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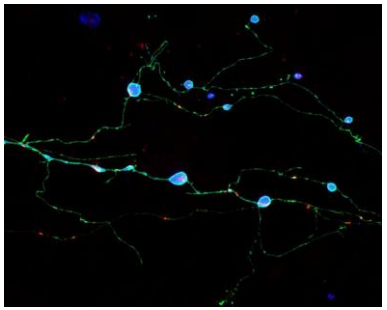
How Toxic Aggregates Form and Kill Brain Cells in Prion Diseases

Scripps Research Discovery Illuminates How Brain Cells Die in Prion Diseases

Researchers show how toxic aggregates are formed inside brain cells, and how to block the cell-killing process—which may also be at work in Alzheimer's and other neurodegenerative diseases.



Neurons grown in culture expressing a mutant prion protein (cyan) that cause prion disease in humans. These neurons display swollen axons that contain toxic mutant prion protein aggregates. Chassefeyre et al. identified genes that account for the formation of these aggregates and showed that reducing their function can inhibit aggregate formation and prevent neuronal dysfunction. **Credit: Adriaan Verhelle and Yin Wu (Scripps Research)**

Prion diseases, such as Creutzfeldt-Jakob Disease (CJD), are fast-moving, fatal dementia syndromes associated with the formation of aggregates of the prion protein, PrP. How these aggregates form within and kill brain cells has never been fully understood, but a new study from scientists at Scripps Research suggests that the aggregates kill neurons by damaging their axons, the narrow nerve fibers through which they send signals to other neurons.

The accumulation of protein aggregates in axons, along with axonal swellings and other signs of dysfunction, are also early features of other neurodegenerative disorders including Alzheimer's and Parkinson's diseases. The discovery of how these prion aggregates form in axons and how to inhibit them, reported in *Science Advances*, may ultimately have a significance that goes far beyond prion diseases.

"We're hopeful that these findings will lead to a better understanding of prion and other neurodegenerative diseases, as well as new strategies for treating them," says study senior author Sandra Encalada, PhD, Arlene and Arnold Goldstein Associate Professor in the Department of Molecular Medicine at Scripps Research.

The researchers in their study closely observed mutant, disease-causing copies of the prion-disease protein PrP forming large aggregates in the axons of neurons, but not in the neurons' main cell bodies. The formation of these aggregates was followed by signs of axon dysfunction and ultimately neuronal death. The scientists found evidence that neurons' waste-disposal processes normally are able to cope with such aggregates when they are within or close to neurons' main cell bodies, but are much less able to do so when the aggregates accumulate far out within axons.

The researchers also identified a complex of key proteins as being responsible for steering PrP into axons and causing aggregation associated with large axonal swellings. They demonstrated that by silencing any one of these proteins they could inhibit the aggregates from forming and protect the neurons from damage and death.

Vulnerable axons

CJD is the most common human prion disease, occurring at the rate of about one case per million people per year worldwide. Most cases are thought to arise spontaneously when PrP somehow is altered in the brain and starts aggregating. Because these aggregates grow by a chain-reaction process that draws in healthy copies of PrP, they can transmit CJD in rare cases —for example, during corneal transplant surgery—from one person to another. About 15 percent of cases are hereditary, caused by mutations that make PrP more likely to aggregate. Prion disorders occur in other mammals and are thought to be due to similar toxic aggregations of different species' PrP proteins.

In the study, Encalada's team used mouse brain cells containing mutant PrP, along with microscopic motion-picture techniques, to

study the initial accumulation of PrP aggregates in axons. A neuron's axon is often very long in relation to its main body—the soma—and has been found to be uniquely vulnerable to disruptions of its delicate systems for transporting essential molecules and getting rid of waste.

PrP's ordinary function in neurons has never been clear, but the protein appears to be normally secreted, via sac-like containers called vesicles, from the soma and the axon, where it sometimes returns to be recycled or degraded as waste. The researchers found in their experiments that mutant PrP produced in the soma is also largely encapsulated in vesicles that get moved into the axon along railways called microtubules.

This movement involves a somewhat complex vesicle trafficking system, and the researchers observed that this system shunts much of the PrP far out into axons, where PrP-containing vesicles gather and merge. Mutant PrP in this situation forms large aggregates—Encalada calls them endoggresomes—that axons can't get rid of. The aggregates lead to axonal swellings, and other signs of dysfunction including reduced neuronal calcium signaling, and ultimately a much faster neuronal death rate compared to neurons with normal PrP.

The researchers also found a way of countering endoggresomes formation. They identified four proteins, Arl8, kinesin-1, Vps41, and SKIP, that are responsible for directing PrP-containing vesicles into axons, carrying them far out into the soma, and merging them with other PrP-containing vesicles to trigger aggregate formation. When they silenced any of these proteins, far fewer PrP-containing vesicles entered axons, the axons showed few or no signs of aggregation, and the neurons functioned normally or almost normally and survived just as well as normal brain cells.

The results point to the tantalizing possibility that prion diseases, and perhaps many other protein-aggregate diseases of the brain, can be prevented or treated by interrupting at least transiently the trafficking process that brings vesicle-encapsulated, aggregate-prone proteins out into axons.

"We're very enthusiastic about discovering molecules that can inhibit this aggregate-forming pathway and studying the effects of such inhibitors in animal models of prion and other neurodegenerative diseases," Encalada says.

Reference: "Endosomal sorting drives the formation of axonal prion protein endoggresomes" by Romain Chassefeyre, Tai Chaiamarit, Adriaan Verhelle, Sammy Weiser Novak, Leonardo R. Andrade, André D. G. Leitão, Uri Manor and Sandra E. Encalada, 22 December 2021, Science.

DOI: 10.1126/sciadv.abg3693

"Endosomal Sorting Drives the Formation of Axonal Prion Protein Endoggresomes" was co-authored by Romain Chassefeyre, Tai Chaiamarit, Adriaan Verhelle, André Leitão and Sandra Encalada, all of Scripps Research; and Sammy Weiser Novak, Leonardo Andrade and Uri Manor, of the Salk Institute for Biological Studies.

The research was funded by the National Institutes of Health (R01AG049483) and others.

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What Causes Cancer? There's a Lot We Don't Know

People with cancer are often desperate to know what caused their disease. Was it something they did? Something they could have prevented?

Diana Kwon

Overall, experts estimate that about 40% of cancers can be explained by known, often modifiable risk factors. Smoking and obesity represent the primary drivers, though a host of other factors — germline mutations, alcohol, infections, or environmental pollutants like asbestos — contribute to cancer risk as well.

But what about the remaining 60% of cancers?

A new analysis suggests that although many of these cases likely have an underlying lifestyle or environmental component, experts still do not fully understand their origin story. And a small but significant number may simply be due to chance.

Here's what experts suspect those missing causes might be, and

why they can be so difficult to confirm.

Possibility 1: Known Risk Factors Contribute More Than We Realize

For certain factors, a straight line can be drawn to cancer.

Take smoking, for instance. Decades of research have helped scientists clearly delineate tobacco's carcinogenic effects. Researchers have pinpointed a unique set of mutations in the tumors of smokers that can be seen when cells grown in a dish are exposed to the carcinogens present in tobacco.

In addition, experts have been able to collect robust data from epidemiologic studies on smoking prevalence as well as associated cancer risks and deaths, in large part because an individual's lifetime tobacco exposure is fairly easy to measure.

"The evidence for smoking is incredibly consistent," Paul Brennan, PhD, a cancer epidemiologist at the World Health Organization's International Agency for Research on Cancer (IARC), told *Medscape Medical News*.

For other known risk factors, such as obesity and air pollution, many more questions than answers remain.

Because of the limitations in how such factors are measured, we are likely downplaying their effects, says Richard Martin, PhD, a professor of clinical epidemiology at the University of Bristol, United Kingdom.

Take obesity. Excess body weight is associated with an increased risk of at least 13 cancers. Although risk estimates vary by study and cancer type, according to a global snapshot from 2012, being overweight or obese accounted for about 4% of all cancers worldwide — 1% in low-income countries and as high as 8% in high-income countries.

However, Brennan believes "we have underestimated the effect of obesity [on cancer]."

A key reason, he says, is most studies use body mass index (BMI) to determine whether someone is overweight or obese, but BMI is a poor measure of body fat. BMI does not differentiate between fat and muscle, which means two people with the same height and weight can have the same BMI, even if one is an athlete who eats lean meats and vegetables while the other lives a sedentary life and consumes large quantities of processed foods and alcohol.

On top of that, studies often only calculate a person's BMI once, and a single measurement can't tell you how a person's weight has fluctuated in recent years or across different stages of their life. However, recent analyses suggest that obesity status over time may be more relevant to cancer risk than one-off measures.

In addition, many studies now suggest that alterations to our gut microbes and high blood insulin level — often seen in people who are overweight or obese — may increase the risk of cancer and speed the growth of tumors.

When these additional factors are considered, the impact of excess body fat may ultimately play a much more significant role in cancer risk. In fact, according to Brennan, "if we estimate [the effects of obesity] properly, it might at some point become the main cause of cancer."

Possibility 2: Environmental or Lifestyle Factors Remain Under the Radar

Researchers have linked many substances we consume or are exposed to in our daily lives — air pollution, toxins from industrial waste, and highly processed foods — to cancer. But the extent or contribution of potential carcinogens in our surroundings, particularly those found almost everywhere at low levels, is still largely unknown.

One simple reason is the effects of many of these substances remain difficult to assess. For instance, it is much harder to study the impact of pollutants found in food or water, in which a given population will share similar exposure levels, vs tobacco, where it

is possible to compare a person who smokes a pack of cigarettes a day to a person who does not smoke.

"If you've got exposures that are ubiquitous, it can be difficult to discern their [individual] roles," Martin said. "There are many causes that we [likely] don't really know because everyone has been exposed."

On the flip side, some carcinogenic substances that people encounter for limited periods might be missed if studies are not performed at the time of exposure.

"What's in the body at age 40 may not reflect what you were exposed at age 5 to 10 on the playground or soccer field," said Graham Colditz, MD, PhD, an epidemiologist and public health expert at Washington University in St. Louis, Missouri. "The technology keeps changing so we can get better measures of what you've got exposure to today, but how that relates to 5, 10, 15 years ago is probably very variable."

In addition, researchers have found that many carcinogens do not cause specific mutations in a cell's DNA; rather, studies suggest that most carcinogens lead to cancer-promoting changes in cells, such as inflammation.

"We need to think of *how* potential carcinogens are causing cancer," Brennan said. Instead of provoking mutations, potential carcinogens may use a "whole other kind of pathway," he explained. When, for instance, inflammation becomes chronic, it may spur a cascade of events that ultimately leads to cancer.

Finally, we don't know much about what causes cancers in low- and middle-income countries. Most of the research to date has been in high-income countries, such the US, Australia, and parts of Europe.

"There's a real lack of robust epidemiological studies in other parts of the world, Latin America, Africa, parts of Asia," Marc Gunter, PhD, a molecular epidemiologist at the IARC, told *Medscape Medical News.*

Possibility 3: Some Cancers Occur by Chance

When it comes to cancer risk, an element of chance may be at play. Cancer can occur in individuals who have very little exposure to known carcinogens or have no family history of cancer.

"We all know there are people who get cancer who eat very healthy diets, are never overweight, and never smoke," Gunter said. "Then there are people on the other end of the extreme who don't get cancer."

But what fraction of cancers are attributable to chance?

A controversial 2017 study published in *Science* suggested that, based on the rate of cell turnover in healthy tissues in the lung, pancreas, and other parts of the body, only about one third of cancers could be linked to environmental or genetic factors. The rest, the authors claimed, occurred because of random mutations that accumulated in a person's DNA — in other words, bad luck.

That study brought on a flood of criticism from scientists who pointed to serious flaws in the work that led the researchers to significantly overestimate the share of chance-related cancers.

The actual proportion of cancers that occur by chance is much lower, according to Brennan. "If you look at international comparisons [of cancer rates] and take a conservative estimate, you see that maybe 10% or 15% of cancers are really chance," he said.

Whether some cancers are due to bad luck or undiscovered risk factors remains an open question.

But the bottom line is many unknown causes of cancer are likely environmental- or lifestyle-related, which means that, in theory, they can be altered, even prevented.

"There is always going to be some element of chance, but you can modify your chance, depending on your lifestyle and maybe other factors, which we don't fully understand yet," Gunter said.

The good news is that when it comes to prevention, there are many ways to modify our behaviors — such as consuming fewer

processed meats, going for a daily walk, or getting vaccinated against cancer-causing viruses — to improve our chances of living cancer-free.

And as scientists better understand more about what causes cancer, possibilities for prevention will only grow.

"There is a constant, slow growth [in knowledge] that is lowering the overall risk of cancer," Brennan said. "We're never going to eliminate cancer, but we will be able to control it as a disease."

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How DNA is preserved in archaeological sediments for thousands of years

Retrieval of ancient human and faunal DNA from sediments offers exciting new opportunities to investigate the distribution of ancient organisms at sites where their skeletal remains are rare or absent

Sediments in which archaeological finds are embedded have long been regarded by most archaeologists as unimportant by-products of excavations. However, in recent years it has been shown that sediments can contain ancient biomolecules, including DNA. "The retrieval of ancient human and faunal DNA from sediments offers exciting new opportunities to investigate the geographical and temporal distribution of ancient humans and other organisms at sites where their skeletal remains are rare or absent," says Matthias Meyer, senior author of the study and researcher at the Max Planck Institute for Evolutionary Anthropology in Leipzig.

To investigate the origin of DNA in the sediment, Max Planck researchers teamed up with an international group of geoarchaeologists—archaeologists who apply geological techniques to reconstruct the formation of sediment and sites—to study DNA preservation in sediment at a microscopic scale. They used undisturbed blocks of sediment that had been previously removed from archaeological sites and soaked in synthetic plastic-like (polyester) resin. The hardened blocks were taken to the laboratory and sliced in sections for microscopic imaging and genetic analysis.

The researchers successfully extracted DNA from a collection of blocks of sediment prepared as long as 40 years ago, from sites in Africa, Asia, Europe and North America. "The fact that these blocks are an excellent source of ancient DNA—including that originating from hominins—despite often decades of storage in plastic, provides access to a vast untapped repository of genetic information. The study opens up a new era of ancient DNA studies that will revisit samples stored in labs, allowing for analysis of sites that have long since been back-filled, which is especially important given travel restriction and site inaccessibility in a pandemic world," says Mike Morley from Flinders University in Australia who led some of the geoarchaeological analyses.

Abundance of micro remains in the sediment matrix

The scientists used blocks of sediment from Denisova Cave, a site located in the Altai Mountains in South Central Siberia where ancient DNA from Neanderthals, Denisovans and modern humans has been retrieved, and showed that small organic particles yielded more DNA than sediment sampled randomly. "It clearly shows that the high success rate of ancient mammalian DNA retrieval from Denisova Cave sediments comes from the abundance of micro remains in the sediment matrix rather than from free extracellular DNA from feces, bodily fluids or decomposing cellular tissue potentially adsorbed onto mineral grains," says Vera Aldeias, co-author of the study and researcher at the University of Algarve in Portugal. "This study is a big step closer to understand precisely where and under what conditions ancient DNA is preserved in sediments," says Morley.

The approach described in the study allows highly localized micro-scale sampling of sediment for DNA analyses and shows that ancient DNA (aDNA) is not uniformly distributed in the sediment;

and that specific sediment features are more conducive to ancient DNA preservation than others. "Linking sediment aDNA to the archaeological micro-context means that we can also address the possibility of physical movement of aDNA between sedimentary deposits," says Susan Mentzer a researcher at the Senckenberg Centre for Human Evolution and Palaeoenvironment (Germany).

Diyendo Massilani, the lead author of the study, was able to recover substantial amounts of Neanderthal DNA from only a few milligrams of sediment. He could identify the sex of the individuals who left their DNA behind, and showed that they belonged to a population related to a Neanderthal whose genome was previously reconstructed from a bone fragment discovered in the cave. "The Neanderthal DNA in these small samples of plastic-embedded sediment was far more concentrated than what we typically find in loose material," he says. "With this approach it will become possible in the future to analyze the DNA of many different ancient human individuals from just a small cube of solidified sediment. It is amusing to think that this is presumably so because they used the cave as a toilet tens of thousands of years ago."

The research was published in *Proceedings of the National Academy of Sciences*.

More information: *Microstratigraphic preservation of ancient faunal and hominin DNA in Pleistocene cave sediments, Proceedings of the National Academy of Sciences, DOI: 10.1073/pnas.2113666118*

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"Battle of the Sexes"' Begins in Womb – Father's and Mother's Genes Tussle Over Nutrition

Cambridge scientists have identified a key signal that the fetus uses to control its supply of nutrients from the placenta, revealing a tug-of-war between genes inherited from the father and from the mother.

The study, carried out in mice, could help explain why some babies grow poorly in the womb.

As the fetus grows, it needs to communicate its increasing needs for food to the mother. It receives its nourishment via blood vessels in the placenta, a specialized organ that contains cells from both baby and mother.

Between 10% and 15% of babies grow poorly in the womb, often showing reduced growth of blood vessels in the placenta. In humans, these blood vessels expand dramatically between mid and late gestation, reaching a total length of approximately 320 kilometers at term.

In a study published today (December 27, 2021) in *Developmental Cell*, a team led by scientists at the University of Cambridge used genetically engineered mice to show how the fetus produces a signal to encourage growth of blood vessels within the placenta. This signal also causes modifications to other cells of the placenta to allow for more nutrients from the mother to go through to the fetus.

Dr. Ionel Sandovici, the paper's first author, said: "As it grows in the womb, the fetus needs food from its mum, and healthy blood vessels in the placenta are essential to help it get the correct amount of nutrients it needs.

"We've identified one way that the fetus uses to communicate with the placenta to prompt the correct expansion of these blood vessels. When this communication breaks down, the blood vessels don't develop properly and the baby will struggle to get all the food it needs."

The team found that the fetus sends a signal known as IGF2 that reaches the placenta through the umbilical cord. In humans, levels of IGF2 in the umbilical cord progressively increase between 29 weeks of gestation and term: too much IGF2 is associated with too much growth, while not enough IGF2 is associated with too little growth. Babies that are too large or too small are more likely to

suffer or even die at birth, and have a higher risk to develop diabetes and heart problems as adults.

Dr. Sandovici added: "We've known for some time that IGF2 promotes the growth of the organs where it is produced. In this study, we've shown that IGF2 also acts like a classical hormone – it's produced by the fetus, goes into the fetal blood, through the umbilical cord and to the placenta, where it acts."

Particularly interesting is what their findings reveal about the tussle taking place in the womb.

In mice, the response to IGF2 in the blood vessels of the placenta is mediated by another protein, called IGF2R. The two genes that produce IGF2 and IGF2R are 'imprinted' – a process by which molecular switches on the genes identify their parental origin and can turn the genes on or off. In this case, only the copy of the *igf2* gene inherited from the father is active, while only the copy of *igf2r* inherited from the mother is active.

Lead author Dr. Miguel Constância, said: "One theory about imprinted genes is that paternally-expressed genes are greedy and selfish. They want to extract the most resources as possible from the mother. But maternally-expressed genes act as countermeasures to balance these demands."

"In our study, the father's gene drives the fetus's demands for larger blood vessels and more nutrients, while the mother's gene in the placenta tries to control how much nourishment she provides. There's a tug-of-war taking place, a battle of the sexes at the level of the genome."

The team say their findings will allow a better understanding of how the fetus, placenta, and mother communicate with each other during pregnancy. This in turn could lead to ways of measuring levels of IGF2 in the fetus and finding ways to use medication to normalize these levels or promote normal development of placental vasculature.

The researchers used mice, as it is possible to manipulate their genes to mimic different developmental conditions. This enables them to study in detail the different mechanisms taking place. The physiology and biology of mice have many similarities with those of humans, allowing researchers to model human pregnancy, in order to understand it better.

Reference: "The Imprinted Igf2-Igf2r Axis is Critical for Matching Placental Microvasculature Expansion to Fetal Growth" by Sandovici, I et al., 27 December 2021, Developmental Cell. DOI: 10.1016/j.devcel.2021.12.005

The lead researchers are based at the Department of Obstetrics and Gynaecology, the Medical Research Council Metabolic Diseases Unit, part of the Wellcome-MRC Institute of Metabolic Science, and the Centre for Trophoblast Research, all at the University of Cambridge.

The research was largely funded by the Biotechnology and Biological Sciences Research Council, Medical Research Council, Wellcome Trust and Centre for Trophoblast Research.

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Scientists Identify Antibodies That Can Neutralize Omicron and Other COVID Variants

The findings could lead to the development of more effective vaccines and antibody treatments for COVID-19 variants.

An international team of scientists have identified antibodies that neutralize omicron and other SARS-CoV-2 variants. These antibodies target areas of the virus spike protein that remain essentially unchanged as the viruses mutate.

By identifying the targets of these "broadly neutralizing" antibodies on the spike protein, it might be possible to design vaccines and antibody treatments that will be effective against not only the omicron variant but other variants that may emerge in the future, said David Veesler, investigator with the Howard Hughes Medical Institute and associate professor of biochemistry at the University of Washington School of Medicine in Seattle. "This finding tells us that by focusing on antibodies that target these highly conserved sites on the spike protein, there is a way to overcome the virus' continual evolution," Veesler said.

Veesler led the research project with Davide Corti of Humabs Biomed SA, Vir Biotechnology, in Switzerland. The study's findings were published on December 23 in the journal *Nature*. The lead authors of the study were Elisabetta Cameroni and Christian Saliba (Humabs), John E. Bowen (UW Biochemistry) and Laura Rosen (Vir).

The omicron variant has 37 mutations in the spike protein, which it uses to latch onto and invade cells. This is an unusually high number of mutations. It is thought that these changes explain in part why the variant has been able to spread so rapidly, to infect people who have been vaccinated and to reinfect those who have previously been infected.

"The main questions we were trying to answer were: how has this constellation of mutations in the spike protein of the omicron variant affected its ability to bind to cells and to evade the immune system's antibody responses," Veesler said.

Veesler and his colleagues speculate that omicron's large number of mutations might have accumulated during a prolonged infection in someone with a weakened immune system or by the virus jumping from humans to an animal species and back again.

To assess the effect of these mutations, the researchers engineered a disabled, nonreplicating virus, called a pseudovirus, to produce spike proteins on its surface, as coronaviruses do. They then created pseudoviruses that had spike proteins with the omicron mutations and those found on the earliest variants identified in the pandemic.

The researchers first looked to see how well the different versions of the spike protein were able to bind to protein on the surface of cells, that the virus uses to latch onto and enter the cell. This protein is called the angiotensin converting enzyme-2 (ACE2) receptor.

They found the omicron variant spike protein was able to bind 2.4 times better than spike protein found in the virus isolated at the very beginning of the pandemic. "That's not a huge increase," Veesler noted, "but in the SARS outbreak in 2002-2003, mutations in the spike protein that increased affinity were associated with higher transmissibility and infectivity." They also found that the omicron version was able to bind to mouse ACE2 receptors efficiently, suggesting omicron might be able to "ping-pong" between humans and other mammals.

The researchers then looked at how well antibodies against earlier isolates of the virus protected against the omicron variant. They did this by using antibodies from patients who had previously been infected with earlier versions of the virus, vaccinated against earlier strains of the virus, or had been infected and then vaccinated.

They found that antibodies from people who had been infected by earlier strains and from those who had received one of the six most-used vaccines currently available all had reduced ability to block infection.

Antibodies from people who had previously been infected and those who had received the Sputnik V or Sinopharm vaccines as well as a single dose of Johnson & Johnson had little or no ability to block – or "neutralize" – the omicron variant's entry into cells. Antibodies from people who had received two doses of the Moderna, Pfizer/BioNTech, and AstraZeneca vaccines retained some neutralizing activity, albeit reduced by 20- to 40-fold, much more than any other variants.

Antibodies from people who had been infected, recovered, and then had two doses of vaccine also had reduced activity, but the reduction was less, about fivefold, clearly demonstrating that vaccination after infection is useful.

Antibodies from people, in this case a group of renal dialysis patients, who had received a booster with a third dose of the mRNA vaccines produced by Moderna and Pfizer/BioNTech showed only a 4-fold reduction in neutralizing activity. "This shows that a third dose is really, really helpful against omicron," Veesler said.

All but one antibody treatments currently authorized or approved to be used with patients exposed to the virus, had no or had markedly reduced activity against omicron in the laboratory. The exception was an antibody called sotrovimab, which had a two- to three-fold reduction of neutralizing activity, the study finds.

But when they tested a larger panel of antibodies that have been generated against earlier versions of the virus, the researchers identified four classes of antibodies that retained their ability to neutralize omicron. Members of each of these classes target one of four specific areas of the spike protein present in not only SARS-CoV-2 variants but also a group of related coronaviruses, called sarbecoviruses. These sites on the protein may persist because they play an essential function that the protein would lose if they mutated. Such areas are called "conserved."

The finding that antibodies are able to neutralize via recognition of conserved areas in so many different variants of the virus suggests that designing vaccines and antibody treatments that target these regions could be effective against a broad spectrum of variants that emerge through mutation, Veesler said.

Reference: "Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift" by Elisabetta Cameroni , John E. Bowen , Laura E. Rosen , Christian Saliba , Samantha K. Zepeda , Katja Culap , Dora Pinto , Laura A. VanBlargan , Anna De Marco , Julia di Iulio , Fabrizia Zatta , Hannah Kaiser , Julia Noack , Nisar Farhat , Nadine Czudnochowski , Colin Havenar-Daughton , Kaitlin R. Sprouse , Josh R. Dillen , Abigail E. Powell , Alex Chen , Cyrus Maher , Li Yin , David Sun , Leah Soriaga , Jessica Bassi , Chiara Silacci-Fregni , Claes Gustafsson , Nicholas M. Franko , Jenni Logue , Najeeha Talat Iqbal , Ignacio Mazzitelli , Jorge Geffner , Renata Grifantini , Helen Chu , Andrea Gori , Agostino Riva , Olivier Giannini , Alessandro Ceschi , Paolo Ferrari , Pietro E. Cippà , Alessandra Franzetti-Pellanda , Christian Garzoni , Peter J. Halfmann , Yoshihiro Kawaoka , Christy Hebner , Lisa A. Purcell , Luca Piccoli , Matteo Samuele Pizzuto , Alexandra C. Walls , Michael S. Diamond , Amalio Telenti , Herbert W. Virgin , Antonio Lanzavecchia , Gyorgy Snell , David Veesler and Davide Corti, 23 December 2021, Nature. DOI: 10.1038/d41586-021-03825-4

The research was supported by the Howard Hughes Medical Institute, the National Institute of Allergy and Infectious Diseases (Dp1AI158186, HHSN272201700059C, HHSN272201400008C), the National Institute of General Medical Sciences (5T32GN008268-32), Fast Grants, the Pew Charitable Trusts, The Burroughs Wellcome Fund, the Center for Research on Influenza Pathogenesis (75N93021C00014), the Japan Agency for Medical Research and Development (JP21wm0125002), the Pew Biomedical Scholars Award, and the Swiss Kidney Foundation.

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Staying below 2° C warming costs less than overshooting and correcting

Most current policies assume we'll need carbon capture, but there's a big cost.

K.E.D Coan

What will it cost if the climate exceeds the Paris Agreement temperature goals this century—even if we later remove carbon dioxide from the air and manage to bring temperatures back down to meet those targets by 2100? And how does that compare with the costs of staying below those targets?

Most plans that are consistent with the Paris Agreement goals assume that temperatures will rise above 1.5° or even 2° C before 2100. They then heavily rely on the success and wide adoption of what are called negative carbon emissions techniques, which involve the removal of carbon dioxide from the atmosphere to bring temperatures back down. That's a gamble for a number of reasons.

"Betting on being able to bring temperatures down after a larger overshoot is very risky because of the uncertain technological feasibility and because of the possibility of setting off irreversible processes in the earth system with even a temporary temperature overshoot," wrote second author Christoph Bertram, of the Potsdam Institute for Climate Impact Research in Germany, in an email to Ars Technica. "Furthermore, such an approach would be unfair to future generations, as it basically would shift more of the mitigation burden on them."

But the alternative—staying below those targets in the first place—is also a significant challenge. Only a few models have looked at such scenarios, and they've received relatively little focus in past

policy discussions. But a recent study from an international collaboration of nearly two dozen climate modeling groups has systematically compared the economic implications of these scenarios using nine commonly used models. The results were unanimous—the economy will be better off if we don't count on repairing the damage later.

Modeling the future

There are a lot of things that determine whether humanity can meet the targets set out in the Paris Agreement. Reducing carbon emissions will require significant action in the agriculture, transportation, and energy sectors, to name just a few of the key players. The economy, land use, population growth, climate mitigation strategies, and, of course, human behavior, all play important roles as well.

The models used to inform climate policies—called integrated assessment models—incorporate various combinations of all of these factors, as well as calculations of how they impact each other. These models are designed to answer "what if?" type questions to inform our policy options. In the case of this current research, the key questions were: "how will carbon emissions, temperatures, and the global GDP compare in the two scenarios" (i.e. if temperatures overshoot the Paris targets, even temporarily, or not); and "how will each of these likely turn out under the world's combined emission reduction pledges (nationally determined contributions) as of 2020?"

Different research groups around the world have developed dozens of models, each of which more or less focuses on certain interactions. For example, one model, MESSAGE, is designed to explore how energy systems can meet demand at minimal costs. Another, REMIND-MAgPIE, focuses more on agricultural production and land use. Other models place more emphasis on environmental effects or technology costs; some even use game theory to predict the impacts of whether climate action is cooperative or not.

By comparing the outputs of nine of these different models, the result of this latest study is the most comprehensive and systematic effort to explore the economic attainability and consequences of current and potential strategies for meeting the Paris targets so far.

Longterm payoffs

Not surprisingly, minimizing temperature overshoot will require much greater investments in the short term (starting within the next 10 years). But all of the models project that these upfront costs will result in a higher global GDP (up to 2 percent higher) by 2100, with most showing benefits already by around 2080. The authors note that greater investments in the short term will likely be fully compensated by more GDP growth in the second half of the century.

"The key is to reach net-zero emissions around mid-century, and our study shows that this requires both a very strong reduction of the use of fossil fuels and additionally at least some scaling up of options for removing carbon from the atmosphere," wrote Bertram. "In the first article based on this study (published in summer), we showed that in the short-term, the critical factor is the decarbonization of the power sector, mostly via rapid expansion of renewable energy."

In order to avoid overshoot, the models estimate that the world needs to reach net-zero emissions by 2045-2065. Allowing overshoot (but achieving targets by 2100) would push our net-zero deadline out to 2060-2070, but this would mean an extra 0.08-0.16° C of warming and the potentially irreversible damage that could accompany that.

Short-sighted pledges

Meeting the Paris targets via a path that allows overshoot also has long-term benefits for GDP, but they're not as high as when temperatures never exceed the goals. Unfortunately, the authors

show that the world's emission pledges as of 2020 are far from achieving either scenario. Under these pledges, carbon emissions will still be two- to several-fold higher than needed. Although these scenarios correlate with a better global GDP for roughly the next 20 years, things go bad afterward, with the GDP reduced by up to 3 percent for the ensuing 60 years (with no predictions for what happens after that).

"I would say that [political discussions] partially already have pivoted to a focus on limiting peak temperature gradually. With the Indian announcement at Glasgow, now the 7 biggest emitters have targets for net-zero emissions in mid-century or thereafter—which already, if fully implemented and achieved, would go a long way for limiting temperature increase," wrote Bertram. "The crucial issue now is that current 2030 targets are not in line with achieving these net-zero targets in a balanced way with immediate decarbonization, and would thus lead to higher peak temperatures than if efforts would be started right away."

Without significantly more action and investments than current policies are allotting, the authors' models project that it won't be feasible to meet the Paris Agreement. A clear caveat of these findings is that these are models and none of them can capture all of the variables involved. But it does say something that they all agree on the general trajectory on which we're headed.

Nature Climate Change, 2021. DOI: 10.1038/s41558-021-01215-2

https://bit.ly/3FNoyoM

DNA Preserved in Lice Glue Reveals South American Mummies' Secrets

Remarkable samples from an ancient culture offer scientists a promising new way to study the past

Brian Handwerk Science Correspondent

Anyone who has ever peered through a magnifying glass and struggled to pick nits knows how effectively female head lice cement each of their eggs to a human hair. Once these pests gain a foothold they are notoriously difficult to dislodge. But even a school nurse might be shocked at their real staying power; scientists have previously found louse eggs still stubbornly stuck to ancient hair after 10,000 years.

And now, researchers have discovered something even more remarkable about the glue lice use to adhere eggs to hair. Invertebrate biologist Alejandra Perotti and her team found that lice cement turns out to be exceptional at trapping and preserving anything it encases—including high-quality ancient human DNA from the lice's hosts. Their study, published this week in *Molecular Biology and Evolution*, was a case of life imitating art. It played out a bit like the scene in *Jurassic Park*, in which dinosaur DNA was preserved by mosquitoes that had sucked dinosaur blood before subsequently becoming sealed in amber.

In this case, female lice had secreted cement from glands in their reproductive organs to affix eggs, called nits, to the hair of ancient humans—who later became 1,500 to 2,000-year-old mummies in Argentina's Andes Mountains. In doing so, the lice trapped skin cells from the human scalps in their cement. Perotti and colleagues sequenced genomes from the skin cells to discover that these ancient inhabitants originally came from rainforests in southern Venezuela and Colombia. What's more, they found that DNA in the glue was kept at quality similar to that typically retrieved from teeth, and superior to that of other common sources like the skull's dense petrous bone. That means examples of ancient hair, clothes and other textiles around the world, with their ubiquitous lice, could end up yielding priceless DNA that identifies their human hosts even if their remains have vanished.

"If you have hair, or if you have clothing, you can find nits attached," says Perotti, of the University of Reading. "We can study thousands of years of the hosts', and lice's, natural and evolutionary

history just by examining the DNA trapped in the cement."

Importantly, Perotti and colleagues' method allows scientists to study DNA without invasive or destructive techniques, like breaking skulls open, which often cause cultural concerns when studying DNA in ancient human remains.

Team members from five different universities are studying South American mummies to learn more about when and how the continent was populated. The two mummies yielding lice for this research were interred some two thousand years ago in the Calingasta Caves and rock shelters of the high Andes Mountains of today's San Juan province in Central West Argentina. In this cold, arid region where even the valleys soar to heights of nearly 10,000 feet, the mummies were exceptionally preserved along with the ectoparasites that shared their lives.

Perotti and colleagues suspected that DNA might exist in the sheath of cement that was used to glue each nit to a strand of hair on the mummies. Using a dye that binds to DNA, and special imaging techniques, they revealed that the nuclei of human cells were in fact trapped and preserved in the louse cement. Then they inserted a tube and extracted that DNA for sampling.

The DNA showed genetic links between these mummies and individuals who lived in Amazonia 2,000 years ago. The evidence demonstrated that the mountain inhabitants of the area, the Ansilta culture, had formerly come from the rainforest regions in what is now southern Venezuela and Colombia. Such information helps to recreate South American prehistory, which is particularly complicated in Argentina where many indigenous groups were eradicated, assimilated or deported centuries ago.

To confirm their findings, the team also analyzed DNA from the nits themselves and compared it other known louse populations. They found that the parasites' migration history mirrored that of their human hosts from the Amazon to the Andes.

"All the nits we analyzed gave the same origin," Perotti says. "That was very interesting. Totally independent of the DNA of the host, it gave us the same evolutionary history."

Because louse cement preserves anything it encases, the team also found sources of environmental DNA that were neither human nor louse. Along with various strains of bacteria they found the earliest evidence of Merkel cell Polymavirus. The virus, discovered in 2008, can cause skin cancer and the researchers now speculate that head lice might play some role in its spread.

The team also examined the nits' morphology and attachment for information about their hosts' lives. For example, lice lay eggs closer to the warmth of the scalp in colder environments and the position of these nits, nearly on the mummies' scalps, suggested that the ancient humans were exposed to extreme cold temperatures which might have played a role in their deaths.

"This work is remarkable on several levels," says David Reed a biologist at the Florida Museum of Natural History who was not involved with the study. "First, the authors were able to sequence the genome from such a small and seemingly insignificant starting material, and second the lice upon these heads contributed to our understanding of human migrations."

Plenty of evidence demonstrates that our ancestors lived with lice for many millions of years. But scientists are only now delving into lice genomes to uncover how the parasites moved, spread and evolved along with their primate, and later human, hosts, around the world.

"Human lice have taught us so much about our history, from contact with archaic hominids to when humans started wearing clothing," Reed says. "It seems that lice still have more to say about our history."

Investigations of mummies and archaeological sites confirm that many ancient groups supported sizable populations of both head

and clothing lice, which can still be found among their remains and artifacts of many types. Scientists have even discovered specialized combs that prehistoric South Americans employed to try and rid themselves of the pests. Luckily for today's scientists, those efforts often failed.

Museum and private collections are filled with lice, scattered among hair, textiles and clothing. Many of these archaeological materials are now entirely out of context, gathered generations ago from unknown sites and not linked to particular places or times. But the nits that endure on these artifacts even long after their human hosts have faded into oblivion are now a newly discovered resource for learning much more about their ancient owners.

"The beauty of gathering info from nits is that they are preserved for thousands of years, attached to hair or clothing," Perotti says. "And now we can link them directly to a specific person."

https://bit.ly/3sVO9YT

Once a 'crazy idea,' patent-pooling nonprofit will help bring COVID-19 pills to world's poor

Medicine patent strategy proved its worth with HIV drugs and now a founder of group sets her sights on Pfizer's vaccine next

By Jon Cohen

In the United States, widespread hope greeted the decision by the Food and Drug Administration last week to authorize the emergency use of two different oral treatments for SARS-CoV-2 infection, which could mark a new era in which pills taken at home can prevent severe COVID-19. Global health advocates are also celebrating the preauthorization decision by the two Big Pharmas producing the treatments to allow generic manufacturers to make low-cost versions accessible to poorer countries.

Each of the treatments, Pfizer's combination of a new antiviral, nirmatrelvir, with an old one, and Merck's molnupiravir, require 5 days of pills, which the U.S. government has purchased for $530 and $712 per treatment course, respectively. That's far too expensive for much of the world, but both companies joined the Medicines Patent Pool (MPP) for their patented treatments. A nonprofit set up in 2010, MPP encourages Big Pharmas to voluntarily cut deals that allow generic manufacturers to produce and sell a company's drugs or vaccines at steep discounts in agreed on regions of the world. "Everyone at the time said this will never happen, this is a crazy idea," says attorney Ellen 't Hoen, who helped establish MPP and remains on its expert advisory group.

Generic makers are expected to cut the cost of either treatment to as low as $20 per treatment course, while Pfizer and Merck will continue to sell the pills to wealthy countries for whatever the market will bear. (Nirmatrelvir is boosted by a second drug, ritonavir, that came to market as an HIV treatment and is widely available as an inexpensive generic.)

MPP modeled itself after a cross-licensing agreement created by the U.S. government to free patents controlled by the Wright brothers and another aviation pioneer, who tied up the entire airline industry. MPP initially set out to make lifesaving antiretrovirals for HIV more accessible to low-income countries and then later branched out to include drugs for hepatitis C and tuberculosis. "This is frankly a dream coming true that the pool is moving into all these various areas of huge need and succeeding," says 't Hoen, who ran the Campaign for Access to Essential Medicines for Doctors Without Borders (MSF) before starting MPP. Deals through the group have led to the supply of more than 18 billion doses of drugs.

*Science*Insider last week spoke with 't Hoen, who now works at Medicines Law & Policy, a coalition of experts who support nonprofits that focus on access to medicines. This interview has been edited for brevity and clarity.

Q: Both MSF and Oxfam issued statements after Merck and Pfizer joined MPP that criticized the deals as too restrictive

because they don't allow generic manufacture in many countries that will need the discount to access the medicines. What do you think?

A: Those big, brand name NGOs [nongovernmental organizations] suffer a little bit from knee jerk responses to things that aren't perfectly perfect. These license agreements were made so quickly for pipeline products that did not have regulatory approval when they obtained the license agreements. The weakness of the patent pool is always that these manufacturers will not be able to supply the entire planet. Pfizer and Merck will want to keep their high-income markets in particular. But having said that, if you read the license agreements carefully, there are no barriers to [generic manufacturers] supplying drugs in countries where patents have not been filed or have not been granted—or where governments have decided to issue a compulsory license. This is incredibly important. [The World Trade Organization allows countries to issue compulsory licenses without a patent owner's consent for national emergencies.]

Q: What has been MPP's biggest success to date?

A: The biggest success is the fact that it has licenses for all recommended HIV treatment regimens and it has established the norm that if you have an important product—and particularly an important medicine that is needed to treat people with HIV—you license to [MPP]. It's almost unthinkable that you would not do that, which is the exact opposite of where we started from 10 years ago. [MPP] has saved many, many lives because these drugs became available at very low cost.

Q: How do these new agreements for Pfizer and Merck's pills compare?

A: This went very fast and it's very important that the pool is able to negotiate these licenses while these products are still pipeline. You don't know at that point whether a product indeed will become very important. You see that now with molnupiravir, which in the beginning looked very promising and now people are saying wow, there are problems with it. But it doesn't matter. It's in there. And if you have the licenses, you don't create further delays. It will be more likely that generic companies will go for the Pfizer product than for molnupiravir I suspect.

Q: Where has the patent pool yet to succeed with COVID-19?

A: It's remarkable that Pfizer is licensing its therapeutics but not its [COVID-19] vaccine. Both Pfizer and Moderna have dug in their heels: They don't want to license their vaccines. They want to keep them within their own, trusted circle of contract manufacturers. And that is a huge problem. What I'm hoping is that this experience Pfizer now has with [MPP] will lead them to take the next, and much more important, step to license its technology. And that would have to include a technology transfer package, in collaboration with the [MPP] and World Health Organization tech transfer initiatives.

Q: And the tech transfer is far more important with a vaccine than with a chemical compound like the drugs?

A: Indeed. Because otherwise, countries would have been issuing compulsory licenses left and right. But you just don't get there with only the patents. You need a package that actually transfers the technology package.

Q: Moderna has already said it's not going to enforce its COVID-19 vaccine patents during the pandemic. So what is it that's needed?

A: That shows that doesn't mean much. Patents in the vaccine area are more complex and much less important than the trade secrets. It's the [manufacturing] know-how that needs to be transferred and you don't find enough of that in the patent. You need the playbook. What I would have liked to have seen, and I hope that in the future we're going to see, is that these vaccines that are all developed with

colossal public financing really become global public goods. And that governments that offer the financing say, "Here's the money, generous money, for the research and development, but you cannot monopolize the knowledge that you create." I hope that will be the lesson that the world will learn from what's happening today.

https://bit.ly/3JCP2vc

Texas Scientists Are Sharing the Design for Their New, Cheap Covid-19 Vaccine

A low-cost, effective vaccine authorized for use in India this week could soon be shared around the world.

By Ed Cara

Despite some truly important medical advances this year, the covid-19 pandemic is far from over, both in the U.S. and even more so in poorer countries with low vaccination rates. But there is hope on the immediate horizon. Cheap, easily stored, and effective covid-19 vaccines are set to be mass-produced and distributed around the world soon enough. That includes one particularly promising vaccine developed by Texas researchers that was just authorized in India this week.

On Tuesday, Indian health regulators granted an emergency use authorization to the Corbevax vaccine, created by scientists from the Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine. The vaccine was further developed and tested in partnership with the Indian pharmaceutical company Biological E, which will handle the local production of the vaccine. Clinical trials have shown that Corbevax is safe and estimates indicate that it's more than 90% effective against the original form of the coronavirus, as well as more than 80% effective against the Delta variant.

"In addition to the obvious humanitarian drive, this is the only way to prevent future variants from emerging."

The researchers are billing their creation as the "world's covid-19 vaccine." Its underlying technology, which uses a piece of the coronavirus spike protein that's grown from yeast cells, has long been used in vaccines, most notably the Hepatitis B vaccine. This design means it can be easily and cheaply scaled up, even in countries with limited resources. Importantly, it can be stored using standard refrigeration, which would allow for more widespread transportation and use than the mRNA vaccines that require special refrigeration.

Moreover, the vaccine technology was developed without patents, and the researchers plan to widely share their blueprints and/or co-develop the vaccine with any willing manufacturers and countries for no added financial gain. As a result, a mass-produced single dose is estimated to run about $1.50. In comparison, Pfizer and Moderna recently inked deals reportedly charging around $25 per dose in Europe.

Biological E has reportedly already produced 150 million doses of Corbevax and should be able to produce 100 million doses a month. The team has reportedly also shared its technology with manufacturers in Indonesia, Bangladesh, and Botswana.

"Our vaccine development program brings together the heart and passion of scientists from so many diverse backgrounds. We are privileged to be able to gift all our know-how and bring this vaccine to many in India and around the world," Maria Elena Bottazzi, one of the vaccine's lead developers and co-director of the Texas Children's Hospital Center for Vaccine Development, told Gizmodo.

There have been ongoing efforts to provide vaccines on the cheap to low and middle-income countries, most notably the COVAX program spearheaded by the World Health Organization. But COVAX has fallen far below expectations, having obtained and distributed less than half of the 2 billion doses it intended to procure by the end of 2021. Wealthier countries have also donated doses,

and the U.S. seemingly pledged earlier this year that it supported waiving patents for existing vaccines like those developed by Pfizer and Moderna—likely an important step for broadening the distribution of these newer, more expensive, and more complex to produce vaccines. But talks to negotiate these waivers have stalled completely, and the U.S. has reportedly done little to actually push for them. Currently, only 58% of the world's population has received at least one vaccine dose, while less than half are fully vaccinated—a disparity that's even worse in many poorer countries. Baylor's vaccine was itself stifled by a lack of resources early on, with the team having failed to secure funding through the Operation Warp Speed initiative implemented last year in the U.S. to accelerate vaccine development. They were able to garner enough funding eventually, largely through charity, but it undoubtedly slowed their timeline. According to Peter Hotez, co-developer and dean of the National School of Tropical Medicine at Baylor, the lack of focus on providing a vaccine for all is one that has had serious consequences—consequences that he hopes his team's vaccine can now start to remedy.

"It's so exciting to be able to make a difference in vaccinating the world," Hotez told Gizmodo. "In addition to the obvious humanitarian drive, this is the only way to prevent future variants from emerging. Had we had the funds to do this sooner, perhaps Southern Africa would have been vaccinated and Omicron might never have emerged."

There are of course still important questions about Cobrevax left to be answered. Notably, it's not yet known how effective it will be against the Omicron variant, which has begun to overtake Delta as the dominant version of the virus. Omicron is concerning because its many mutations allow it to more easily infect people with some prior immunity created through vaccination or infection (on the plus side, this immunity appears to still blunt its severity). The team plans to have data on Omicron soon, however, and there is existing data suggesting that Cobrevax may be better at providing durable protection in general than some other vaccines. It's possible that Cobrevax could also be used as a booster to other vaccines, and other data has shown booster shots do restore some protection against Omicron infection.

Corbevax isn't the only vaccine that could become a boon to poorer countries. Just this week, Mexico became the latest to authorize the three-dose vaccine created by Cuba called Abdala. Abdala and another Cuban vaccine, Soberna 02, are similarly developed using long-established and cheap vaccine technology, and clinical trials have shown that the vaccines were over 90% effective against illness. Following a summer peak of the pandemic, Cuba's covid-19 cases have plummeted as the vaccination rate has soared to over 90% with at least one dose. The country is still waiting for the WHO to decide whether it will approve its covid-19 vaccines, though, which will likely be needed to garner widespread use outside of the country. Should that happen, Cuba has promised to spread its technology to the rest of the world as well.

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High-Speed Impacts May Have Shaped Venus' History – And Explain Why It Is Uninhabitable

New modeling suggests fast collisions could explain why Earth is habitable while Venus is not.

New modeling suggests large, high-speed impacts during Venus' early history could reconcile the differences between Venus and its rocky sister planet, Earth.

The two planets are alike in many ways. They have similar sizes, masses, and densities, and they are relatively similar distances from the Sun. Yet some key differences — such as habitability, atmospheric composition, and plate tectonics — have remain unexplained.

High-speed impacts could help explain why Earth is habitable while Venus is not, according to new research being presented at the AGU Fall Meeting 2021.

"Early on, in the beginning of the Solar System, the impactors would have been immense," said Simone Marchi, a planetary scientist at Southwest Research Institute, who presented the study on Thursday, December 16, 2021. "If an early impactor was larger than, say, a few hundred kilometers in diameter, it could have affected the deep interior of a planet, along with its surface and atmosphere. These colossal collisions would basically affect everything about a planet."

Recent work from a different research group showed impactors during Venus' late accretionary phase, around 4.5 to 4.0 billion years ago, could have hit the planet at much higher speeds, on average, than those colliding with Earth. More than one-quarter of collisions with Venus would have occurred at velocities of at least 30 kilometers per second (about 67,100 miles per hour).

The new research demonstrates the large, high-speed impacts on Venus lead to twice as much mantle melting than impact-induced melting on Earth. High-speed impactors hitting Venus at a shallow angle would have resulted in complete melting of the mantle, according to the new research.

When even just one of these massive, high-velocity impactors hit Venus, it would have interrupted and essentially reset the planet's evolution, according to Marchi. Venus could have gone from a solid rocky body to a molten mess in moments, altering the mineralogy and physical structure of the planet's interior and surface. Any pre-existing atmosphere would have been largely blasted away and replaced by volatile gases emerging from the melt. A single high-speed impact could have ultimately determined whether or not tectonic plates formed, which is an important aspect of habitability.

While large impacts likely pummeled both Earth and Venus, the latter could have undergone substantial more melting and disruption due to the high speed of its impacts, setting the planets on divergent evolutionary pathways. For both planets, and the Solar System as a whole, these early collisions had big consequences on their habitability — or lack thereof — today.

"These collisions were responsible for shaping the Solar System. It's not a stretch of the imagination to say that lacking these processes, we would live in a completely different environment, and perhaps we wouldn't be here," Marchi said. "We need to ask how much of the planet we live on today was shaped by these early, violent events."

Meeting: American Geophysical Union Fall Meeting 2021

https://bit.ly/330lzLe

Plant Scientists Find Recipe for Anti-Cancer Compound in Herbs Like Thyme and Oregano

Thyme and oregano possess an anti-cancer compound that suppresses tumor development, but adding more to your tomato sauce isn't enough to gain significant benefit.

The key to unlocking the power of these plants is in amplifying the amount of the compound created or synthesizing the compound for drug development. Researchers at Purdue University achieved the first step toward using the compound in pharmaceuticals by mapping its biosynthetic pathway, a sort of molecular recipe of the ingredients and steps needed.

"These plants contain important compounds, but the amount is very low and extraction won't be enough," said Natalia Dudareva, a Distinguished Professor of Biochemistry in Purdue's College of Agriculture, who co-led the project. "By understanding how these compounds are formed, we open a path to engineering plants with higher levels of them or to synthesizing the compounds in microorganisms for medical use.

"It is an amazing time for plant science right now. We have tools

that are faster, cheaper, and provide much more insight. It is like looking inside the cell; it is almost unbelievable."

Thymol, carvacrol and thymohydroquinone are flavor compounds in thyme, oregano, and other plants in the Lamiaceae family. They also have antibacterial, anti-inflammatory, antioxidant, and other properties beneficial to human health. Thymohydroquinone has been shown to have anti-cancer properties and is particularly of interest, said Dudareva, who also is director of Purdue's Center for Plant Biology.

In collaboration with scientists from Martin Luther University Halle-Wittenberg in Germany and Michigan State University, the team uncovered the entire biosynthetic pathway to thymohydroquinone, including the formation of its precursors thymol and carvacrol, and the short-lived intermediate compounds along the way.

The findings alter previous views of the formation of this class of compounds, called phenolic or aromatic monoterpenes, for which only a few biosynthetic pathways have been discovered in other plants, she said. The work is detailed in a paper published in the Proceedings of the National Academy of Sciences.

"These findings provide new targets for engineering high-value compounds in plants and other organisms," said Pan Liao, co-first author of the paper and a postdoctoral researcher in Dudareva's lab. "Not only do many plants contain medicinal properties, but the compounds within them are used as food additives and for perfumes, cosmetics, and other products."

Now that this pathway is known, plant scientists could develop cultivars that produce much more of the beneficial compounds or it could be incorporated into microorganisms, like yeast, for production. The latter method involves a fermentation process to obtain the valuable compounds, as is true for many plant-based products, he said.

The fermentation process is so important to food and beverage, pharmaceutical, and biofuels production that Purdue now offers a fermentation science major.

A $5 million grant from the National Science Foundation supported the research. Using RNA sequencing and correlation analysis, the team screened more than 80,000 genes from plant tissue samples and identified the genes needed for thymohydroquinone production. Based on what was known about the compound structure and through metabolite profiling and biochemical testing, the team identified the biosynthetic pathway.

"The intermediate formed in the pathway was not what had been predicted," Liao said. "We found that the aromatic backbone of both thymol and carvacrol is formed from ?-terpinene by a P450 monooxygenase in combination with a dehydrogenase via two unstable intermediates, but not *p*-cymene, as was proposed."

More pathways are being discovered now because of the ability to use RNA sequencing to perform high-throughput gene expression analysis, Dudareva said.

The results of this research also will be useful for biochemistry and plant sciences research of other species of plants, she said.

"We, as scientists, are always comparing pathways in different systems and plants," Dudareva said. "We are always in pursuit of new possibilities. The more we learn, the more we are able to recognize the similarities and differences that could be key to the next breakthrough."

Reference: "The biosynthesis of thymol, carvacrol, and thymohydroquinone in Lamiaceae proceeds via cytochrome P450s and a short-chain dehydrogenase" by Sandra T. Krause, Pan Liao, Christoph Crocoll, Benoît Boachon, Christiane Förster, Franziska Leidecker, Natalie Wiese, Dongyan Zhao, Joshua C. Wood, C. Robin Buell, Jonathan Gershenzon, Natalia Dudareva and Jörg Degenhardt, 20 December 2021, Proceedings of the National Academy of Sciences. DOI: 10.1073/pnas.2110092118

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https://wb.md/3mSGV4d

New Data Support a Causal Role for Depression in Alzheimer's

Researchers have known for some time that depression is associated with Alzheimer's disease (AD), but a causal link has been elusive.

Pauline Anderson

Now, using newly available data, they have uncovered genetic evidence of a causal role for depression in AD.

As depression typically affects those in early or midlife and dementia often occurs in later life, "it's fascinating to see a connection between the two brain illnesses that manifest in different time windows," co-investigator Aliza P. Wingo, MD, associate professor of psychiatry and behavioral science, Emory University, Atlanta, Georgia, told *Medscape Medical News.*

"If we can treat the depression early on, we may help reduce risk for dementia for our patients later in life," Wingo said. The findings were published online December 16 in *Biological Psychiatrry.*

Postmortem Data

The investigators, who are all from the Emory University Center for Neurodegenerative Disease, wanted to clarify the genetic basis underlying the association between the established link between depression and dementia risk.

They used data from the largest and most recent genome-wide association studies (GWAS). These included a 2019 analysis of depression among 807,553 individuals and a 2019 study of AD among 455,258 individuals, all of European ancestry. For sensitivity analyses, they used results from two additional AD GWAS.

The researchers also accessed postmortem brain samples from participants in the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP). These participants were cognitively normal at enrollment, underwent annual clinical evaluations, and agreed to donate their brains.

They also assessed brain samples donated by participants in the Banner Sun Health Research Institute Longitudinal study of healthy aging, Alzheimer's and Parkinson's disease.

The brain samples allowed researchers to use deep brain proteomic data to help determine molecular links between depression and AD.

After quality control, the analysis included 8356 proteins in 391 ROS/MAP participants and 7854 proteins in 196 Banner participants.

Results showed a small but significant positive genetic correlation between depression and AD, suggesting the two conditions have a shared genetic basis.

The investigators also applied a framework called "Mendelian randomization" to determine causality between depression and AD.

After assessing the effect of 115 independent single-nucleotide polymorphisms (SNPs) from the GWAS of depression, they uncovered significant evidence "that the SNPs cause depression, which in turn cause AD," said Wingo.

One-Way Relationship

The researchers conducted the same analysis on 61 significant SNPs from the GWAS of AD but did not find evidence to conclude AD causes depression. "We found genetic evidence supporting a causal role of depression in AD but not vice versa," Wingo said.

In addition, the investigators identified 75 brain transcripts (messenger RNA) and 28 brain proteins regulated by the depression-predisposing genetic variants. Of these, 46 brain transcripts and seven proteins were significantly associated with at least one AD feature — for example, beta-amyloid, tau tangles, and cognitive trajectory.

"These findings support the notion that the depression risk variants contribute to AD via regulating expression of their corresponding

transcripts in the brain," the investigators write.

It is only recently that large enough studies have allowed researchers sufficient power to reach these conclusions, co-investigator Thomas Wingo, MD, said in an interview.

These additional "insights" into the relationship between depression and AD might "motivate" clinicians more to screen for and treat depressive symptoms, Wingo noted.

The new results also have implications for developing therapeutics to treat depression, she said. "If we target the genes, the brain proteins, that are shared risk between depression and AD, the medications that target that gene might mitigate risk for AD later on," she added.

However, the investigators advised caution. "A lot of this is still unknown," said Thomas Wingo. For example, it is not clear whether successfully treating depression mitigates the eventual risk of dementia, which is "a very important topic of inquiry and one we continue to work on," he added. He noted a significant number of patients do not respond well to existing antidepressants such as selective serotonin reuptake inhibitors (SSRIs).

Need for Further Research

Commenting on the findings for *Medscape Medical News*, Claire Sexton, DPhil, director of scientific programs and outreach, Alzheimer's Association, said the study contributes to the debate about whether depression increases risk for AD, whether AD increases risk for depression, or both.

"These newly published findings strengthen our understanding of the role of depression as a risk factor for Alzheimer's dementia," said Sexton, who was not involved with the research.

While experts do not yet fully understand the impact of treating depression on dementia risk, "the findings emphasize the importance of assessing mental health status, particularly depression, and getting it properly diagnosed and treated in a timely manner," she said.

However, she agreed more research in this area is needed. "Importantly, these findings need replication in broader, more diverse study populations," Sexton said.

A study funded by the Alzheimer's Association may provide more information on the link between depression and AD. It will investigate whether machine learning, an advanced computer science technique, can better predict cognitive decline compared with traditional methods.

Over a period of 6 months, researchers will collect smartphone conversations from 225 older adults with dementia, mild cognitive impairment, or no cognitive impairment. They will also have data from cognitive tests, brain scans, and biomarkers such as cerebrospinal fluid samples to study brain changes associated with AD.

The novel method of analysis should be able to identify subtle differences in speech quality to indicate which depressive symptoms an individual might be experiencing.

"The study could help us further understand the potential impact of depression in the risk of developing dementia," said Sexton.

Aliza Wingo and Thomas Wingo have reported no relevant financial relationships.

Biol Psychiatry. Published online December 16, 2021. Abstract

https://nyti.ms/32Uwkyq

Studies Suggest Why Omicron Is Less Severe: It Spares the Lungs

Compared with earlier variants, Omicron may cause less damage to the lungs, new animal research suggests.

By Carl Zimmer and Azeen Ghorayshi

A spate of new studies on lab animals and human tissues are providing the first indication of why the Omicron variant causes milder disease than previous versions of the coronavirus.

In studies on mice and hamsters, Omicron produced less damaging

infections, often limited largely to the upper airway: the nose, throat and windpipe. The variant did much less harm to the lungs, where previous variants would often cause scarring and serious breathing difficulty.

"It's fair to say that the idea of a disease that manifests itself primarily in the upper respiratory system is emerging," said Roland Eils, a computational biologist at the Berlin Institute of Health, who has studied how coronaviruses infect the airway.

In November, when the first report on the Omicron variant came out of South Africa, scientists could only guess at how it might behave differently from earlier forms of the virus. All they knew was that it had a distinctive and alarming combination of more than 50 genetic mutations.

Previous research had shown that some of these mutations enabled coronaviruses to grab onto cells more tightly. Others allowed the virus to evade antibodies, which serve as an early line of defense against infection. But how the new variant might behave inside of the body was a mystery.

"You can't predict the behavior of virus from just the mutations," said Ravindra Gupta, a virologist at the University of Cambridge.

Over the past month, more than a dozen research groups, including Dr. Gupta's, have been observing the new pathogen in the lab, infecting cells in Petri dishes with Omicron and spraying the virus into the noses of animals.

As they worked, Omicron surged across the planet, readily infecting even people who were vaccinated or had recovered from infections.

But as cases skyrocketed, hospitalizations increased only modestly. Early studies of patients suggested that Omicron was less likely to cause severe illness than other variants, especially in vaccinated people. Still, those findings came with a lot of caveats.

For one thing, the bulk of early Omicron infections were in young people, who are less likely to get seriously ill with all versions of the virus. And many of those early cases were happening in people with some immunity from previous infections or vaccines. It was unclear whether Omicron would also prove less severe in an unvaccinated older person, for example.

Experiments on animals can help clear up these ambiguities, because scientists can test Omicron on identical animals living in identical conditions. More than half a dozen experiments made public in recent days all pointed to the same conclusion: Omicron is milder than Delta and other earlier versions of the virus.

On Wednesday, a large consortium of Japanese and American scientists released a report on hamsters and mice that had been infected with either Omicron or one of several earlier variants. Those infected with Omicron had less lung damage, lost less weight and were less likely to die, the study found.

Although the animals infected with Omicron on average experienced much milder symptoms, the scientists were particularly struck by the results in Syrian hamsters, a species known to get severely ill with all previous versions of the virus.

"This was surprising, since every other variant has robustly infected these hamsters," said Dr. Michael Diamond, a virologist at Washington University and a co-author of the study.

Several other studies on mice and hamsters have reached the same conclusion. (Like most urgent Omicron research, these studies have been posted online but have not yet been published in scientific journals.)

The reason that Omicron is milder may be a matter of anatomy. Dr. Diamond and his colleagues found that the level of Omicron in the noses of the hamsters was the same as in animals infected with an earlier form of the coronavirus. But Omicron levels in the lungs were one-tenth or less of the level of other variants.

A similar finding came from researchers at the University of Hong

Kong who studied bits of tissue taken from human airways during surgery. In 12 lung samples, the researchers found that Omicron grew more slowly than Delta and other variants did.

The researchers also infected tissue from the bronchi, the tubes in the upper chest that deliver air from the windpipe to the lungs. And inside of those bronchial cells, in the first two days after an infection, Omicron grew faster than Delta or the original coronavirus did.

These findings will have to be followed up with further studies, such as experiments with monkeys or examination of the airways of people infected with Omicron. If the results hold up to scrutiny, they might explain why people infected with Omicron seem less likely to be hospitalized than those with Delta.

Coronavirus infections start in the nose or possibly the mouth and spread down the throat. Mild infections don't get much further than that. But when the coronavirus reaches the lungs, it can do serious damage.

Immune cells in the lungs can overreact, killing off not just infected cells but uninfected ones. They can produce runaway inflammation, scarring the lung's delicate walls. What's more, the viruses can escape from the damaged lungs into the bloodstream, triggering clots and ravaging other organs.

Dr. Gupta suspects that his team's new data give a molecular explanation for why Omicron doesn't fare so well in the lungs.

Many cells in the lung carry a protein called TMPRSS2 on their surface that can inadvertently help passing viruses gain entry to the cell. But Dr. Gupta's team found that this protein doesn't grab on to Omicron very well. As a result, Omicron does a worse job of infecting cells in this manner than Delta does. A team at the University of Glasgow independently came to the same conclusion.

Through an alternative route, coronaviruses can also slip into cells that don't make TMPRSS2. Higher in the airway, cells tend not to carry the protein, which might explain the evidence that Omicron is found there more often than the lungs.

Dr. Gupta speculated that Omicron evolved into an upper-airway specialist, thriving in the throat and nose. If that's true, the virus might have a better chance of getting expelled in tiny drops into the surrounding air and encountering new hosts.

"It's all about what happens in the upper airway for it to transmit, right?" he said. "It's not really what happens down below in the lungs, where the severe disease stuff happens. So you can understand why the virus has evolved in this way."

While these studies clearly help explain why Omicron causes milder disease, they don't yet answer why the variant is so good at spreading from one person to another. The United States logged more than 580,000 cases on Thursday alone, the majority of which are thought to be Omicron.

"These studies address the question about what may happen in the lungs but don't really address the question of transmissibility," said Sara Cherry, a virologist at the Perelman School of Medicine at the University of Pennsylvania.

Dr. Diamond said he wanted to wait for more studies to be carried out, especially in people instead of animals, before endorsing the hypothesis that TMPRSS2 is the key to understanding Omicron. "I think it is still premature on this," he said.

Scientists know that part of Omicron's contagiousness comes from its ability to evade antibodies, allowing it to easily get into cells of vaccinated people far more easily than other variants. But they suspect that Omicron has some other biological advantages as well.

Last week, researchers reported that the variant carries a mutation that may weaken so-called innate immunity, a molecular alarm that rapidly activates our immune system at the first sign of an invasion in the nose. But it will take more experiments to see if this is indeed one of Omicron's secrets to success.

"It could be as simple as, this is a lot more virus in people's saliva and nasal passages," Dr. Cherry said. But there could be other explanations for its efficient spread: It could be more stable in the air, or better infect new hosts. "I think it's really an important question," she said.

https://bit.ly/3JE8wj9

Evolution Keeps Making And Unmaking Crabs, And Nobody Knows Why

No creature excites evolutionary biologists – or divides taxonomists – quite like crabs

Clare Watson

Our planet's convoluted history of evolving life has spawned countless weird and wonderful creatures, but none excite evolutionary biologists – or divide taxonomists – quite like crabs.

When researchers attempted to reconcile the evolutionary history of crabs in all their raucous glory just earlier this year, they arrived at the conclusion that the defining features of crabbiness have evolved at least five times in the past 250 million years.

What's more, crabbiness has been *lost* possibly seven times or more. This repeated evolution of a crab-like body plan has happened so often it has its own name: carcinization. (And yes, if you lose crabbiness to evolution, it's called decarcinization.)

Frog crabs (Raninidae) are one unusual example. Features of the crab body plan were also lost en route to almost-legless Puerto Rican sand crabs (*Emerita portoricensis*) and various lop-sided hermit crabs – but then red king crabs regained crabby features at the last evolutionary minute.

Why evolution keeps crafting and shafting the crab-like body plan remain but a mystery, though evolution must be doing something right in fashioning crabby creatures time and time again.

There are thousands of crab species, which thrive in almost every habitat on Earth, from coral reefs and abyssal plains to creeks, caves and forests.

Crabs also boast an impressive display of sizes. The smallest, the pea crab (*Pinnothera faba*), measures just millimeters, while the largest, the Japanese spider crab (*Macrocheira kaempferi*), spans nearly 4 meters (around 12 feet) from claw to claw.

With their species richness, extravagant array of body shapes and rich fossil record, crabs are an ideal group to study trends in biodiversity through time. But finding some order in the chaos of crabs is an ongoing challenge.

What's a crab, anyway?

It gets weirder, because not every crab is a crab, so to speak. There are 'true' crabs, such as mud crabs and swimmer crabs. Yet we also have so-called false crabs, such as shell-shy hermit crabs with their spiraling abdomens, or the spike-covered king crabs.

The most visible difference between true and false crabs is how many walking legs they have: true crabs have four pairs of lanky legs, whereas false crabs only have three, with another pint-sized pair at the rear.

Both true and false crabs evolved their wide, flat, hard upper shell and tucked tails independently of one another, from a common ancestor that had none of those features, suggests an analysis published in March 2021, led by evolutionary biologist Joanna Wolfe of Harvard University.

But it wasn't a straightforward path after true and false crabs split. Evolution has made and remade crabs over the past 250 million years: once or twice in true crabs and at least three times during the evolution of false crabs, Wolfe and colleagues think.

Crabs have long stumped taxonomists who have invariably misclassified species as true or false crabs due to their striking similarities.

Besides figuring out where species belong in the tree of life, understanding exactly how many times evolution has crafted the

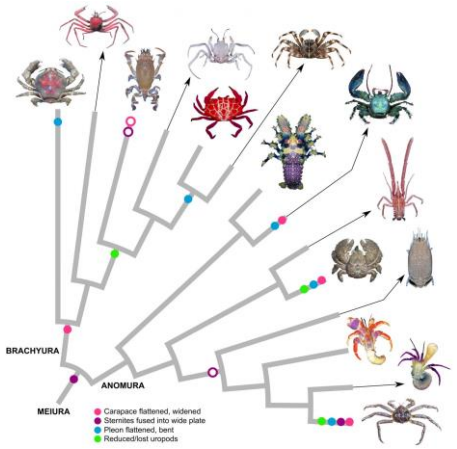
crab-like body form and why, could reveal something about what drives convergent evolution.

"There has to be some kind of evolutionary advantage to be this crablike shape," crab expert and Wolfe's co-author Heather Bracken-Grissom told Popular Science in 2020, when carcinization had sent the internet into a spin.

As with many subjects, evolutionary biologists have plenty of ideas, but no firm answers on carcinization. Due to the narrow focus of past research on select crab species, "the unparsimonious history of crab body plan evolution must be reconciled", the team writes.

To make a start, the trio of researchers compiled data on crab morphology, behavior and natural history, from living species and fossils, and identified the gaps in genetic data which might help to resolve puzzling evolutionary relationships.

"Almost half of the branches on the crab tree of life remain dark," they write.



Above: Phylogenetic tree showing examples of carcinized and decarcinized clades, with colored dots noting characteristics on the branches. **(Joanna M. Wolfe)**

Most carcinized crabs have developed hard, calcified shells to protect themselves from predators – a clear advantage – but then some crabs have abandoned this protection, for reasons unknown.

Walking sideways, silly as it seems, means crabs are supremely agile, able to make a speedy exit in either direction without losing sight of a predator, should one appear. But sideways walking is not observed in all carcinized lineages (there are forward-walking spider crabs) and some uncarcinized hermit crabs can walk sideways, too.

That some crabs evolved outsized claws to become shell-crushing predators in an ecological arms race also cannot fully explain the timing or successes of early crab evolution.

Like anything in science, nothing is ever settled and evolution will continue on its merry way. Though with increasing amounts of genomic information on living and fossilized crab species, rest assured taxonomists are steadily piecing together what makes a crab, a crab.

This "will allow us to resolve the multiple origins and losses of 'crab' body forms through time and identify the timing of origin of key evolutionary novelties and body plans," says Wolfe.

More than that, studying crabs provides a tantalizing prospect for evolutionary sleuths who think it might be possible to anticipate the predictable shapes evolution makes based on environmental factors and genetic cues.

"Examining crab evolution provides a macroevolutionary timescale of 250 million years ago for which, with enough phylogenetic and genomic data, we might be able to predict the morphology that would result," says Bracken-Grissom.

A crab-like shape might be a safe bet.

The paper was published in *BioEssays*.

https://bit.ly/31i2X8L

How a handful of prehistoric geniuses launched humanity's technological revolution

A few clever people created many of history's big inventions, which were then shared

by Nicholas R. Longrich, The Conversation

For the first few million years of human evolution, technologies changed slowly. Some three million years ago, our ancestors were making chipped stone flakes and crude choppers. Two million years ago, hand-axes. A million years ago, primitive humans sometimes

used fire, but with difficulty. Then, 500,000 years ago, technological change accelerated, as spearpoints, firemaking, axes, beads and bows appeared.

This technological revolution wasn't the work of one people. Innovations arose in different groups—modern Homo sapiens, primitive sapiens, possibly even Neanderthals—and then spread. Many key inventions were unique: one-offs. Instead of being invented by different people independently, they were discovered once, then shared. That implies a few clever people created many of history's big inventions. And not all of them were modern humans.

The tip of the spear

500,000 years ago in southern Africa, primitive Homo sapiens first bound stone blades to wooden spears, creating the spearpoint. Spearpoints were revolutionary as weaponry, and as the first "composite tools"—combining components.

The spearpoint spread, appearing 300,000 years ago in East Africa and the Mideast, then 250,000 years ago in Europe, wielded by Neanderthals. That pattern suggests the spearpoint was gradually passed on from one people to another, all the way from Africa to Europe.

Catching fire

400,000 years ago hints of fire, including charcoal and burnt bones, became common in Europe, the Mideast and Africa. It happened roughly the same time everywhere—rather than randomly in disconnected places—suggesting invention, then rapid spread. Fire's utility is obvious, and keeping a fire going is easy.

Starting a fire is harder, however, and was probably the main barrier. If so, widespread use of fire likely marked the invention of the fire-drill—a stick spun against another piece of wood to create friction, a tool still used today by hunter-gatherers.

Curiously, the oldest evidence for regular fire use comes from Europe—then inhabited by Neanderthals. Did Neanderthals master fire first? Why not? Their brains were as big as ours; they used them for something, and living through Europe's ice-age winters, Neanderthals needed fire more than African Homo sapiens.

The axe

270,000 years ago in central Africa, hand-axes began to disappear, replaced by a new technology, the core-axe. Core-axes looked like small, fat hand-axes, but were radically different tools.

Microscopic scratches show core-axes were bound to wooden handles—making a true, hafted axe. Axes quickly spread through Africa, then were carried by modern humans into the Arabian peninsula, Australia, and ultimately Europe.

Ornamentation

The oldest beads are 140,000 years old, and come from Morocco. They were made by piercing snail shells, then stringing them on a cord. At the time, archaic Homo sapiens inhabited North Africa, so their makers weren't modern humans.

Beads then appeared in Europe, 115,000–120,000 years ago, worn by Neanderthals, and were finally adopted by modern humans in southern Africa 70,000 years ago.

Bow and arrow

The oldest arrowheads appeared in southern Africa over 70,000 years ago, likely made by the ancestors of the Bushmen, who've lived there for 200,000 years.

Bows then spread to modern humans in East Africa, to south Asia 48,000 years ago, on to Europe 40,000 years ago, and finally to Alaska and the Americas, 12,000 years ago.

Neanderthals never adopted bows, but the timing of the bow's spread means it was likely used by Homo sapiens against them.

Trading technology

It's not impossible that people invented similar technologies in different parts of the world at roughly the same time, and in some cases, this must have happened.

But the simplest explanation for the archaeological data we have is that instead of reinventing technologies, many advances were made just once, then spread widely. After all, assuming fewer innovations requires fewer assumptions.

But how did technology spread? It's unlikely individual prehistoric people traveled long distances through lands held by hostile tribes (although there were obviously major migrations over generations), so African humans probably didn't meet Neanderthals in Europe, or vice versa.

Instead, technology and ideas diffused—transferred from one band and tribe to the next, and the next, in a vast chain linking modern Homo sapiens in southern Africa to archaic humans in North and East Africa, and Neanderthals in Europe.

Conflict could have driven exchange, with people stealing or capturing tools and weapons. Native Americans, for example, got horses by capturing them from the Spanish. But it's likely that people often just traded technologies, simply because it was safer and easier. Even today, modern hunter-gatherers, who lack money, still trade—Hadzabe hunters exchange honey for iron arrowheads made by neighboring tribes, for example.

Archaeology shows such trade is ancient. Ostrich eggshell beads from South Africa, up to 30,000 years old, have been found over 300 kilometers from where they were made. 200,000—300,000 years ago, archaic Homo sapiens in East Africa used tools from obsidian sourced from 50–150 kilometers away, further than modern hunter-gatherers typically travel.

Last, we shouldn't overlook human generosity—some exchanges may simply have been gifts. Human history and prehistory were doubtless full of conflict, but then as now, tribes may have had peaceful interactions—treaties, marriages, friendships—and may simply have gifted technology to their neighbors.

Stone Age geniuses

The pattern seen here—single origin, then spread of innovations—has another remarkable implication. Progress may have been highly dependent on single individuals, rather than being the inevitable outcome of larger cultural forces.

Consider the bow. It's so useful that its invention seems both obvious and inevitable. But if it really was obvious, we'd see bows invented repeatedly in different parts of the world. But Native Americans didn't invent the bow—neither did Australian Aborigines, nor people in Europe and Asia.

Instead, it seems one clever Bushman invented the bow, and then everyone else adopted it. That hunter's invention would change the course of human history for thousands of years to come, determining the fates of peoples and empires.

The prehistoric pattern resembles what we've seen in historic times. Some innovations were developed repeatedly—farming, civilisation, calendars, pyramids, mathematics, writing, and beer were invented independently around the world, for example. Certain inventions may be obvious enough to emerge in a predictable fashion in response to people's needs.

But many key innovations—the wheel, gunpowder, the printing press, stirrups, the compass—seem to have been invented just once, before becoming widespread.

And likewise a handful of individuals—Steve Jobs, Thomas Edison, Nikola Tesla, the Wright Brothers, James Watt, Archimedes—played outsized roles in driving our technological evolution, which implies highly creative individuals had a huge impact.

That suggests the odds of hitting on a major technological innovation are low.

Perhaps it wasn't inevitable that fire, spearpoints, axes, beads or bows would be discovered when they were. Then, as now, one person could literally change the course of history, with nothing more than an idea.

https://bit.ly/3eLNSzn

There's Something About Eating Mushrooms That Seems to Lower Depression Risk

A large-scale analysis of people who eat mushrooms suggests they have a lower risk of developing depression.

Carly Cassella

The association is still a mystery, and for now, the authors say the data should be interpreted with caution. There's always a chance the results are a mere correlation, especially since eating more mushrooms didn't seem to lower the odds of depression any further.

That said, this is one of the first large observational studies on general mushroom consumption and depression. It includes the diet and mental health data of more than 24,000 adults across the United States from 2005 to 2016.

The findings don't differentiate between various types of mushrooms, but they are consistent with several small clinical trials on lion's mane mushrooms (*Hericium erinaceus*), which found eating certain types of fungi can help reduce depression and anxiety.

"The study adds to the growing list of possible health benefits of eating mushrooms," says public health scientist Joshua Muscat from the Pennsylvania State University.

What it is specifically about some mushrooms that makes them good for our health is still a puzzle.

White button mushrooms (*Agaricus bisporus*) are the most commonly eaten fungi in the US and are full of potassium, which is thought to help lower anxiety. Other edible mushrooms like lion's mane are known to contain neurotrophic factors linked to brain health, as well as anti-inflammatory agents, which are thought to help alleviate symptoms of depression.

But nutrition science is tricky business. Mushrooms host a variety of vitamins, minerals and antioxidants that could be contributing to their apparent antidepressant effects. Teasing out which factors are at play will require many more molecular, clinical, and epidemiological studies.

Nevertheless, there's a powerful antioxidant known as ergothioneine contained in mushrooms that scientists have their eye on. Humans can only get it through diet, and mushrooms have it in the highest concentrations of any fresh foods we consume.

In recent animal models, this antioxidant has been found to cross the bloodstream barrier that separates the brain from the rest of the body, which suggests ergothioneine could have some effect on neurological health.

Other animal models suggest this antioxidant plays a role in gut health, too, where there are also neurons that can also impact a person's mood. Whether the same can be said of humans remains to be investigated.

"Mushrooms are the highest dietary source of the amino acid ergothioneine – an anti-inflammatory which cannot be synthesized by humans," says epidemiologist Djibril Ba from Penn State.

"Having high levels of this may lower the risk of oxidative stress, which could also reduce the symptoms of depression."

Still, that's just a potential explanation. More research among larger cohorts will need to study what is different about specific mushrooms and how those differences ultimately impact human health.

The data in this case came from the US National Health and Nutrition Examination Survey, in which participants nationwide were asked to recall how many mushrooms they'd eaten in the two days prior. Their depression was then measured using a standardized patient health questionnaire.

The observed association between mushroom consumption and lower odds of depression was independent of other confounding factors, like social status, economic status, lifestyle risk factors, self-reported disease, and medication use.

The people most likely to eat mushrooms were college-educated, non-Hispanic white women, according to the authors. But the link to depression was only clear when they compared mushroom eaters to non-eaters.

Within the cohort of mushroom eaters, those who ate them relatively a lot, didn't seem to show any additional benefits.

In a further analysis of the data, the authors compared those who ate one serving of mushrooms per day with those who ate one serving of red or processed meat. Interestingly, the substitution was not associated with lower odds of depression.

Clearly, there's still a lot we don't know about the relationship between mushrooms and mental health. But given how often the relationship keeps popping up in studies, it's worth exploring more.

"These findings highlight the potential clinical and public health importance of mushroom consumption as a means of reducing depression and preventing diseases," the authors conclude.

The study was published in the *Journal of Affective Disorders*.