the mosquitoes' genetic code.

The project's first results were published on Dec. 28 in *Philosophical Transactions of the Royal Society B,* titled "Making gene drive biodegradable."

Zach Adelman, Ph.D, and Kevin Myles, Ph.D., both professors in the Texas A&M College of Agriculture and Life Sciences Department of Entomology are the principal investigators. Over five years, the team will receive $3.9 million in funding from the National Institute of Allergy and Infectious Diseases to test and fine-tune the self-deleting gene technology.

"People are wary of transgenes spreading in the environment in an uncontrolled manner. We feel that ours is a strategy to potentially prevent that from happening," Adelman said. "The idea is, can we program a transgene to remove itself? Then, the gene won't persist in the environment.

"What it really comes down to is, how do you test a gene drive in a real-world scenario?" he added. "What if a problem emerges? We think ours is one possible way to be able to do risk assessment and field testing."

A crucial target for mosquito control

Many genetic engineering proposals revolve around inserting into mosquitoes a select set of new genes along with a "gene drive." A

gene drive is a genetic component that forces the new genes to spread in the population.

"A number of high-profile publications have talked about using a gene drive to control mosquitoes, either to change them so they can't transmit malaria parasites anymore, or to kill off all the females so the population dies out," Adelman said.

An often-voiced worry is that such genetic changes could carry unintended or harmful consequences.

One plan makes the cut

In the project's first publication, the colleagues describe three ways for an introduced genetic change to remove itself after a designated period of time. The time period could, for instance, be 20 generations of mosquitoes, or about a year. The team modeled how the genes would spread among mosquitoes based on generation times and parameters of an average mosquito's life. Of the three methods, the team has chosen one to pursue further.

This method takes advantage of a process all animals use to repair damaged DNA, Adelman said. Inside cell nuclei, repair enzymes search for repeated genetic sequences around broken DNA strands. The repair enzymes then delete what's between the repeats, he said.

So, Adelman and Myles' team plans to test in fruit flies and mosquitoes a gene drive, a DNA-cutting enzyme and a small repeat of the insect's own DNA.

Once the introduced enzyme cuts the DNA, the insect's own repair tools should jump into action. The repair tools will cut out the genes for the gene drive and the other added sequences. At least, that's what should happen in theory.

Failure is not just an option, it's part of the plan

The team has already started lab work to test different gene drives and determine how long they last in flies and mosquitoes. The goal is to see a gene drive spread rapidly through a lab insect population. After a few generations, the added genes should disappear and the population should again consist of wild-type individuals.

"We assigned various rates of failure for how often the mechanism does not work as expected," Adelman said. "The models predict that even with a very high rate of failure, if it succeeds just 5% of the time, that's still enough to get rid of the transgene."

http://wb.md/2WXDpYW

The Autopsy, a Fading Practice, Revealed Secrets of COVID-19

The COVID-19 pandemic has helped revive the autopsy.

Marion Renault, Associated Press

New York (AP) - When the virus first arrived in U.S. hospitals, doctors could only guess what was causing its strange constellation of symptoms: What could explain why patients were losing their sense of smell and taste, developing skin rashes, struggling to breathe and reporting memory loss on top of flu-like coughs and aches?

At hospital morgues, which have been steadily losing prominence and funding over several decades, pathologists were busily dissecting the disease's first victims — and finding some answers.

"We were getting emails from clinicians, kind of desperate, asking, 'What are you seeing?'" said NYU Langone's Dr. Amy Rapkiewicz. 'Autopsy,' she pointed out, means to see for yourself. "That's exactly what we had to do."

Early autopsies of deceased patients confirmed the coronavirus does not just cause respiratory disease, but can also attack other vital organs. They also led doctors to try blood thinners in some COVID-19 patients and reconsider how long others should be on ventilators.

"You can't treat what you don't know about," said Dr. Alex Williamson, a pathologist at Northwell Health in New York. "Many lives have been saved by looking closely at someone's death."

Autopsies have informed medicine for centuries — most recently helping to reveal the extent of the opioid epidemic, improve cancer care and demystify AIDS and anthrax. Hospitals were once judged by how many autopsies they performed.

But they've lost stature over the years as the medical world instead turned to lab tests and imaging scans. In 1950, the practice was conducted on about half of deceased hospital patients. Today, those rates have shrunk to somewhere between 5% and 11%.

"It's really kind of a lost tool," said Louisiana State University pathologist Dr. Richard Vander Heide.

Some hospitals found it even harder this year. Safety concerns about transmission forced many hospital administrators to stop or seriously curb autopsies in 2020. The pandemic also led to a general dip in the total number patients at many hospitals, which drove down autopsy rates in some places. Large hospitals around the country have reported conducting fewer autopsies in 2020.

"Overall, our numbers are down, pretty significantly," from 270 autopsies in recent years to about 200 so far this year, said Dr. Allecia Wilson, director of autopsies and forensic services at Michigan Medicine in Ann Arbor.

At the University of Washington in Seattle, pathologist Dr. Desiree Marshall couldn't conduct COVID-19 autopsies in her usual suite because, as one of the hospital's oldest facilities, it lacks the proper ventilation to safely conduct the procedure. Marshall ended up borrowing the county medical examiner offices for a few cases early on, and has been working out of the school's animal research facilities since April.

Other hospitals went the opposite way, performing far more autopsies even under difficult circumstances to try to better understand the pandemic and keep up with a surge of deaths that has resulted in at least 400,000 more U.S. deaths than normal.

At New Orleans University Medical Center, where Vander Heide works, pathologists have performed about 50% more autopsies than they have in recent years. Other hospitals in Alabama, California, Tennessee, New York and Virginia say they'll also surpass their usual annual tally for the procedure.

Their results have shaped our understanding of what COVID-19 does to the body and how we might combat it.

In spring and early summer, for example, some seriously sick coronavirus patients were on ventilators for weeks at a time. Later, pathologists discovered such extended ventilation could cause extensive lung injury, leading doctors to rethink how they use ventilators during the pandemic.

Doctors are now exploring whether blood thinners can prevent microscopic blood clots that had been discovered in patients early in the pandemic.

Autopsy studies also indicated the virus may travel through the blood stream or hitch a ride on infected cells, spreading to and impacting a person's blood vessels, heart, brain, liver, kidneys and colon. This finding helped explain the virus's wide range of symptoms.

More findings are sure to come: Pathologists have stocked freezers with coronavirus-infected organs and tissues collected during autopsies, which will help researchers study the disease as well as possible cures and treatments. Future autopsies will also help them understand the disease's toll on long haulers, those who suffer symptoms for weeks or months after infection.

Despite these life-saving discoveries being made during the pandemic, financial realities and a dwindling workforce mean it's unlikely that the ancient medical practice will fully rebound when the outbreak wanes.

Hospitals are not required to provide autopsy services, and in those that do perform them, the procedure's costs are not directly covered by most private insurance or by Medicare.

"When you consider there's no reimbursement for this, it's almost an altruistic practice," said Rutgers University pathologist Dr. Billie Fyfe-Kirschner. "It's vitally important but we don't have to fund it."

Added into the mix: The number of experts who can actually perform autopsies is critically low. Estimates suggest the U.S. has only a few hundred forensic pathologists but could use several thousand — and less than one in 100 graduating medical school students enters the profession each year.

Some in the field hope the 2020 pandemic could boost recruitment to the field — just like the "CSI boom" of the early 2000s, Northwell's Williamson said.

Michigan Medicine's Wilson is more skeptical, but even still she can't imagine her work becoming totally obsolete. Learning from the dead to treat the living — it's a pillar of medicine, she said.

It helped doctors understand the mysteries of 1918's influenza pandemic, just at is now helping them understand the mysteries of COVID-19 more than a century later.

"They were in the same situation," Vander Heide said of the doctors trying to save lives in 1918. "The only way to learn what was going on was to open up the body and see."

http://bit.ly/3aYTjKT

Plastic pipes are polluting drinking water systems after wildfires

And it's a risk in urban fires, too.

Andrew J. Whelton, Amisha Shah, and Kristofer P. Isaacson

When wildfires swept through the hills near Santa Cruz, California, in 2020, they released toxic chemicals into the water supplies of at least two communities. One sample found benzene, a carcinogen, at 40 times the state's drinking water standard. Our testing has now confirmed a source of these chemicals, and it's clear that wildfires aren't the only blazes that put drinking water systems at risk.

In a new study, we heated plastic water pipes commonly used in buildings and water systems to test how they would respond to nearby fires.

Some common types of drinking water pipes: Black plastic is HDPE; white is PVC; yellow is CPVC; red, maroon, orange, and blue are PEX; green is PP; and gray is polybutylene. The metal pipes are lead, iron and copper. **Andrew Whelton/Purdue University, CC BY-ND**

The results, released Dec. 14, show how easily wildfires could trigger widespread drinking water contamination. They also show the risks when only part of a building catches fire and the rest remains in use. In some of our tests, heat exposure caused more than 100 chemicals to leach from the damaged plastics.

As environmental engineers, we advise communities on drinking water safety and disaster recovery. The western U.S.'s extreme wildfire seasons are putting more communities at risk in ways they might not realize. Just this year, more than 52,000 fires destroyed more than 17,000 structures – many of them homes connected to water systems. Heat-damaged plastic pipes can continue to leach chemicals into water over time, and ridding a water system of the contamination can take months and millions of dollars.

A baffling source of contamination

The cause of drinking water contamination after wildfires has baffled authorities since it was discovered in 2017.

After the 2017 Tubbs Fire and 2018 Camp Fire, chemicals were found in buried water distribution networks, some at levels comparable to hazardous waste. Contamination was not in the water

treatment plants or drinking water sources. Some homeowners found drinking water contamination in their plumbing.

Tests revealed volatile organic compounds had reached levels that posed immediate health risks in some areas, including benzene levels that exceeded the EPA hazardous waste threshold of 500 parts per billion. Benzene was found at a level 8,000 times the federal drinking water limit and 200 times the level that causes immediate health effects. Those effects can include dizziness, headaches, skin and throat irritation and even unconsciousness, among other risks.

The problem with plastics

Plastics are ubiquitous in drinking water systems. They are often less expensive to install than metal alternatives, which hold up against high heat but are vulnerable to corrosion.

Today, water pipes under the street and those that deliver water to customers' water meters are increasingly made of plastic. Pipes that transport the drinking water from the meter to the building are often plastic. Water meters also sometimes contain plastics. Private wells can have plastic well casings as well as buried plastic pipes that deliver well water to plastic storage tanks and buildings.

Pipes inside buildings that carry hot and cold water to faucets can also be plastic, as can faucet connectors, water heater dip tubes, refrigerator and ice maker tubing.

To determine if plastic pipes could be responsible for drinking water contamination after wildfires, we exposed commonly available plastic pipes to heat. The temperatures were similar to the heat from a wildfire that radiates toward buildings but isn't enough to cause the pipes to catch fire.

We tested several popular plastic drinking water pipes, including high-density polyethylene (HDPE), crosslinked polyethylene (PEX), polyvinyl chloride (PVC) and chlorinated polyvinylchloride (CPVC).

Benzene and other chemicals were generated inside the plastic pipes just by heating. After the plastics cooled, these chemicals then leached into the water. It happened at temperatures as low as 392 degrees Fahrenheit. Fires can exceed 1,400 degrees.

While researchers previously discovered that plastics could release benzene and other chemicals into the air during heating, this new study shows heat-damaged plastics can directly leach dozens of toxic chemicals into water.

What to do about contamination

A community can stop water contamination from spreading if damaged pipes can be quickly isolated. Without isolation, the contaminated water may move to other parts of the water system, across town or within a building, causing further contamination.

During the CZU Lightning Complex Fire near Santa Cruz, one water utility had water distribution system valves that seemed to have contained the benzene-contaminated water.

Rinsing heat-damaged pipes won't always remove the contamination. While helping Paradise, California, recover from the 2018 Camp Fire disaster, we and the U.S. Environmental Protection Agency estimated that some plastic pipes would have required more than 100 days of nonstop water rinsing to be safe for use. Instead, officials decided to replace the pipes.

Even if a home is undamaged, we recommend testing the water in private wells and service lines if fire was on the property. If contamination is found, we recommend finding and removing the heat-damaged plastic contamination sources. Some plastics can slowly leach chemicals like benzene over time, and this could go on for months to years, depending on the scale of contamination and water use. Boiling the water doesn't help and can release benzene into the air.

Avoiding widespread contamination

Communities can take steps to avoid contaminated drinking water in the event of a fire. Water companies can install network isolation valves and backflow prevention devices, to prevent contaminated water moving from a damaged building into the utility pipe network. Insurance companies can use pricing to encourage property owners and cities to install fire-resistant metal pipes instead of plastic. Rules for keeping vegetation away from meter boxes and buildings can also lessen the chance heat reaches plastic water system components.

Homeowners and communities rebuilding after fires now have more information about the risks as they consider whether to use plastic pipes. Some, like the town of Paradise, have chosen to rebuild with plastic and accept the risks. In 2020, the city had another wildfire scare and residents were forced to evacuate again.

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http://bit.ly/38Pf50M

In 1110, The Moon Vanished From The Sky. We May Finally Know Why

Almost a millennium ago, a major upheaval occurred in Earth's atmosphere

Peter Dockrill

Almost a millennium ago, a major upheaval occurred in Earth's atmosphere: a giant cloud of sulphur-rich particles flowed throughout the stratosphere, turning skies dark for months or even years, before ultimately falling down to Earth.

We know this event happened because researchers have drilled and analysed ice cores - samples taken from deep within ice sheets or glaciers, which have trapped sulphur aerosols produced by volcanic eruptions reaching the stratosphere and settling back on the surface. Ice can thus preserve evidence of volcanism over incredibly long timescales, but pinpointing the precise date of an event that shows up in the layers of an ice core is still tricky business.

In this case, scientists had assumed the sulphurous deposit was left by a major eruption unleashed in 1104 by Iceland's Hekla, a volcano sometimes called the 'Gateway to Hell'. Since the thin strip of ice ranks among the largest sulfate deposition signals of the last millennium, it sounds plausible.

Only, what if the accepted timeline of an ice core turns out to be time-warped? A few years ago, one study concluded that a timescale called the Greenland Ice Core Chronology 2005 (GICC05) was off by up to seven years in the first millennium CE, and by up to four years early in the next millennium.

Those findings, according to research published in April 2020 - led by palaeoclimatologist Sébastien Guillet from the University of Geneva in Switzerland - mean Hekla couldn't have been the culprit for the giant sulphate signal after all.

"A prominent discovery arising from this revised ice-core dating is a major and hitherto unrecognised bipolar volcanic signal with sulfate deposition starting in late 1108 or early 1109 CE and persisting until early 1113 CE in the Greenland record," Guillet and his co-authors explain in their paper, noting that evidence for the same event can also be seen in a similarly revised Antarctic ice core chronology.

To investigate what might have been responsible for leaving these ancient tracks at both the top and the bottom of the world, the team combed historical documentation, looking for medieval records of strange, dark-looking lunar eclipses that could correspond to the stratospheric haze of major eruptive events.

"The spectacular atmospheric optical phenomena associated with high-altitude volcanic aerosols have caught the attention of chroniclers since ancient times," the team writes.

"In particular, the reported brightness of lunar eclipses can be employed both to detect volcanic aerosols in the stratosphere and to quantify stratospheric optical depths following large eruptions."

According to NASA records based on astronomical retrocalculation, seven total lunar eclipses would have been observable in Europe in the first 20 years of the last millennium, between 1100 and 1120 CE. Among these, a witness to a lunar eclipse that occurred in May 1110 wrote of the exceptional darkness of the Moon during the phenomenon.

"On the fifth night in the month of May appeared the Moon shining bright in the evening, and afterwards by little and little its light diminished, so that, as soon as night came, it was so completely extinguished withal, that neither light, nor orb, nor anything at all of it was seen," an observer wrote in the *Peterborough Chronicle*.

Many astronomers have since discussed this mysterious and unusually dark lunar eclipse. Centuries after it occurred, the English astronomer Georges Frederick Chambers wrote about it, saying: "It is evident that this [eclipse] was an instance of a 'black' eclipse when the Moon becomes quite invisible instead of shining with the familiar coppery hue".

Despite the event being well-known in astronomy history, though, researchers have never suggested it might have been caused by the presence of volcanic aerosols in the stratosphere, even though that's the most likely cause, the new study suggests.

"We note that no other evidence of volcanic dust veil, such as a dimming of the Sun, red twilight glows and/or reddish solar haloes, could be found during our investigations for the years 1108–1110 CE," the researchers write.

If the timing is right, then what volcano was responsible for the sulphur cloud, given Hekla is now out of the frame?

While it's impossible to know for sure, the team thinks the most probable explanation is Japan's Mount Asama, which produced a giant, months-long eruption in the year 1108 – significantly larger than a subsequent eruption in 1783 that killed over 1,400 people.

A diary entry recorded by a statesman describes the 1108 event: "There was a fire at the top of the volcano, a thick layer of ash in the governor's garden, everywhere the fields and the rice fields are rendered unfit for cultivation. We never saw that in the country. It is a very strange and rare thing."

In addition to witness accounts, the researchers also looked at tree ring evidence, which suggests 1109 CE was an exceptionally cold year (about 1 degree Celsius cooler in the Northern Hemisphere), based on significantly thinner tree rings. Other historical documentation, in particular accounts of climatic and societal impacts in the years 1109–1111 CE, corroborate the hypothesis that an 1108 eruption (or a series of eruptions that began that year), could have led to disastrous effects on affected communities.

The researchers found an "abundance of testimonies referring to adverse weather, crop failures, and famines in these years", noting that the "assembled evidence suggests that the subsistence difficulties, which began in 1109, deepened into famine in several regions of western Europe".

Of course, those long-ago hardships can't be taken as proof of any particular eruptive event, but the researchers say all the evidence, taken together, suggests a 'forgotten' cluster of volcanic eruptions in 1108 to 1110 unleashed terrible consequences on humanity. We're only rediscovering them now.

The findings are reported in *Scientific Reports*.

http://bit.ly/2Leb4e1

A New Therapy to Prevent People With SARS-CoV-2 From Getting Sick Just Started Trials

Could give those who have already been exposed to SARS-CoV-2 protection from developing COVID-19

Jacinta Bowler

Scientists in the UK have just recruited the first participants in the world to be part of a new long-acting antibody study. If the treatment is effective, it could give those who have already been exposed to SARS-CoV-2 protection from developing COVID-19.

"We know that this antibody combination can neutralise the virus," explains University College London Hospitals (UCLH) virologist Catherine Houlihan. "So we hope to find that giving this treatment via injection can lead to immediate protection against the development of COVID-19 in people who have been exposed – when it would be too late to offer a vaccine."

This might not be the first antibody treatment for COVID-19 you've heard of. Outgoing US President Donald Trump was given monoclonal antibodies when he came down with the disease, and in the US two different antibody treatments - casirivimab and imdevimab – received emergency approval back in November. But those antibody treatments are given to patients with mild or moderate COVID-19, who risk progressing to a severe version of the disease.

"In a clinical trial of patients with COVID-19, casirivimab and imdevimab, administered together, were shown to reduce COVID-19-related hospitalisation or emergency room visits in patients at high risk for disease progression within 28 days after treatment when compared to placebo," the FDA explained in a press statement when the drugs were approved.

This new antibody therapy, called AZD7442 and developed by UCLH and AstraZeneca, is a little different. AZD7442 is a combination of two monoclonal antibodies AZD8895 and AZD1061, which both target the receptor binding domain of the SARS-CoV-2 spike protein. "By targeting this region of the virus's spike protein, antibodies can block the virus's attachment to human cells, and, therefore, is expected to block infection," the team wrote on the US ClinicalTrials.gov website.

"Amino acid substitutions have been introduced into the antibodies to both extend their half-lives, which should prolong their potential prophylactic benefit, and decrease Fc effector function in order to decrease the potential risk of antibody-dependent enhancement of disease."

Antibodies are little Y-shaped proteins that lock on to a particular section - called an antigen - of a virus, bacterium or other pathogen, and either 'tag' it to be attacked by the immune system, or directly block the pathogen from invading our cells. Normal antibodies are produced by your body after an infection, while monoclonal antibodies are cloned in a lab and can be injected into a person already infected, to give the immune system a hand in the fight.

The researchers are hoping that AZD7442 – which is just starting the Storm Chaser study (the name for its phase 3 trial) – provides protection for those that have been exposed to the virus but do not yet have symptoms. Effectively, they're trying to stop COVID-19 happening in the first place.

"If you are dealing with outbreaks in settings such as care homes, or if you have got patients who are particularly at risk of getting severe COVID, such as the elderly, then this could well save a lot of lives," University of East Anglia infectious disease expert Paul Hunter told *The Guardian*. "If you live with your elderly grandmother and you or someone else in the house gets infected, then you could give her this to protect her."

But they're also hoping it might be effective longer term, over a 6-12 month period, meaning people who can't receive the vaccine for medical reasons have another option to keep themselves safe from the disease.

The researchers are looking at how this could work for people with compromised immune systems in a second trial called PROVENT.

"We will be recruiting people who are older or in long-term care, and who have conditions such as cancer and HIV which may affect

the ability of their immune system to respond to a vaccine," UCLH infectious diseases consultant Nicky Longley told *The Guardian*.

"We want to reassure anyone for whom a vaccine may not work that we can offer an alternative which is just as protective."

We're looking forward to seeing where this leads.

http://bit.ly/2KT0VUj

A single gene 'invented' haemoglobin several times

While haemoglobin appeared independently in several species, it descends from a gene transmitted by their last common ancestor

Thanks to the marine worm Platynereis dumerilii, an animal whose genes have evolved very slowly, scientists from CNRS, Université de Paris and Sorbonne Université, in association with others at the University of Saint Petersburg and the University of Rio de Janeiro, have shown that while haemoglobin appeared independently in several species, it actually descends from a single gene transmitted to all by their last common ancestor. These findings were published on 29 December 2020 in *BMC Evolutionary Biology*.

Having red blood is not peculiar to humans or mammals. This colour comes from haemoglobin, a complex protein specialized in transporting the oxygen found in the circulatory system of vertebrates, but also in annelids (a worm family whose most famous members are earthworms), molluscs (especially pond snails) and crustaceans (such as daphnia or 'water fleas'). It was thought that for haemoglobin to have appeared in such diverse species, it must have been 'invented' several times during evolution. But recent research has shown that all of these haemoglobins born 'independently' actually derive from a single ancestral gene.

Researchers from the Institut Jacques Monod (CNRS/Université de Paris), the Laboratoire Matière et Systèmes Complexes (CNRS/Université de Paris), the Station Biologique de Roscoff (CNRS/Sorbonne Université), the Universities of Saint Petersburg (Russia) and Rio de Janeiro (Brazil), conducted this research on Platynereis dumerilii, a small marine worm with red blood.

It is considered to be an animal that evolved slowly, because its genetic characteristics are close to those of the marine ancestor of most animals, Urbilateria[(1)]. Studying these worms by comparing them with other species with red blood has helped in tracing back to the origins of haemoglobins.

The research focused on the broad family to which haemoglobins belong: globins, proteins present in almost all living beings that 'store' gases like oxygen and nitric oxide. But globins usually act inside the cells because they do not circulate in the blood like haemoglobin.

This work shows that in all species with red blood, it is the same gene that makes a globin called 'cytoglobin' that independently evolved to become a haemoglobin-encoding gene. This new circulating molecule made oxygen transport more efficient in their ancestors, who became larger and more active.

Scientists now want to change scale and continue this work by studying when and how the different specialized cells of bilaterian vascular systems emerged.

[(1)]Urbilateria is the last common ancestor of bilaterians, i.e. animals with bilateral (left-right) symmetry and complex organs, apart from species with simpler organization such as sponges and jellyfish.

http://wb.md/2JBTQHc

Complete Blood Count Scoring Can Predict COVID-19 Severity

Can predict within 3 days those with COVID-19 who are most likely to progress to critical illness

Damian McNamara

A scoring system based on 10 parameters in a complete blood count (CBC) with differential within 3 days of hospital presentation predict those with COVID-19 who are most likely to progress to

critical illness, new evidence shows. Advantages include prognosis based on a common and inexpensive clinical measure, as well as automatic generation of the score along with CBC results, note investigators in the observational study conducted throughout 11 European hospitals.

"COVID-19 comes along with specific alterations in circulating blood cells that can be detected by a routine hematology analyzer, especially when that hematology analyzer is also capable to recognize activated immune cells and early circulating blood cells, such as erythroblast and immature granulocytes," senior author Andre van der Ven, MD, PhD, infectious diseases specialist and professor of international health at Radboud University Medical Center's Center for Infectious Diseases in Nijmegen, the Netherlands, told *Medscape Medical News*.

Furthermore, van der Ven said, "these specific changes are also seen in the early course of COVID-19 disease, and more in those that will develop serious disease compared to those with mild disease."

The study was published online December 21 in the journal *eLife*.

The study is "almost instinctively correct. It's basically what clinicians do informally with complete blood count…looking at a combination of results to get the gestalt of what patients are going through," Samuel Reichberg, MD, PhD, associate medical director of the Northwell Health Core Laboratory in Lake Success, New York, told *Medscape Medical News* when asked to comment.

"This is something that begs to be done for COVID-19. I'm surprised no one has done this before," he added.

Van der Ven and colleagues created an algorithm based on 1587 CBC assays from 923 adults. They also validated the scoring system in a second cohort of 217 CBC measurements in 202 people. The findings were concordant — the score accurately predicted the need for critical care within 14 days in 70.5% of the development cohort and 72% of the validation group.

The scoring system was superior to any of the 10 parameters alone. Over 14 days, the majority of those classified as noncritical (NC) within the first 3 days remained clinically stable, whereas the "clinical illness" (CI) group progressed. Clinical severity peaked on day 6.

Most previous COVID-19 prognosis research was geographically limited, carried a high risk for bias and/or did not validate the findings, Van der Ven and colleagues note.

Early Identification, Early Intervention

The aim of the score is "to assist with objective risk stratification to support patient management decision-making early on, and thus facilitate timely interventions, such as need for ICU or not, before symptoms of severe illness become clinically overt, with the intention to improve patient outcomes, and not to predict mortality," the investigators note.

Van der Ven and colleagues developed the score based on adults presenting from February 21 to April 6, with outcomes followed until June 9. Median age of the 982 patients was 71 years and approximately two thirds were men. They used a Sysmex Europe GmbH XN-1000 (Hamburg, Germany) hemocytometric analyzer in the study. Only 7% of this cohort was not admitted to a hospital. Another 74% were admitted to a general ward and the remaining 19% were transferred directly to the ICU.

The scoring system includes parameters for neutrophils, monocytes, red blood cells and immature granulocytes, and when available, reticulocyte and iron bioavailability measures.

The researchers report significant differences over time in the neutrophil-to-lymphocyte ratio between the critical illness and non-critical groups ($P < .001$), for example. They also found significant differences in hemoglobin levels between cohorts after day 5.

The system generates a score from 0 to 28. Sensitivity for correctly predicting the need for critical care increased from 62% on day 1 to 93% on day 6.

A More Objective Assessment of Risk

The study demonstrated that SARS-CoV-2 infection is characterized by hemocytometric changes over time. These changes, reflected together in the prognostic score, could aid in the early identification of patients whose clinical course is more likely to deteriorate over time.

The findings also support other work that shows men are more likely to present to the hospital with COVID-19, and that older age and presence of comorbidities add to overall risk. "However," the researchers note, "not all young patients had a mild course, and not all old patients with comorbidities were critical."

Therefore, the prognostic score can help identify patients at risk for severe progression outside other risk factors and "support individualized treatment decisions with objective data," they add.

Reichberg called the concept of combining CBC parameters into one score "very valuable." However, he added that incorporating an index into clinical practice "has historically been tricky."

The results "probably have to be replicated," Reichberg said.

He added that it is likely a CBC-based score will be combined with other measures. "I would like to see an index that combines all the tests we do [for COVID-19], including complete blood count."

Van der Ven shared the next step in his research. "The algorithm should be installed on the hematology analyzers so the prognostic score will be automatically generated if a full blood count is asked for in a COVID-19 patient," he said. "So implementation of score is the main focus now."

Andre J van der Ven disclosed an ad hoc consultancy agreement with Sysmex Europe GmbH. Sysmex Europe provided the reagents in the study free of charge; no other funders were involved. Reichberg has disclosed no relevant financial relationships.

eLife. Published online December 21, 2020. Full text

http://nyti.ms/3pIHZ9C

Can 4 Seconds of Exercise Make a Difference?

Four seconds of intense intervals, repeated until they amount to a minute of total exertion, led to rapid improvements in strength and fitness in middle-aged and older adults.

By Gretchen Reynolds

In what is probably the definitive word on how little exercise we can get away with, a new study finds that a mere four seconds of intense intervals, repeated until they amount to about a minute of total exertion, lead to rapid and meaningful improvements in strength, fitness and general physical performance among middle-aged and older adults.

The study relied on a type of specialized stationary bicycle that is not widely available, but, even so, the results suggest that strenuous but super-abbreviated workouts can produce outsize benefits for our health and well-being, a timely message as we plan our New Year's exercise resolutions.

I have often written about the potential benefits of brief, high-intensity interval training, or H.I.I.T., an approach to exercise that consists of quick spurts of draining physical effort, followed by rest, with the sequence repeated multiple times. In studies, short H.I.I.T. workouts typically produce health gains that are equal to or more pronounced than much longer, gentler workouts.

But the ideal length of the intervals in these workouts has been unsettled. Researchers studying H.I.I.T. agree that the optimal interval span should stress our muscles and other bodily systems enough to jump-start potent physiological changes but not so much that we groan, give up and decline to try that workout ever again. In practice, those dueling goals have led H.I.I.T. scientists to study intervals ranging from a protracted four minutes to a quickie 20 seconds.

But Ed Coyle, an exercise physiologist at the University of Texas in Austin, and his graduate assistant Jakob Allen suspected that even 20-second spurts, performed intensely, might exceed some exercisers' tolerance. So, he decided to start looking for the shortest possible interval that was still effective. And in the new study, which was published this week in Medicine & Science in Sports & Exercise, he and his colleagues settled on a blink-swift four seconds.

They arrived at that number by first working with competitive athletes at the university's human performance lab. Muscular and fit, the athletes generated enormous speed and power on specialized stationary bicycles that feature a heavy flywheel and no resistance. During fitness testing on these bikes, most of the athletes would reach their maximum power output and all-out aerobic effort after about two seconds of hard pedaling. (Dr. Coyle has equity in the company that manufactures the bicycles, but says this monetary involvement does not affect research results from his lab.)

The rest of us, Dr. Coyle and his colleagues reasoned, probably would require twice as long — or about four seconds. By that point, the researchers thought, most people should have massively stimulated their muscles and aerobic systems but not yet exhausted them. If the riders then rested for a minute or so before sprinting again, they should be able to repeat the all-out efforts again and again.

To test that idea, the researchers turned initially to eight healthy college students, asking them to sprint on the bikes for four seconds periodically throughout the day, to see if these short, strenuous workouts would counteract some of the undesirable metabolic effects of sitting all day and eating poorly. They did, as I wrote about in April.

But that study focused on robust, young adults and repeated, if diminutive, workouts sprinkled throughout the day. The scientists now wondered if a more practical, single session of four-second sprints would be enough exercise to improve health and fitness in out-of-shape adults well past their college years.

So, they recruited 39 of them, men and women aged 50 to 68 who were sedentary but had no other major health concerns. They tested the volunteers' current aerobic fitness, muscular power and mass, arterial flexibility, and ability to perform what are called "activities of daily living," such as getting up out of a chair.

The volunteers began visiting the performance lab three times a week. There, they completed a brief workout of repeated four-second intervals on the lab's specialized bikes. At first, they sprinted for four seconds, with Dr. Allen calling out a second-by-second countdown, followed by 56 seconds of rest, repeating that sequence 15 times, for a total of 60 seconds of intervals. Over two months, though, the riders' rest periods declined to 26 seconds and they increased their total number of sprints to 30 per session.

At the end of eight weeks, the scientists retested everyone and found substantial differences. On average, riders had increased their fitness by about 10 percent, gained considerable muscle mass and strength in their legs, reduced the stiffness of their arteries and outperformed their previous selves in activities of daily living, all from about three to six minutes a week of actual exercise.

A majority of the volunteers also told the researchers during follow-up interviews that they enjoyed the workouts and would continue them, if possible, Dr. Coyle said.

The upshot, he said, is that these intervals, despite being as brief as possible, effectively boosted health and fitness in ordinary adults.

Of course, most of us do not have access to the kind of specialized stationary bicycles used in this study. Nor do we have a researcher helpfully hollering out four-second countdowns for us. To reach similar, all-out efforts in more typical workouts, Dr. Coyle said, we might need to sprint up a hill or staircase as hard as possible or run and jump in place vigorously or furiously pedal our spin bike.

In these situations, the time needed to achieve all-out effort is likely to be more than four seconds, he said. But even if the time commitment is doubled, most of us probably could resolve to exercise in 2021 often and intensely for eight seconds at a time.

http://nyti.ms/2KNDkEO

The Risks of the Covid Vaccine, in Context

We should expect some people to experience side effects. The shot is still safer than the disease.

By Aaron E. Carroll*

At this point, most of us have heard about allergic reactions to Covid-19 vaccines: the doctor in Boston who had to administer his EpiPen, the hospital worker in Alaska who had trouble breathing. But it's not at all surprising that allergic reactions happen. What matters most is the severity and the rate at which they occur. And for the Covid vaccines, there's no doubt that the value of vaccination outweighs the risk.

The Centers for Disease Control and Prevention issued updated guidance on administering the Covid vaccines on Dec. 19. The agency noted that a small number of people had experienced significant allergic reactions. The C.D.C. recommended that everyone who received a vaccine be observed for at least 15 minutes. Those with a history of severe allergic reactions to pretty much anything should be observed for 30 minutes.

Anaphylaxis — a potentially life-threatening allergic reaction — is nothing to be ignored. It's most commonly associated with allergies to foods, like peanuts, or bee stings, and it's the reason many people carry EpiPens. Often, immediate administration of epinephrine is the only thing that can prevent death.

Even so, an average of around 60 people die each year from hornet, wasp and bee stings and three times as many die from food allergies. When the C.D.C. updated its guidance, at least six out of hundreds of thousands of recipients had experienced a severe allergic reaction, but all of them recovered with treatment.

The news media has covered these reactions, and it's understandable that the public would be concerned about the dangers of new medications, especially ones that were developed so quickly and under such enormous pressure.

But put those numbers in context: More than 2.1 million people in the United States have received a dose of a vaccine at this point. So far, according to reports, about 11 severe allergic reactions — representing about one in 190,000 doses administered — have been noted. This is still higher than the overall rate of anaphylaxis in vaccinations, at 1.3 per one million given, but that may be only because we are being much more careful about monitoring reactions at the moment.

Context also matters. About one in 10 Americans have reported an allergic reaction to penicillins. About one in 100, perhaps, have a true allergy to that class of drugs (I'm one of them). Between one in 2,500 and one in 5,000 experience anaphylaxis. But pediatricians like me dispense penicillin all the time, with minimal concerns. We do so because most allergic reactions are minor and serious ones can be managed, and because we believe that the benefits outweigh the harms.

Every potential bad outcome of a Covid vaccine should be weighed against the chance of getting sick or dying from the disease.

Using data from Indiana, which has conducted multiple statewide studies on the prevalence of Covid-19, colleagues from the I.U.P.U.I. Fairbanks School of Public Health and I calculated the disease's infection fatality rate. We found that, for people 60 years and older who were not living in jails or nursing homes, Covid-19 killed about one in 58 of those infected. For people between the ages of 40 and 59, it was about one in 833, and for people younger

than 40 it was about one in 10,000. For those who were not white, the fatality rate was more than three times that for whites.

While a vast majority of people who develop Covid-19 survive, more than 670,000 Americans have been hospitalized with the disease this year; scientists are still struggling to treat so-called long-haulers, who endure long-term effects of the disease. A recent study in JAMA Internal Medicine also showed that when the coronavirus is more prevalent in an area, outcomes worsen. Surges are occurring all over now.

Getting a vaccine appears to be orders of magnitude safer than getting infected with the virus.

In order for the crisis to end, we need herd immunity. The only way to reach that is to get most people immunized or infected. Based on the numbers above, the latter would be a tragedy. Scaring people unnecessarily away from the former would result in more infections, more deaths and more economic and societal hardship. We should definitely be transparent and plain about the risks and benefits of the vaccines, but we need to put numbers in context of the risks of Covid-19.

Vaccines aren't perfect. In the coming weeks and months, we can expect to read about people who were immunized and got sick anyway. This won't mean that the vaccine is a failure; it will simply show, as we already know, that the shots are not 100 percent effective.

Those of us who communicate about public health have too often failed to be clear during this pandemic. Many Americans wound up being confused about masks, tests and certainly in how we should think about risk. This has not only led to confusion. It likely also led to sickness and death. Let's do better with vaccines. There's a real chance we can stop this pandemic in 2021 if we get this right.

Covid-19 Vaccines ›

Answers to Your Vaccine Questions

With distribution of a coronavirus vaccine beginning in the U.S., here are answers to some questions you may be wondering about:

If I live in the U.S., when can I get the vaccine? *While the exact order of vaccine recipients may vary by state, most will likely put medical workers and residents of long-term care facilities first. If you want to understand how this decision is getting made, this article will help.*

When can I return to normal life after being vaccinated? *Life will return to normal only when society as a whole gains enough protection against the coronavirus. Once countries authorize a vaccine, they'll only be able to vaccinate a few percent of their citizens at most in the first couple months. The unvaccinated majority will still remain vulnerable to getting infected. A growing number of coronavirus vaccines are showing robust protection against becoming sick. But it's also possible for people to spread the virus without even knowing they're infected because they experience only mild symptoms or none at all. Scientists don't yet know if the vaccines also block the transmission of the coronavirus. So for the time being, even vaccinated people will need to wear masks, avoid indoor crowds, and so on. Once enough people get vaccinated, it will become very difficult for the coronavirus to find vulnerable people to infect. Depending on how quickly we as a society achieve that goal, life might start approaching something like normal by the fall 2021.*

If I've been vaccinated, do I still need to wear a mask? *Yes, but not forever. Here's why. The coronavirus vaccines are injected deep into the muscles and stimulate the immune system to produce antibodies. This appears to be enough protection to keep the vaccinated person from getting ill. But what's not clear is whether it's possible for the virus to bloom in the nose — and be sneezed or breathed out to infect others — even as antibodies elsewhere in the body have mobilized to prevent the vaccinated person from getting sick. The vaccine clinical trials were designed to determine whether vaccinated people are protected from illness — not to find out whether they could still spread the coronavirus. Based on studies of flu vaccine and even patients infected with Covid-19,*

researchers have reason to be hopeful that vaccinated people won't spread the virus, but more research is needed. In the meantime, everyone — even vaccinated people — will need to think of themselves as possible silent spreaders and keep wearing a mask. Read more here.

Will it hurt? What are the side effects? *The Pfizer and BioNTech vaccine is delivered as a shot in the arm, like other typical vaccines. The injection into your arm won't feel different than any other vaccine, but the rate of short-lived side effects does appear higher than a flu shot. Tens of thousands of people have already received the vaccines, and none of them have reported any serious health problems. The side effects, which can resemble the symptoms of Covid-19, last about a day and appear more likely after the second dose. Early reports from vaccine trials suggest some people might need to take a day off from work because they feel lousy after receiving the second dose. In the Pfizer study, about half developed fatigue. Other side effects occurred in at least 25 to 33 percent of patients, sometimes more, including headaches, chills and muscle pain. While these experiences aren't pleasant, they are a good sign that your own immune system is mounting a potent response to the vaccine that will provide long-lasting immunity.*

Will mRNA vaccines change my genes? *No. The vaccines from Moderna and Pfizer use a genetic molecule to prime the immune system. That molecule, known as mRNA, is eventually destroyed by the body. The mRNA is packaged in an oily bubble that can fuse to a cell, allowing the molecule to slip in. The cell uses the mRNA to make proteins from the coronavirus, which can stimulate the immune system. At any moment, each of our cells may contain hundreds of thousands of mRNA molecules, which they produce in order to make proteins of their own. Once those proteins are made, our cells then shred the mRNA with special enzymes. The mRNA molecules our cells make can only survive a matter of minutes. The mRNA in vaccines is engineered to withstand the cell's enzymes a bit longer, so that the cells can make extra virus proteins and prompt a stronger immune response. But the mRNA can only last for a few days at most before they are destroyed.*

Dr. Carroll is a pediatrician, a professor and a contributing opinion writer.

http://bit.ly/384aKYv

Organic meats found to have approximately the same greenhouse impact as regular meats

Took into account the emissions produced during different stages of the production

by Bob Yirka , Phys.org

A trio of researchers from the Technical University of Munich, the University of Greifswald and the University of Augsburg have found that the meat production process for organic meats produces approximately the same amounts of greenhouse gases as does the conventional meat production process. In their paper published in the journal *Nature Communications*, Maximilian Pieper, Amelie Michalke and Tobias Gaugler describe their study of the impact of global food production on climate change and what they found.

As the planet continues to warm, researchers continue working to better understand the sources of greenhouse emissions. In this new effort, the researchers looked at greenhouse emissions related to food production.

In looking at food production, the researchers placed food products into three main categories: conventional meat production, organic meat production and plant-based food production. They also took into account the emissions produced during different stages of the production process—emissions produced while growing and processing feed and fertilizer, for example, and methane released by animals and from their manure.

The data revealed little difference in greenhouse gas emissions from conventional meat production and that grown organically. They found that emission reductions by organically grown animals (in which fertilizer is not used to produce feed) were often offset by increases in methane released due to slower growth rates and the need to raise more animals, as organically fed animals tend to produce less meat. More specifically, they found very little

difference in emissions between conventionally produced beef and beef grown organically. They also found that organically grown chickens produced slightly more emissions than those grown conventionally, and that organic pork produced fewer emissions than conventional pork.

The researchers suggest the need for meat taxes that reflect the environmental cost of their production. They calculated such a tax for conventional beef would raise its price by approximately 40% while organic beef would see a price increase of just 25% (because it is already more expensive than regular beef). Prices for animal-related products, such as cheese or milk, would also rise. Prices for food plants, on the other hand, would remain nearly the same.

More information: *Maximilian Pieper et al. Calculation of external climate costs for food highlights inadequate pricing of animal products, Nature Communications (2020). DOI: 10.1038/s41467-020-19474-6*

http://bit.ly/38aW8GV

A Freakishly Well-Preserved Woolly Rhino Was Plucked From Siberia's Melting Tundra

Melting permafrost in the icy north of Siberia is revealing a veritable graveyard of frozen prehistoric animals.

Carly Cassella

In recent decades, locals and scientists in the Russian Republic of Yakutia have uncovered the ancient carcasses of two cave lion cubs, a bison, a horse, a baby woolly rhinoceros, and the most intact woolly mammoth ever found.

(Valery Plotnikov/The Siberian Times)

As climate change continues to pull back this crucial carpet of ice, we're bound to uncover more. Close to where the world's first and, reportedly only, baby woolly rhino was found, residents have now discovered another of its kind, and this time, the carcass is almost 80 percent intact.

Preserved in ice for tens of thousands of years, this juvenile woolly rhino still has its thick, reddish-brown hair, all of its limbs, and most of its internal organs, including its intestines.

To date, this furry little creature is the best-preserved woolly rhino found in the Arctic Yakutia and may even be the most intact ever discovered anywhere in the world.

"The young rhino was between three and four years old and lived separately from its mother when it died, most likely by drowning," palaeontologist Valery Plotnikov from the Russian Academy of Sciences, who made the first description of the find, told The Siberian Times.

"The gender of the animal is still unknown. We are waiting for the radiocarbon analyses to define when it lived, the most likely range of dates is between 20,000 and 50,000 years ago."

The hair on this long-dead creature might look patchy and bedraggled now, but it speaks of a much thicker and luscious past. Looking at the layout of the hairs, scientists think the animal most likely died with its summer coat, although further lab analysis is needed.

To do that, however, more ice needs to form. Found downstream of the Tirekhtyakh River in August, the rhino carcass is in a particularly tricky spot to access.

Yakutia's vast, remote territory only has a few roads, and in the summertime, many places are only accessible by boat or by air. Not until winter do things start to open up. This is when a network of temporary ice roads begin to form, allowing truckers to transport goods to the region's northernmost settlements.

Yet, even without a closer examination of the carcass, it's clear this find is a big one. Previously, the only other woolly rhino found in

this region was an even younger baby named Sasha, and her hair was more strawberry blonde.

Both discoveries have Plotnikov thinking woolly rhinos were already adapted to the freezing climate from a young age. Marks on the horns of this recent one suggest it foraged for food.

"There are soft tissues in the back of the carcass, possibly genitals and part of the intestine," he told RT. "This makes it possible to study the excreta, which will allow us to reconstruct the paleoenvironment of that period."

The team already has plans to send the rhino to the capital of Yakutia for further analysis. The carcass will then be sent to Sweden, where researchers are working to sequence the genomes of multiple rhinos to better understand their history and why they went extinct.

http://bit.ly/2X1WkSq

Traditional Ghanaian medicines show promise against tropical diseases

Traditional Ghanaian medicines which work in the lab against schistosomiasis, onchocerciasis and lymphatic filariasis

The discovery of new drugs is vital to achieving the eradication of neglected tropical diseases (NTDs) in Africa and around the world. Now, researchers reporting in *PLOS Neglected Tropical Diseases* have identified traditional Ghanaian medicines which work in the lab against schistosomiasis, onchocerciasis and lymphatic filariasis, three diseases endemic to Ghana.

The major intervention for NTDs in Ghana is currently mass drug administration of a few repeatedly recycled drugs, which can lead to reduced efficacy and the emergence of drug resistance. Chronic infections of schistosomiasis, onchocerciasis and lymphatic filariasis can be fatal. Schistosomiasis is caused by the blood flukes *Schistosome haematobium* and *S. mansoni*. Onchocerciasis, or river blindness, is caused by the parasitic worm *Onchocerca volvulus*. Lymphatic filariasis, also called elephantiasis, is caused by the parasitic filarial worm *Wuchereria bancrofti*.

In the new work, Dorcas Osei-Safo of the University of Ghana, and colleagues obtained--from the Ghana Federation of Traditional Medicines Practitioners Association--15 traditional medicines used for treating NTDs in local communities. The medicines were available in aqueous herbal preparations or dried powdered herbs. In all cases, crude extracts were prepared from the herbs and screened in the laboratory for their ability to treat various NTDs.

Two extracts, NTD-B4-DCM and NTD-B7-DCM, displayed high activity against *S. mansoni* adult worms, decreasing the movement of the worms by 78.4% and 84.3% respectively. A different extract, NTD-B2-DCM, was the most active against adult *Onchocera onchengi* worms, killing 100% of males and more than 60% of females. Eight of 26 crude extracts tested, including NTD-B4-DCM and NTD-B2-DCM, also exhibited good activity against trypanosomes--parasites that cause other human diseases but weren't the original targets of the traditional medicines.

"By embracing indigenous knowledge systems which have evolved over centuries, we can potentially unlock a wealth of untapped research and shape it by conducting sound scientific investigations to produce safe, efficacious and good quality remedies," the researchers say.

Peer-reviewed; Experimental study; Cells

In your coverage please use this URL to provide access to the freely available article in PLOS Neglected Tropical Diseases:

http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0008919

Citation: Twumasi EB, Akazue PI, Kyeremeh K, Gwira TM, Keiser J, Cho-Ngwa F, et al. (2020) Antischistosomal, antionchocercal and antitrypanosomal potentials of some Ghanaian traditional medicines and their constituents. PLoS Negl Trop Dis 14(12): e0008919. https://doi.org/10.1371/journal.pntd.0008919

Funding: DOS, KK, RKA, AF, LEA, RAO are grant recipients of the Worldwide Universities Network Research Development Fund 2017 from the Worldwide Universities Network (UK) and grant number 18-191 RG/CHE/AF/AC_G - FR 3240303659 from The

World Academy of Sciences. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Competing Interests: The authors have declared that no competing interests exist.

http://bit.ly/2KPk5uy

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

A massive study published in 2020 found evidence that blood iron levels could play a role in influencing how long you live.

David Nield

It's always important to take longevity studies with a big grain of salt, but the research was impressive in its breadth, covering genetic information from well over 1 million people across three public databases. It also focused on three key measures of ageing: lifespan, years lived free of disease (referred to as healthspan), and making it to an extremely old age (AKA longevity).

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

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

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

"We speculate that our findings on iron metabolism might also start to explain why very high levels of iron-rich red meat in the diet has been linked to age-related conditions such as heart disease." While correlation doesn't necessarily mean causation, the researchers used a statistical technique called Mendelian randomisation to reduce bias and attempt to infer causation in the data.

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

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

"It is clear from the association of age-related diseases and the well-known ageing loci APOE and FOXO3 that we are capturing the human ageing process to some extent," wrote the researchers in their paper published in July 2020.

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

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

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

"Our ultimate aim is to discover how ageing is regulated and find ways to increase health during ageing," says Joris Deelen who studies the biology of ageing at the Max Planck Institute for Biology of Ageing in Germany. "The 10 regions of the genome we have discovered that are linked to lifespan, healthspan, and longevity are all exciting candidates for further studies."

The research has been published in *Nature Communications*.

http://bit.ly/3hEdDT0

Endangered ferrets get experimental COVID-19 vaccine

While humans are still awaiting a jab with a coronavirus vaccine, endangered black-footed ferrets in Colorado have already gotten their shots.

By Stephanie Pappas - Live Science Contributor

One hundred and twenty of the ferrets (*Mustela nigripes*) — once thought completely extinct — have been vaccinated with an experimental veterinary COVID-19 vaccine, according to the Associated Press.

Here, black-footed ferrets are being bred in captivity in northern Colorado.
(Image: © Kathryn Scott Osler/The Denver Post via Getty Images)

Ferrets are highly susceptible to dying from SARS-CoV-2, the virus that causes COVID-19. Minks, a close cousin of ferrets, have already been found to contract coronavirus in fur farms and, alarmingly, in the wild. This is dangerous because any time the virus transmits between humans and animals, it has more opportunities to develop mutations.

"For highly contagious respiratory viruses, it's really important to be mindful of the animal reservoir," Corey Casper, a vaccinologist and chief executive of the Infectious Disease Research Institute in Seattle, told Colorado Public Radio (CPR). "If the virus returns to the animal host and mutates, or changes, in such a way that it could be reintroduced to humans, then the humans would no longer have that immunity. That makes me very concerned."

Black-footed ferrets are native to grasslands on the northern Great Plains. They were once believed to be extinct, but a few individuals were rediscovered in Wyoming in 1981, according to the U.S. Fish & Wildlife Service. Thanks to a captive breeding and release program, an estimated 370 black-footed ferrets exist in the wild.

Due to these low numbers and ferrets' susceptibility to coronaviruses, conservationists feared the SARS-CoV-2 pandemic would threaten this fragile recovery. Scientists at the National Black-footed Ferret Conservation Center near Fort Collins, Colorado, began injecting their captive breeding population with an experimental vaccine in late summer. The vaccine is different from the ones thus far approved in humans. It uses a purified segment of the vaccine — the spike protein — and an adjuvant chemical that promotes immune response rather than the mRNA platform used by the human coronavirus vaccines.

The center has now completed the inoculations, leaving 60 ferrets unvaccinated in case something goes wrong with the vaccine, according to CPR.

So far, the vaccinated ferrets appear healthy, and tests show SARS-CoV-2 antibodies in their blood. However, it's not yet clear whether the vaccine actually protects against the disease, because those efficacy trials have not yet been completed in the ferrets. Efficacy trials are the equivalent of the Phase 3 trials in humans that recently enabled Pfizer and Moderna's vaccines to receive emergency use authorization (EUA) from the Food and Drug Administration (FDA).

"We can do these sorts of things experimentally in animals that we can't do in humans," Rocke told CPR.

http://bit.ly/2X3tdOm

New UK COVID-19 vaccine recommendations say 'it is reasonable' for people to mix and match different shots, even though there's not yet evidence that works

Hilary Brueck

With both AstraZeneca and Pfizer's shots now authorized for emergency use, the UK has two different COVID-19 vaccines

available to fight the pandemic. Both of them require people to get two shots, several weeks apart. But, if people forget which one they got first, or, if providers run out of one kind or the other, the UK government is now saying: no worries.

In guidance freshly updated on New Year's Eve, one day after AstraZeneca's vaccine was authorized for use in the UK, the British government suggested that people may mix and match their two COVID-19 shots — and government experts even think there's a chance people may get better protection from coronavirus infections in that way.

If "the same vaccine is not available, or if the first product received is unknown, it is reasonable to offer one dose of the locally available product to complete the schedule," the UK's new advice for providers reads.

However, both experts and government officials agree that mixing two vaccines together in the hopes of providing people with more robust protection from coronavirus infections is still a risky, untested strategy.

The 'Wild West' of vaccination campaigns

Even the British government writes in its new guidance that "there is no evidence on the interchangeability of the COVID-19 vaccines." "We're kind of in this Wild West," Dr. Phyllis Tien, an infectious disease physician at the University of California, San Francisco, told the New York Times. "None of this is being data driven right now."

It's possible that mixing different vaccines together could provide people with more robust protection from infection — and government officials in the UK are launching a so-called 'mix and match' trial, to find out if that's the case.

"The idea is that you can maximize the strength of that immune response to protect people," Kate Bingham, chair of the UK's vaccine task force, said during a recent briefing.

Britain has cleared two different vaccines for emergency use so far. First, Pfizer/BioNTech's vaccine was given the green light in the UK on December 2, and then AstraZeneca/University of Oxford's followed, on December 30. Both of these vaccines were designed to be administered as two shots, given several weeks apart. But they are not the same kind of inoculation, nor were they designed to be taken together.

Pfizer's vaccine is a new kind of messenger RNA vaccine, while AstraZeneca is using viral vector technology. Working together, it's possible they could provide people with a solid one-two punch of both good cellular (from AstraZeneca) and good antibody (from Pfizer) virus response, as Business Insider's Kate Duffy recently reported.

"Antibodies block the uptake of viruses into cells, and the cellular T-cells identify those cells that have been infected and take them out," Bingham said. "You ideally want to have both."

But John Moore, a vaccine expert at Cornell University, wants more evidence that strategy can really work before it is recommended.

Moore told the Times that officials "seem to have abandoned science completely now and are just trying to guess their way out of a mess."

Less than 2% of the population in the UK is vaccinated, with a fast-spreading new variant on the loose

The UK has recently been slammed by more coronavirus infections, a surging wave fueled in part by what is suspected to be a fast-spreading coronavirus variant. The new variant, called B.1.1.7, is not more deadly, and experts expect vaccines will be successful at fighting it, too.

The country is now pushing to get as many people vaccinated as possible with one COVID-19 vaccine dose, before administering them their second booster shot.

"At this stage of the pandemic, prioritizing the first doses of vaccine for as many people as possible on the priority list will protect the greatest number of at risk people overall in the shortest possible time," UK officials said in a statement on Tuesday.

Fewer than 1.5% of people in the UK have gotten shots so far, according to Bloomberg's COVID-19 vaccine tracker.

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Why Do We Dream? A New Theory on How It Protects Our Brains

A gift bestowed on the brain by evolution: tremendous adaptability

By David Eagleman and Don Vaughn

When he was two years old, Ben stopped seeing out of his left eye. His mother took him to the doctor and soon discovered he had retinal cancer in both eyes. After chemotherapy and radiation failed, surgeons removed both his eyes. For Ben, vision was gone forever.

But by the time he was seven years old, he had devised a technique for decoding the world around him: he clicked with his mouth and listened for the returning echoes. This method enabled Ben to determine the locations of open doorways, people, parked cars, garbage cans, and so on. He was echolocating: bouncing his sound waves off objects in the environment and catching the reflections to build a mental model of his surroundings.

Echolocation may sound like an improbable feat for a human, but thousands of blind people have perfected this skill, just like Ben did. The phenomenon has been written about since at least the 1940s, when the word "echolocation" was first coined in a *Science* article titled "Echolocation by Blind Men, Bats, and Radar."

How could blindness give rise to the stunning ability to understand the surroundings with one's ears? The answer lies in a gift bestowed on the brain by evolution: tremendous adaptability.

Whenever we learn something new, pick up a new skill, or modify our habits, the physical structure of our brain changes. Neurons, the cells responsible for rapidly processing information in the brain, are interconnected by the thousands—but like friendships in a community, the connections between them constantly change: strengthening, weakening, and finding new partners. The field of neuroscience calls this phenomenon "brain plasticity," referring to the ability of the brain, like plastic, to assume new shapes and hold them. More recent discoveries in neuroscience suggest that the brain's brand of flexibility is far more nuanced than holding onto a shape, though. To capture this, we refer to the brain's plasticity as "livewiring" to spotlight how this vast system of 86 billion neurons and 0.2 quadrillion connections rewires itself every moment of your life.

Neuroscience used to think that different parts of the brain were predetermined to perform specific functions. But more recent discoveries have upended the old paradigm. One part of the brain may initially be assigned a specific task; for instance, the back of our brain is called the "visual cortex" because it usually handles sight. But that territory can be reassigned to a different task. There is nothing special about neurons in the visual cortex: they are simply neurons that happen to be involved in processing shapes or colors in people who have functioning eyes. But in the sightless, these same neurons can rewire themselves to process other types of information.

Mother Nature imbued our brains with flexibility to adapt to circumstances. Just as sharp teeth and fast legs are useful for survival, so is the brain's ability to reconfigure. The brain's livewiring allows for learning, memory, and the ability to develop new skills.

In Ben's case, his brain's flexible wiring repurposed his visual cortex for processing sound. As a result, Ben had more neurons

available to deal with auditory information, and this increased processing power allowed Ben to interpret soundwaves in shocking detail. Ben's super-hearing demonstrates a more general rule: the more brain territory a particular sense has, the better it performs.

Recent decades have yielded several revelations about livewiring, but perhaps the biggest surprise is its rapidity. Brain circuits reorganize not only in the newly blind, but also in the sighted who have temporary blindness. In one study, sighted participants intensively learned how to read Braille. Half the participants were blindfolded throughout the experience. At the end of the five days, the participants who wore blindfolds could distinguish subtle differences between Braille characters much better than the participants who didn't wear blindfolds. Even more remarkably, the blindfolded participants showed activation in visual brain regions in response to touch and sound. When activity in the visual cortex was temporarily disrupted, the Braille-reading advantage of the blindfolded participants went away. In other words, the blindfolded participants performed better on the touch-related task because their visual cortex had been recruited to help. After the blindfold was removed, the visual cortex returned to normal within a day, no longer responding to touch and sound.

But such changes don't have to take five days; that just happened to be when the measurement took place. When blindfolded participants are continuously measured, touch-related activity shows up in the visual cortex in about an hour.

What does brain flexibility and rapid cortical takeover have to do with dreaming? Perhaps more than previously thought. Ben clearly benefited from the redistribution of his visual cortex to other senses because he had permanently lost his eyes, but what about the participants in the blindfold experiments? If our loss of a sense is only temporary, then the rapid conquest of brain territory may not be so helpful.

And this, we propose, is why we dream.

In the ceaseless competition for brain territory, the visual system has a unique problem: due to the planet's rotation, all animals are cast into darkness for an average of 12 out of every 24 hours. (Of course, this refers to the vast majority of evolutionary time, not to our present electrified world.) Our ancestors effectively were unwitting participants in the blindfold experiment, every night of their entire lives.

So how did the visual cortex of our ancestors' brains defend its territory, in the absence of input from the eyes?

We suggest that the brain preserves the territory of the visual cortex by keeping it active at night. In our "defensive activation theory," dream sleep exists to keep neurons in the visual cortex active, thereby combating a takeover by the neighboring senses. In this view, dreams are primarily visual precisely because this is the only sense that is disadvantaged by darkness. Thus, only the visual cortex is vulnerable in a way that warrants internally-generated activity to preserve its territory.

In humans, sleep is punctuated by rapid eye movement (REM) sleep every 90 minutes. This is when most dreaming occurs. (Although some forms of dreaming can occur during non-REM sleep, such dreams are abstract and lack the visual vividness of REM dreams.)

REM sleep is triggered by a specialized set of neurons that pump activity straight into the brain's visual cortex, causing us to experience vision even though our eyes are closed. This activity in the visual cortex is presumably why dreams are pictorial and filmic. (The dream-stoking circuitry also paralyzes your muscles during REM sleep so that your brain can simulate a visual experience without moving the body at the same time.) The anatomical precision of these circuits suggests that dream sleep is biologically

important—such precise and universal circuitry rarely evolves without an important function behind it.

The defensive activation theory makes some clear predictions about dreaming. For example, because brain flexibility diminishes with age, the fraction of sleep spent in REM should also decrease across the lifespan. And that's exactly what happens: in humans, REM accounts for half of an infant's sleep time, but the percentage decreases steadily to about 18% in the elderly. REM sleep appears to become less necessary as the brain becomes less flexible.

Of course, this relationship is not sufficient to prove the defensive activation theory. To test it on a deeper level, we broadened our investigation to animals other than humans. The defensive activation theory makes a specific prediction: the more flexible an animal's brain, the more REM sleep it should have to defend its visual system during sleep. To this end, we examined the extent to which the brains of 25 species of primates are "pre-programmed" versus flexible at birth. How might we measure this? We looked at the time it takes animals of each species to develop. How long do they take to wean from their mothers? How quickly do they learn to walk? How many years until they reach adolescence? The more rapid an animal's development, the more pre-programmed (that is, less flexible) the brain.

As predicted, we found that species with more flexible brains spend more time in REM sleep each night. Although these two measures—brain flexibility and REM sleep—would seem at first to be unrelated, they are in fact linked.

As a side note, two of the primate species we looked at were nocturnal. But this does not change the hypothesis: whenever an animal sleeps, whether at night or during the day, the visual cortex is at risk of takeover by the other senses. Nocturnal primates, equipped with strong night vision, employ their vision throughout the night as they seek food and avoid predation. When they subsequently sleep during the day, their closed eyes allow no visual input, and thus, their visual cortex requires defense.

Dream circuitry is so fundamentally important that it is found even in people who are born blind. However, those who are born blind (or who become blind early in life) don't experience visual imagery in their dreams; instead, they have other sensory experiences, such as feeling their way around a rearranged living room or hearing strange dogs barking. This is because other senses have taken over their visual cortex. In other words, blind and sighted people alike experience activity in the same region of their brain during dreams; they differ only in the senses that are processed there. Interestingly, people who become blind after the age of seven have more visual content in their dreams than those who become blind at younger ages. This, too, is consistent with the defensive activation theory: brains become less flexible as we age, so if one loses sight at an older age, the non-visual senses cannot fully conquer the visual cortex.

If dreams are visual hallucinations triggered by a lack of visual input, we might expect to find similar visual hallucinations in people who are slowly deprived of visual input while awake. In fact, this is precisely what happens in people with eye degeneration, patients confined to a tank-respirator, and prisoners in solitary confinement. In all of these cases, people see things that are not there.

We developed our defensive activation theory to explain visual hallucinations during extended periods of darkness, but it may represent a more general principle: the brain has evolved specific circuitry to generate activity that compensates for periods of deprivation. This might occur in several scenarios: when deprivation is regular and predictable (e.g., dreams during sleep), when there is damage to the sensory input pathway (e.g., tinnitus or phantom limb syndrome), and when deprivation is unpredictable

(e.g., hallucinations induced by sensory deprivation). In this sense, hallucinations during deprivation may in fact be a feature of the system rather than a bug.

We're now pursuing a systematic comparison between a variety of species across the animal kingdom. So far, the evidence has been encouraging. Some mammals are born immature, unable to regulate their own temperature, acquire food, or defend themselves (think kittens, puppies, and ferrets). Others are born mature, emerging from the womb with teeth, fur, open eyes, and the abilities to regulate their temperature, walk within an hour of birth, and eat solid food (think guinea pigs, sheep, and giraffes). The immature animals have up to 8 times more REM sleep than those born mature. Why? Because when a newborn brain is highly flexible, the system requires more effort to defend the visual system during sleep.

Since the dawn of communication, dreams have perplexed philosophers, priests, and poets. What do dreams mean? Do they portend the future? In recent decades, dreams have come under the gaze of neuroscientists as one of the field's central unsolved mysteries. Do they serve a more practical, functional purpose? We suggest that dream sleep exists, at least in part, to prevent the other senses from taking over the brain's visual cortex when it goes unused. Dreams are the counterbalance against too much flexibility. Thus, although dreams have long been the subject of song and story, they may be better understood as the strange lovechild of brain plasticity and the rotation of the planet.

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http://bit.ly/3b7Inum

When a little bit of poison is good for you: Inside the theory of dose response

How the concept of dose response shaped modern science and vaccinology

By Amit Chandra - Luke Shors

"For if one drinks much from a bottle marked 'poison,' it's almost certain to disagree with one sooner or later."

—Lewis Carroll, "Alice's Adventures in Wonderland"

In the early 16th century, a Swiss physician named Paracelsus changed the course of the healing arts with his theories on chemical treatments for disease. A literal renaissance man given the era, he was part scientist, part alchemist, and part philosopher. Three hundred years before the advent of Pasteur's germ theory, Paracelsus advised patients to keep their wounds clean to avoid infection. His study of chemicals revealed both their curative and harmful properties, and he noted that any treatment turns toxic once the dose is high enough. Paracelsus' simple yet profound insight that "the dose makes the poison" challenged the prevailing wisdom that poisons were inherently toxic. He noted that the known poisons of the day were substances that were toxic at low-doses. Yet, dilute these substances enough and they could be rendered harmless or, in some cases, even beneficial.

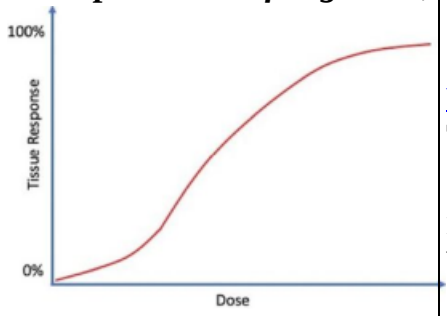
This theory is now known as **dose response**. It has become one of the key frameworks of environmental science, modern medicine, and public health. Put simply, it states that the larger the dose of a chemical or exposure, the greater the magnitude of its effect. Thus, low doses of a toxin can have zero to minimal effect, while large doses become deadly. For therapeutic chemicals, or "drugs," benefits initially rise with increasing doses before crossing a threshold toward toxicity, or overdose.

In modern medicine, dose response theory is foundational for both toxicology and pharmacology, and also carries over to the worlds of microbiology, virology, and oncology. Although in each scenario, the theory is labelled "dose response," its application differs according to the properties of the substance. In recent months, for example, dose response has been hotly debated alongside speculation on the exposure risk of COVID-19. What is the potential for virus exposure via the groceries you buy? What about the mail delivered to your home? Could you get sick from takeout food? The answer lies in the question: how much 'dose' is required to get ill?

A brief history of dose response theory ***Go To Video Page***

For many chemical substances, the dose response theory of toxicity depends on five important variables that predict a subject's response to an exposure:

1. ***The dose or amount;***
2. ***The chemical properties of the substance;***
3. ***The time over which the substance is administered;***
4. ***The characteristics of the subject that receives the dose; and***
5. ***The extent to which the subject is able to eliminate or metabolize the substance through the processes of digestion, metabolism, and excretion.***



If you plot the administered dose of a substance versus its effect on a living organism, you often get a "dose response" curve that typically resembles the letter 'S'.

As you can see in the curve, low level exposures may have no effect on an organism up to a certain threshold. For example, many adults are familiar with the toxic effects of drinking alcohol — just ask any college student how they feel on Sunday morning. Ripe bananas also contain trace amounts of alcohol, but few individuals eat a banana and worry about their ability to drive home. While a certain dose of alcohol causes intoxication, it has no harmful effect beneath its toxic threshold. As intoxication rises past a second threshold, its effect turns deadly.

Poisons and the canary in the coal mine

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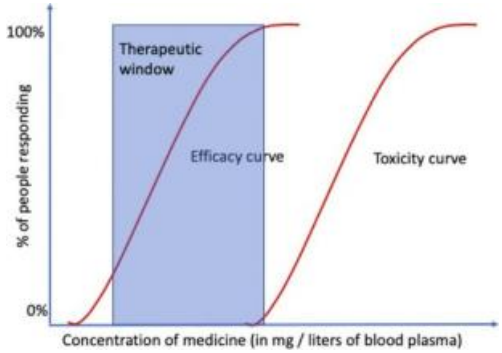
The "canary in a coal mine" is a well-known idiom that has a historical antecedent. In the early 20th century, miners brought captive birds with them into the mine shafts. The humble canary would fall dead as a result of increasing toxins — particularly carbon monoxide — in the air. Being a small creature with rapid respiration and a fast metabolism, toxins accumulate in a bird's system much faster than they would in larger animals. Thus, the miners received advanced warning of an exposure of which they would otherwise be unaware. In other words, the canary had a lower dose response threshhold than humans.

Animals that are prone to showing toxic effects and serve as harbingers of environmental degradation have come to be known as "sentinel species." Cats are susceptible to mercury poisoning, crayfish to water pollution, and bees to air pollution. Even in antiquity, people recognized that when the plague arrived, the rats were the first to die.

The dose also makes the medicine

If the dose makes the poison, it also makes the medicine. For medicines, small doses will have minimal to no effect. Larger doses begin to demonstrate their beneficial effect above a threshold — often referred to by clinicians as the "effective" or "therapeutic" dose. Increasing doses from this threshold increases the magnitude of the therapeutic effect up until it approaches toxic levels. This range is known as the therapeutic window.

Acetaminophen, for example, is safely metabolized by liver enzymes within its therapeutic window. Metabolism is a multi-stage process that, at an intermediate stage, generates a toxic metabolite known as N-acetyl-p-benzoquinone imine (NAPQI). If a person has chronic liver disease, or if they take too much of the drug, NAPQI accumulates in their bloodstream and eventually causes permanent liver failure.



Over several centuries, medical researchers have used a process of trial and error to find therapeutic functions of substances long regarded as toxins. The bark, leaves, and seeds of the yew tree (Taxus baccata) have been known to be poisonous for centuries. The witches' brew from Shakespeare's "Macbeth" even cited "slips of yew, silvered in the moon's eclipse" as a main ingredient. Yet, the compound Paclitaxel, derived from the same plant, treats opportunistic infections in AIDS patients as well as a variety of cancers.

For cancer chemotherapy treatments in particular, one must walk a fine line, using the toxicity of a substance to preferentially destroy cancer cells without killing the patient. In this way, tumors are similar to sentinel species. The rapid rate of cellular metabolism that makes cancer cells dangerous also makes them susceptible to toxic exposures as they more quickly incorporate the dose. Cancer treatments then exploit the differential uptake of chemotherapy between healthy and tumor cells to deliver a targeted dose.

Is dose response theory always right?

Paracelsus' doctrine may have been profound, but does that mean it is universally correct? There are at least four cases that complicate dose-response theory as succinctly stated by Paracelsus:

Carcinogens. It is generally believed that there is no "safe" dose for exposure to cancer causing agents and hence, carcinogens are inherently poisonous. Although the likelihood of cancer increases with the exposure dose, a single mutation to a single DNA base pair can be enough to result in cancer.

A cancerous cell, through its uncontrolled growth, escalates its own dose. The seemingly harmless single cancer cell divides to give rise to two such cells, then four, then eight, triggering a geometric expansion towards a cancerous tumor.

Even this line of reasoning however, is disputed by additional nuance. Communities that live at high altitudes are exposed to greater levels of cosmic radiation. Assuming a linear relationship between carcinogen dose (UV radiation) and cancer even at low doses, one would expect these communities to demonstrate higher rates of certain cancers. Yet, no such evidence exists to reveal this expected cancer cluster. This has led to the hypothesis that low-doses of radiation stimulate mechanisms in the body that serve to repair DNA damage. The body's mechanism for culling dead or dangerous cells may effectively limit these micro dose exposures before they give rise to cancerous masses.

Bioaccumulators In 1958, after noting rising mortality in birds of prey following the widespread spraying of insecticide in New England, conservation biologist Rachel Carson identified the agricultural pesticide DDT as the highly toxic culprit. This finding was published in her influential book Silent Spring. Because raptors were at the top of the food pyramid, the fish they preyed on had in turn eaten smaller fish, which had nibbled on plants contaminated by runoff. At each level of the feeding chain, DDT levels became further concentrated in the organism.

his process, known as "bioaccumulation," arises from the fact that some toxins cannot be metabolized or excreted, and thus become increasingly concentrated up the food chain. Consequently, although there may be a safe dose for a single exposure, bioaccumulation results in the exposure becoming more pronounced over time until a harmful dose is reached. Applying this principle of bioaccumulation to people, particularly those who eat meat and are, therefore, exposed to higher accumulated doses, led to the wide-scale ban of DDT in the US and other high-income countries.

Endocrine Disruptors. Compounds that disrupt the human endocrine system are another example where the apparent simplicity of the dose response curve begins to break down. Endocrine disruptors are chemicals that are similar in structure to the hormones circulating in the human body. Hormone imbalances can have dire health consequences, particularly for the human fetus. Fetal exposure to a microdose of a certain sex hormone can lead to the malformation of sex organs, while the same dose exposure would have zero impact on an adult. Even stranger, the dose response curve for endocrine disruptors may be "non-monotonic" — that is, not show a consistent relationship between increasing dose and increasing effect. Small doses may yield significant effects, medium doses may have no effect, and high doses again may show an effect. Any number of puzzling curves have been proposed by toxicologists and researchers in order to explain these phenomena. They all call into question the dose response relationship conceived of by Paracelsus.

Viruses and bacteria. Like cancer, viruses and bacteria have the innate capability to escalate their own dose. A single viral particle that infects a host cell can make millions of copies of itself. This implies that, in theory, there is no lower limit or no truly safe dose. Yet, like cancers, we also do not typically see this play out. Some noroviruses may cause an infection in 50% of people exposed to as low a dose as 20 viral particles. Meanwhile, other viruses and bacteria may be harmless, or in some cases symbiotic, at much higher numbers. The human gut, for example, is a celebration of the therapeutic benefit of many bacteria and even some viruses that work to maintain the body's homeostasis.

What about for the novel coronavirus?

Studies of swab samples demonstrate that New York subways are populated by all manner of viruses and microbes, including everything from anthrax to the plague. And yet exposure of millions of subway riders to these pathogens do not lead to clinical cases of exotic diseases. Similarly, more and more evidence suggests handling a bag of groceries with traces of SARS-CoV-2 virus is not going to make most people sick.

Although in theory there may be no safe dose, as a practical matter, many humans are quite resilient to all kinds of exposures. Recent evidence demonstrates that wearing masks protects wearers by reducing the exposure dose of COVID-19.

Of course, some of us may be the proverbial 'canary in the coal mine' for certain exposures based on our increased susceptibility to the disease. And in the case of many chemicals on the market today, we are all canaries in the coal mine. The experiment, as it were, is ongoing.

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