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Tuberculosis Vaccine Could Reverse Type 1 Diabetes, Study Shows

Causes of Type 1 diabetes significantly reversed for several years after two injections of tuberculosis vaccine injected a few weeks apart

By Glenn Fleishman

The causes of Type 1 diabetes can be significantly reversed over several years with just two injections of a common tuberculosis vaccine injected a few weeks apart, researchers at Massachusetts General Hospital (MGH) announced Thursday in a paper published in the journal *Nature*.

Researchers found a substantial reduction in the blood-sugar marker HbA1c that is used to diagnose diabetes. All subjects with diabetes who received the vaccine had a 10% reduction after three years and 18% after four years, bringing them below the cutoff point for a clinical diagnosis. Those subjects followed for a full eight years retained most of the reduction.

Participants who received a placebo or were in a reference group that followed normal diabetic management saw their blood sugar measurement rise by a few percentage points during the same periods followed. Subjects of the study receiving the vaccine or placebo continued to use insulin during the study period.

The study's principal director, Dr. Denise Faustman, director of the MGH Immunobiology Laboratory, told FierceBiotech and other news outlets, "Nobody thought you could intervene with an immunotherapy in people 10, 20 years out. To have data showing durability for 8 years, without revaccination, is remarkable."

A 10% reduction in Hb1Ac reduces the risk of death as a result of diabetes by 21%, and drops by 37% other complications, like blindness and loss of feeling in hands and feet, according to a 2000 study.

The study followed a relatively small number of people: 52 total with Type 1 diabetes, only 12 of whom received injections. Of the 12, nine received the vaccine and three the placebo. All 52 had follow-up measurements through five years. And three of those who received the vaccine were followed for eight years.

Medical researchers not involved in the study expressed a range of high to very mild skepticism about the validity of the study due almost entirely to its small size. "This could be something that happened by chance because people were a bit more diligent or leaner or more compliant with diet," Dr. Adrian Vella, an endocrinologist at the Mayo Clinic, said in an interview with NBC News. However, Dr. Joseph Bellanti, a professor of pediatrics and microbiology-immunology at Georgetown Medical Center, said in an interview with WBUR that was "cautiously optimistic" because of the quality of the study's design.

A failure to produce enough insulin, Type 1 diabetes affects an estimated 20 to 40 million people globally. The more common form Type 2, resulting from obesity and lack of exercise, affects at least 400 million people. Diabetes incidence has more than quadrupled in the last 40 years.

The study relied on the bacillus Calmette-Guérin (BCG) vaccine, which has been used in humans since 1921. Its use is limited in the United States, because the form of bacteria it protects against, *Mycobacterium tuberculosis*, is rare in this country. The CDC generally recommends against its use as it creates false positives from a TB test that's routine in the U.S. However, it's been administered to an estimated 4 billion people.

Based on initial mice tests, researchers expected the vaccine would prompt regeneration of the pancreas, which produces insulin. Instead, they write in their paper, a form of white blood cells starts to metabolize sugar more aggressively—10 to 20 times as much as they normally consume.

However, the long delay in a measurable effect wasn't a surprise. A number of studies using BCG that have produced outcomes such as slowing the progress of multiple sclerosis and other autoimmune diseases show a long onset.

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Ancient brewing was not a Hittite or miss process

Research finds 4000-year-old Anatolian beer was very likely delicious.

Andrew Masterson reports.

Beer-makers in the ancient Hittite empire – which centred on Anatolia in modern Turkey – carefully controlled their brews according to the season, altered flavours according to taste, and used a bittering agent thousands of years before the domestication of hops.

A Hittite relief depicting agriculture and trade. **Wikimedia commons**

Those are some of the main findings emerging from research by Michael Brown from the Institut für Ur- und Frühgeschichte und Vorderasiatische Archäologie in Heidelberg, Germany, and published in the *Journal of Archaeological Science: Reports*.

Absent from Brown's paper, however, is the discovery that Hittite beer – at least the style derived from biological and archaeological evidence unearthed at a temple brewery site in Kuşaklı-Sarissa in north-central Anatolia, dating to the second millennium BCE – would not have been out of place in a modern gastro-pub.

"It's not mentioned in the paper but we did brew a small trial batch in the lab while writing up the chemical analyses," he says. "Surprisingly pleasant, a bit like Belgium Duvel!"

The Hittite empire arose around 1600 BCE, and reached its height about two centuries later when its reach included the northern Levant and Upper Mesopotamia. Sources attest that beer-drinking fulfilled several ceremonial and religious functions.

To further flesh out this picture, Brown analysed residues obtained from archaeological samples in order to understand the materials and techniques used by the brewers at the site. Kuşaklı-Sarissa's use for beer-making was easily confirmed by the presence of calcium oxalate, a substance that forms when oxalic acid bonds with calcium in water. The molecule is a strong (although not conclusive) indicator of barley-based brewing, especially when found on ceramic vessels.

The containers found at the site (and mirrored by those at a second brewery unearthed in the old Hittite capital of Boğazköy-Hattusa) included large vessels for mashing, and narrow-necked amphorae that could be easily sealed with clay to prevent bacterial contamination.

Some of the beer being brewed, Brown suggests, was consumed through reed straws stuck straight into the fermentation vessels. Most, however, would have been sealed up and left to mature.

Grain remnants found at the site were overwhelmingly from barley. The kernels were much larger than those from other parts of the of wider archaeological dig, implying, says Brown, that they were deliberately selected for beer-making.

Smaller concentrations of Emmer wheat kernels were also found – suggesting that the brewers sometimes made mixed-grain ales, or even pure wheat beers.

Brown cites research published in 2011 that established that brewing practices varied substantially across the Hittite empire, and were also influenced by seasonal temperatures.

For instance, grain was dried by spreading it over mats placed on the flat roofs of buildings. Fresh grains were turned over twice a day, achieving germination, the researchers found, in as little as four days.

There is also some evidence that the Hittites combined malted and unmalted grains in the mashing process, perhaps in an effort to produce lower-alcohol brews. (The result, notes Brown, would have been "not always the desired outcome".)

Ancient beers, it has often been assumed, would have been significantly sweet, mainly because hops – the important bittering agent used today – was not deployed until the late Medieval period.

The Hittites, Brown's research discovered, very likely achieved the same result using a different botanical. His residue analysis revealed significant quantities – between one and two per cent – of seeds from plants in the genus *Polygonum*, which includes buckwheat and knotweed among about 220 other species.

The 4000-year-old samples were too degraded to enable precise identification, but polygonum seeds are known to contain high concentrations of phenolic compounds, which impart a bitter taste.

Brown points out that there is no specific Hittite word so far translated that specifies "bitter", and at least two that imply "sweet" in a beer context. This, he said, should not be used to infer that all Hittite beers were sugary to taste.

Rather, it is more likely to mean that bitter-tasting beers were the norm, and that sweet ones – such as *marnuan*, a honey beer, and *Walhi*, another sweetened form – were speciality brews that, again, might not be out of place in a groovy little downtown bar in Berlin.

The research fails to pinpoint the exact source the Kuşaklı-Sarissa brewers used to secure the other essential ingredient for alcohol-making: yeast. Brown identifies several possibilities, including honey-mead, grape-wine and hardwood bark from nearby woodland. Regardless of origin, however, he notes that yeast reserves were very likely stored in sugar-rich worts – the liquid extracted from the mashing process – in narrow-necked bottles for use during the colder months when the key species, *Saccharomyces cerevisiae*, was in short supply.

Remnant yeast populations were also very likely to be present all year round on the porous surfaces of the brewery's clay vessels and walls – a fact, Brown suggests, that "would have served to increase consistency between successive fermentations".

The research strong suggests that 4000 years ago the Hittites were serving up beers that were varied, deliberate, and ranged in alcohol content. Brown's brewing experiment also established that the drinks in question were very likely sophisticated and delicious.

His results, he concludes, may well be of interest to more than just archaeologists and historians.

"This study establishes a theoretical basis for future experimental reconstruction and highlights novel ingredients potentially of interest to modern craft brewers," he writes.

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Why life on Earth first got big

Some of the earliest complex organisms on Earth - possibly some of the earliest animals to exist - got big not to compete for food, but to spread their offspring as far as possible.

Emily Mitchell

The research, led by the University of Cambridge, found that the most successful organisms living in the oceans more than half a billion years ago were the ones that were able to 'throw' their offspring the farthest, thereby colonising their surroundings. The results are reported in the journal *Nature Ecology and Evolution*.

Prior to the Ediacaran period, between 635 and 541 million years ago, life forms were microscopic in size, but during the Ediacaran, large, complex organisms first appeared, some of which - such as a type of organism known as rangeomorphs - grew as tall as two metres. These organisms were some of the first complex organisms on Earth, and although they look like ferns, they may have been some of the first animals to exist - although it's difficult for scientists to be entirely sure. Ediacaran organisms do not appear to have mouths, organs or

means of moving, so they are thought to have absorbed nutrients from the water around them.

As Ediacaran organisms got taller, their body shapes diversified, and some developed stem-like structures to support their height.

In modern environments, such as forests, there is intense competition between organisms for resources such as light, so taller trees and plants have an obvious advantage over their shorter neighbours. "We wanted to know whether there were similar drivers for organisms during the Ediacaran period," said Dr Emily Mitchell of Cambridge's Department of Earth Sciences, the paper's lead author. "Did life on Earth get big as a result of competition?"

Artist's impression of rangeomorphs, fern-like organisms that lived during the Ediacaran Period. **Charlotte Kenchington**

Mitchell and her co-author Dr Charlotte Kenchington from Memorial University of Newfoundland in Canada examined fossils from Mistaken Point in south-eastern Newfoundland, one of the richest sites of Ediacaran fossils in the world. Earlier research hypothesised that increased size was driven by the competition for nutrients at different water depths. However, the current work shows that the Ediacaran oceans were more like an all-you-can-eat buffet.

"The oceans at the time were very rich in nutrients, so there wasn't much competition for resources, and predators did not yet exist," said Mitchell, who is a Henslow Research Fellow at Murray Edwards College. "So there must have been another reason why life forms got so big during this period."

Since Ediacaran organisms were not mobile and were preserved where they lived, it's possible to analyse whole populations from the fossil record. Using spatial analysis techniques, Mitchell and Kenchington found that there was no correlation between height and competition for food. Different types of organisms did not occupy different parts of the water column to avoid competing for resources - a process known as tiering.

"If they were competing for food, then we would expect to find that the organisms with stems were highly tiered," said Kenchington. "But we found the opposite: the organisms without stems were actually more tiered than those with stems, so the stems probably served another function."

According to the researchers, one likely function of stems would be to enable the greater dispersion of offspring, which rangeomorphs produced by expelling small propagules. The tallest organisms were surrounded by the largest clusters of offspring, suggesting that the benefit of height was not more food, but a greater chance of colonising an area.

"While taller organisms would have been in faster-flowing water, the lack of tiering within these communities shows that their height didn't give them any distinct advantages in terms of nutrient uptake," said Mitchell. "Instead, reproduction appears to have been the main reason that life on Earth got big when it did."

Despite their success, rangeomorphs and other Ediacaran organisms disappeared at the beginning of the Cambrian period about 540 million years ago, a period of rapid evolutionary development when most major animal groups first appear in the fossil record.

The research was funded by the Natural Environment Research Council, the Cambridge Philosophical Society, Murray Edwards College and Newnham College, Cambridge.

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Genes linking Alzheimer's and Down syndrome discovered

Scientists are a step closer to understanding which genes are responsible for early onset Alzheimer's disease in people with Down syndrome

Scientists are a step closer to understanding which genes are responsible for early onset Alzheimer's disease in people with Down syndrome, thanks to a new study led by researchers at the Francis Crick Institute and UCL along with an international group of collaborators.

The findings could pave the way for future medicines to prevent the disease in these individuals, and provide insights into the mechanisms that cause dementia in the general population.

Around 1 in 800 people are born with Down syndrome, which arises in people carrying an extra copy of chromosome 21. By the time they reach their 60s, around two thirds of those with Down syndrome will have early onset Alzheimer's.

The high rates of Alzheimer's in people with Down syndrome were previously thought to be caused by a particular gene on chromosome 21 called APP. Chromosome 21 contains 231 genes, but APP was the prime suspect because it produces amyloid precursor proteins. These are involved in generating amyloid beta proteins, which build up in the brain in Alzheimer's patients.

In this study, published in the journal *Brain*, researchers found that extra copies of other genes on chromosome 21 increase Alzheimer's-like brain pathology and cognitive impairments in a mouse model of Down syndrome.

Dr Frances Wiseman, Senior Research Fellow at UCL, and first author of this study, said: "We've shown for the first time that genes other than APP are playing a role in early-onset Alzheimer's disease in our model of Down Syndrome. Identifying what these genes are, and what pathways are involved in the earliest stages of neurodegeneration, could help us to one day intervene with these pathways to prevent the disease in people with Down syndrome."

The team compared mice that produce APP amyloid protein with, and without, the presence of human chromosome 21, to tease apart the contributions of APP and other genes in Alzheimer's disease.

They found that mice with an extra copy of all the genes on chromosome 21 had more signs of Alzheimer's disease than mice without. The mice with extra copies of all genes on chromosome 21 had greater levels of amyloid beta and more protein clumps or 'plaques' inside part of the brain that controls memory, and performed worse on memory tests.

The team then looked at what was causing the increased build-up of amyloid-beta and plaques in the brains of mice with extra copies of all the genes on human chromosome 21. They found that these mice produced more of a particular type of amyloid beta protein that is more prone to forming clumps.

Dr Victor Tybulewicz, Group Leader at the Francis Crick Institute and co-senior author of the paper, said: "Down syndrome has historically been very difficult to model in a mouse, because the genes that we have on chromosome 21 are spread across three different chromosomes in mice. Only after years of refining our mouse models can we study the earliest stages of Alzheimer's, and other diseases, in the context of Down syndrome."

Elizabeth Fisher, Professor of Neurogenetics at UCL, and co-senior author of the paper, added: "Although we're looking at Alzheimer's disease through the lens of Down syndrome, this international collaboration provides insight into the earliest stages of disease progression, which may be applicable to modulating Alzheimer's disease in the general population."

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Why Cancer Rates Are Higher in Flight Attendants

Flight attendants may have a higher risk of a number of cancers, a new study finds.

By Cari Nierenberg, Live Science Contributor

Researchers found that women and men on U.S. cabin crews have higher rates of many types of cancer, compared with the general population. This includes cancers of the breast, cervix, skin, thyroid

and uterus, as well as gastrointestinal system cancers, which include colon, stomach, esophageal, liver and pancreatic cancers.

One possible explanation for these increased rates is that flight attendants are exposed to a lot of known and potential carcinogens, or cancer-causing agents, within their work environment, said lead study author Irina Mordukhovich, a research associate at Harvard University's T.H. Chan School of Public Health.

One of those carcinogens is cosmic ionizing radiation, which is elevated at higher altitudes, Mordukhovich told Live Science. This type of radiation is particularly damaging to DNA and is a known cause of breast cancer and nonmelanoma skin cancer, she said.

Air cabin crews receive the highest yearly dose of ionizing radiation on the job of all U.S. workers, she added.

In the new study, the researchers looked at data from more than 5,300 flight attendants from different airlines who completed an online survey as part of the Harvard Flight Attendant Health Study. The analysis looked at the cancer rates in these flight attendants compared to a group of about 2,700 people who had a similar income and educational status but were not flight attendants.

The researchers found that in female flight attendants, the rates of breast cancer were about 50 percent higher than in women from the general population. In addition, melanoma rates were more than two times higher and nonmelanoma skin cancer rates were about four times higher in female flight attendants compared with women from the general population. (Nonmelanoma skin cancers include basal cell and squamous cell carcinomas.) These elevated cancer rates were observed despite indications of good-health behaviors, such as low levels of smoking and obesity, in the flight-attendant group as a whole, the study authors said. Cancer rates in male flight attendants were nearly 50 percent higher for melanoma and about 10 percent higher for nonmelanoma skin cancers compared with men from the general population group, according to the findings.

Risks of very frequent flying

The potential cancer risks for flight attendants are not limited to cosmic ionizing radiation. Cabin crew members are also regularly exposed to more UV radiation than the general population, which can make these workers more vulnerable to skin cancers, Mordukhovich said.

In addition, some studies have found that circadian rhythm disruptions, such as jet lag, might be linked with an increased risk of cancer, she said. These disruptions could lead to changes in immune function and cell metabolism, which can reduce the suppression of tumors.

Another possible threat to the health of cabin crew members is chemical exposure, according to the study. The women and men who worked as flight attendants prior to 1988, when smoking was first banned on some U.S. flights, were routinely exposed to secondhand smoke while on board the aircraft.

Other chemical contaminants found in the cabin may include engine leakages, pesticides and flame retardants, which contain compounds that may act as hormone disruptors and increase the risk of some cancers, Mordukhovich said.

Further complicating matters is that flight attendants in the U.S. don't have the same occupational protections as their counterparts in the European Union. There, exposure levels to radiation as well as work schedules are routinely monitored and adjusted to make sure flight attendants don't exceed certain guidelines for carcinogen exposure, Mordukhovich said.

There has been only limited research on the health of flight attendants, but they may not be the only air travelers to experience higher rates of cancer. The rates may also be higher for pilots and people who fly often as passengers, Mordukhovich said. Studies of pilots have generally shown higher rates of skin and prostate cancers, she noted, adding that pilots also have been found to have circadian rhythm

disruption, but these workers have somewhat more built-in protections around their scheduling and rest times than flight attendants do.

Although the cancer risks for frequent flyers have not yet been studied, there is no reason to suspect these people would not have similar risks as those faced by cabin crews, Mordukhovich said.

Some limitations of the study are that researchers were not able to take into consideration individual UV exposures, such as sunbathing habits or leisure-time activities, which could influence skin cancer risk. In addition, cancer rates were self-reported by study participants, and these diagnoses were not confirmed by a check of their medical records by the researchers, according to the study.

The study was published online today (June 25) in the journal Environmental Health.

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Myth that persistent musculoskeletal pain with no obvious cause can be cured

Clinicians need to be more honest with patients about what they can really expect

It's a myth that most persistent musculoskeletal pain with no obvious cause can be cured, argue experts in an editorial published online in the British Journal of Sports Medicine. Doctors and other healthcare professionals need to be a lot more honest with patients about what they can really expect, write Professor Jeremy Lewis, of the University of Hertfordshire and Central London Community Healthcare NHS Trust, and Professor Peter O'Sullivan, of Curtin University, Perth, and Bodylogic Physiotherapy, Perth, Australia.

There's no magic fix and patients may have to live with their pain as they would any other long term condition, they say.

The fact that most persistent musculoskeletal pain that isn't the result of injury or trauma has no obvious cause has prompted the development of two unfortunate trends, the authors suggest.

Firstly, structural changes that are commonly seen on the x-rays and scans of people with no pain, such as rotator cuff (muscles over the upper arm bone) tears and intervertebral (spinal) disc degeneration, are often used to explain the pain.

This may not only prompt avoidance behaviours, but also a desire for corrective treatment, leading to unnecessary surgery on tendons, cartilage and bones that aren't the cause of the pain.

Secondly, some clinicians have arguably invented 'treatments' for conditions that may not actually exist or be readily detected, and for which there is no good evidence that they work.

"These two trends have created an expectation that interventions (frequently 'passive') will provide a 'cure,' and typically quickly, with minimal self-contribution," write the authors.

But the reality is that many musculoskeletal pain conditions are associated with disability and won't respond to current (passive) treatment. And they should be managed in the same way that other long term conditions, such as diabetes, are--with a focus not on providing a cure, but on minimising the impact on an individual's wellbeing, they suggest.

This includes lifestyle changes, such as stopping smoking and stress management, to enable that person to take control of their condition, rather than expecting the clinician to do this with various treatments.

"We need to reframe what is currently doable and achievable in the management of many non-traumatic musculoskeletal presentations, and honest and open conversations regarding the outcome evidence for these disorders needs to be sensitively communicated," they argue.

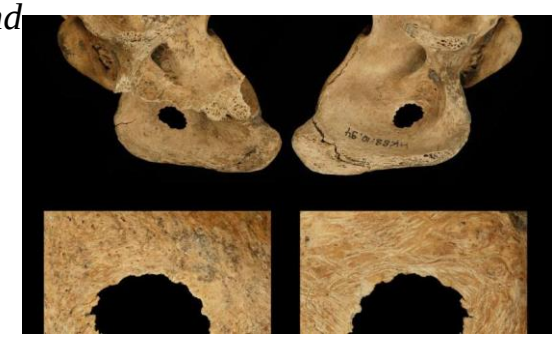
"For patients, creating an understanding and expectation that, as with other chronic health conditions, there is no magic cure for persistent and disabling musculoskeletal pain conditions...is the key...By doing this, we can...be more honest with the level and type of care we can and should currently offer, and the outcomes that may be achieved."

http://bit.ly/2tGbTkh

Neanderthals hunted in bands and speared prey up close: study

Neanderthals were capable of sophisticated, collective hunting strategies, according to an analysis of prehistoric animal remains from Germany that contradicts the enduring image of these early humans as knuckle-dragging brutes.

The cut marks—or "hunting lesions"—on the bones of two 120,000-year-old deer provide the earliest "smoking gun" evidence such weapons were used to stalk and kill prey, according to a study the journal *Nature Ecology and Evolution*.



Microscopic imaging and ballistics experiments reproducing the impact of the blows confirmed that at least one was delivered with a wooden spear at low velocity.

Front and back view of a hunting lesion in a cervical vertebra of an extinct fallow deer, killed by Neandertals 120.000 years ago on a lake shore close to current-day Halle (Germany). **Credit: Eduard Pop, MONREPOS Archaeological Research Centre and Museum for Human Behavioural Evolution, Römisch-Germanisches Zentralmuseum, Leibniz-Researchinstitute for Archaeology**

"This suggests that Neanderthals approached animals very closely and thrust, not threw, their spears at the animals, most likely from an underhand angle," said Sabine Gaudzinski-Windheuser, a researcher at Johannes Gutenberg-University Mainz, Germany.

"Such a confrontational way of hunting required careful planning and concealment, and close cooperation between individual hunters," she told AFP.

Neanderthals lived in Europe from about 300,000 years ago until they died out 30,000 years ago, overtaken by our species.

It was long thought that these evolutionary cousins—modern Europeans and Asians have about two percent of Neanderthal DNA—were not smart enough to compete, and lacked symbolic culture, a trait supposedly unique to modern humans.

Estimated impact angle shown in relation to a standing fallow deer for the hunting lesion observed in the pelvis of an extinct fallow deer, killed by Neandertals 120,000 years ago on a lake shore close to current-day Halle (Germany). **Credit: Eduard Pop, MONREPOS Archaeological Research Centre and Museum for Human Behavioural Evolution, Römisch-Germanisches Zentralmuseum, Leibniz-Researchinstitute for Archaeology**

But recent finds have revealed a species with more intelligence and savoir faire than suspected.

They buried their dead in ritual fashion, created tools, and painted animal frescos on cave walls at least 64,000 years ago, 20,000 years before homo sapiens arrived in Europe.

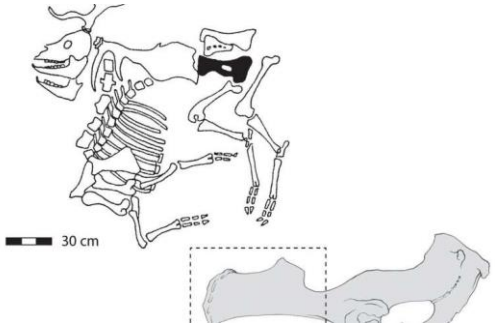
Secrets of old bones

Hominins—the term used to describe early human species, as well as our own—most likely started hunting with weapons more than half-a-million years ago.

300,000- to 400,000-year-old wooden staves found in England and Germany are the oldest known spear-like implements likely used for killing prey. But there was no physical evidence as to their use, leaving scientists to speculate. The new find from the Neumark-Nord area of Germany removes that doubt, said Gaudzinski-Windheuser. "As far as spear use is concerned, We now finally have the 'crime scene' fitting to the proverbial 'smoking gun'," she said.

Lake shore excavations from the same site since the 1980s have yielded tens of thousands of bones from large mammals, including red and fallow deer, horses and bovids.

They have also turned up thousands of stone artefacts, attesting to a flourishing Neanderthal presence in what was a forest environment during an interglacial period 135,000 and 115,000 years ago.



Front and back view of a hunting lesion in the pelvis of an extinct fallow deer, killed by Neandertals 120,000 years ago on a lake shore close to current-day Halle (Germany). **Eduard Pop, MONREPOS Archaeological Research Centre and Museum for Human Behavioural Evolution, Römisch-Germanisches Zentralmuseum, Leibniz-Researchinstitute for Archaeology**

The old deer bones examined for the study were unearthed more than 20 years ago, but new technologies helped unlock their secrets: which injuries were lethal, what kind of weapon was used, and whether the spears were thrown from a distance or thrust from close up.

The damage done was also especially pronounced, making "the forensic style replication and analysis in this paper possible," wrote Annemieke Milks, a researcher at the Institute of Archaeology at University College London.

"The ballistics work is experimental archaeology at its best," she commented, also in Nature Ecology and Evolution.

We should also allow for the possibility that Neanderthals threw their spears as well, she added.

More information: *Sabine Gaudzinski-Windheuser et al. Evidence for close-range hunting by last interglacial Neanderthals, Nature Ecology & Evolution (2018).* DOI: 10.1038/s41559-018-0596-1

http://bit.ly/2lGOqLA

New diagnosis method could help spot head and neck cancers earlier

Oral squamous cell carcinomas (OSCCs) are the most common head and neck cancers, but are often diagnosed late.

Now, researchers in Germany have developed a new cell-based test that could help provide earlier and more reliable diagnosis of OSCCs. Writing in *Science Physical Oncology*, the researchers explain how they tested the mechanical properties of OSCC cells, and found they were 'softer' than benign cells.

Lead authors Professor Josef Käs and Professor Torsten W. Remmerbach, from the University of Leipzig, said: "Early diagnosis and treatment of OSCCs is essential to enabling recovery. But in up to 60 per cent of cases the diagnosis is late because the growth has not been recognised, or has been mistaken as harmless."

The research team examined if cells' mechanical properties could be used as a marker for malignancy. As well as being softer than benign cells, the team saw that cancer cells exhibited a faster contraction than their benign counterparts when testing the relaxation behaviour after stress release.

Professor Remmerbach said: "This new way of drawing distinction between malignant and benign cells could enable an early confirmation of cancer diagnoses, by testing cell samples of suspect oral lesions."

The researchers used an optical stretcher to analyse the properties of the cells. Their experiments revealed that cells of primary OSCCs were deformed by 2.9 per cent, rendering them softer than cells of healthy mucosa, which were deformed only by 1.9 per cent.

Co-author Dr Jörg Schnauß said: "What we found also has implications for the way studies in cancer research are carried out. Many studies are performed with cancer cell lines rather than

primary cells. When comparing the mechanical properties of both, our results showed that long time culturing leads to softening of cells. "This softening in the culturing process could potentially affect the significance of test results. Because of that, we suggest that future research uses primary cells to ensure accuracy."

https://bbc.in/2Neq3Ij

Papua New Guinea polio outbreak declared

An outbreak of polio has been confirmed in Papua New Guinea, 18 years after the country was declared free of the disease.

The World Health Organization (WHO) says the virus was detected in a six-year-old boy in April.

The same strain of the virus has now been detected in other healthy children in the same community, making it officially an outbreak.

Polio has no cure and can lead to irreversible paralysis.

It mainly affects children under the age of five, and can only be prevented by giving a child multiple vaccine doses.

"We are deeply concerned about this polio case in Papua New Guinea, and the fact that the virus is circulating," said Pascoe Kase, Papua New Guinea's heath secretary. "Our immediate priority is to respond and prevent more children from being infected."

The US Centers for Disease Control and Prevention said at the end of last week that the same virus that was found in the six-year-old boy was also found in samples taken from two healthy children in the same community, the WHO said. This means the virus is circulating in the community, representing an outbreak, it added.

Immediate steps to stop the spread of the highly contagious disease include large-scale immunisation campaigns and strengthening surveillance systems that help detect it early.

Papua New Guinea has not had a case of wild poliovirus since 1996, and the country was certified as polio-free in 2000 along with the rest of the WHO Western Pacific Region.

What is polio?

Polio, or poliomyelitis, mainly affects children aged under five

It is a highly infectious disease caused by a virus. It invades the nervous system and can cause total paralysis in a matter of hours

Initial symptoms include fever, fatigue, headache, vomiting, stiffness of the neck and pains in the limbs

One in 200 infections leads to irreversible paralysis. Among those paralysed, 5% to 10% die when their breathing muscles become immobilised

Only three countries in the world have never stopped transmission of polio: Pakistan, Afghanistan and Nigeria ***Source:*** ***World Health Organization***

Only 61% of children in the area affected - Morobe province on the northern coast of the country - currently receive the recommended three doses of polio vaccine, the WHO says.

Inadequate sanitation and hygiene were also issues, it added.

Because of the region's isolation and the planned immunisation, the risk of the virus spreading to other countries is low, the WHO said.

There were some 20 cases of polio globally in 2017, with these cases occurring in just two countries: Afghanistan and Pakistan.

Will the world ever become polio-free?

Smitha Mundasad, global health correspondent

As recently as four decades ago, polio left 1,000 children paralysed every single day. The world has come a long way since then. Now, there are just a few countries where it is endemic and there have been just 15 cases so far this year. Zero seems tantalisingly close.

The good news is that polio is one of the few diseases that we actually have the ability to get down to zero. That is partly because it only infects humans - this means animals can't act as hidden reservoirs. And there are relatively inexpensive and effective vaccines that can offer protection for many years. Add in good sanitation and we are well equipped to battle the disease.

But global health experts say until it is completely eradicated, there remains a risk of polio spreading globally.

And areas like Morobe province in Papua New Guinea are particularly vulnerable as low vaccination rates and weak public health systems provide the ideal breeding grounds for cases to re-emerge.

https://wb.md/2IEwHxl

Atopic Dermatitis: Five Promising Targeted Therapies

Promising New Therapies for Atopic Dermatitis

Graeme M. Lipper, MD

Atopic dermatitis (AD) is a T-cell-driven, chronic inflammatory skin disease with a prevalence of up to 10% in adults and 25% in children.[1,2] Classic AD presents during infancy with recurrent facial dermatitis, morphing during childhood into chronic inflammatory flexural patches and lichenified plaques. Characteristics include pruritus, associated atopic diathesis (asthma, allergic rhinitis/conjunctivitis, food allergies), impaired epidermal barrier function, and such comorbid conditions as sleep disruption and failure to thrive.

Our understanding of the pathophysiology of another chronic inflammatory skin disease—psoriasis—has undergone a revolution over the past decade, yielding novel and highly effective immune-targeted therapies for this notoriously tough-to-treat chronic skin disease. In a similar vein, researchers are now mapping the immune dysregulation behind AD, which is characterized by chronic activation of the Th2 immune response.[3]

Systemic T-cell-suppressing therapies, such as azathioprine, methotrexate, mycophenolate mofetil, and cyclosporine, are effective at controlling moderate to severe AD (all as off-label indications). However, these treatments are limited by side effects, including immunosuppression, risk for cancer, and multiorgan toxicity, especially when taken chronically.

In contrast, dupilumab, a human monoclonal antibody targeting the interleukin-4 receptor alpha (IL-4R-alpha), received US Food and Drug Administration (FDA) approval for the treatment of moderate to severe AD in adults, in part on the basis of its remarkable safety profile and efficacy similar to that of some broader and more toxic immunosuppressive agents.[4]

Far from being a unique "unicorn" drug, dupilumab is the first in a long-line of promising drugs in the developmental pipeline. The following is a brief review of four promising biologics for moderate to severe AD and a fifth category of "small molecules" capable of targeting and inhibiting the atopic Th2 immune response.

Dupilumab: A Human Monoclonal Antibody Against IL-2R-Alpha

Dupilumab inhibits signaling of the proinflammatory Th2 cytokines IL-4 and IL-13. It was the first FDA-approved (March 2017) biologic agent to treat adults with moderate to severe AD that was refractory to topical corticosteroid therapy. The indication for AD was based on randomized, placebo-controlled clinical trials (SOLO 1 and SOLO 2)[4] involving adults in whom topical corticosteroid treatment had failed.

Adults with moderate to severe AD (SOLO 1, n = 671; SOLO 2, n = 708) were randomly assigned to receive dupilumab (300 mg subcutaneously) or placebo weekly or the same dose of dupilumab every other week alternating with placebo, for 16 weeks.

The primary outcome measure was an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear) and a score reduction of two or more points from baseline to week 16. Key findings include the following:

- The primary outcome measure was achieved in 38% of patients in SOLO 1 and 36% in SOLO 2 who injected dupilumab every other week versus 10% in the placebo group. Weekly dupilumab dosing did not improve efficacy.
- Dupilumab also improved secondary outcome measures, including > 75% improvement on the Eczema Area and Severity

Index (EASI 75), improved pruritus and quality-of-life scores, and reduced symptoms of anxiety and depression.

- Injection-site reactions and conjunctivitis were more frequent in the dupilumab versus placebo groups. Adverse events and laboratory values were otherwise similar in the treatment and placebo arms.

Lebrikizumab: Anti-IL-13 Monoclonal Antibody Targeting Soluble IL-13

IL-13 plays a central role in type 2 (Th2) inflammation, with levels of IL-13 mRNA correlating with AD severity. Lebrikizumab is still in clinical trials, including TREBLE,[5] a randomized, placebo-controlled 12-week trial of topical corticosteroid plus lebrikizumab every 4 weeks versus placebo involving 209 adults aged 18-75 years with moderate to severe AD. Key findings included the following:

- At week 12, significantly more patients who received lebrikizumab 125 mg by subcutaneous injection every 4 weeks achieved EASI-50 (a 50% improvement) compared with the placebo group (82.4% vs 62.3%, respectively).
- Adverse event rates were similar between the lebrikizumab and placebo groups.
- The benefit of lebrikizumab was probably blunted by protocol-mandated use of topical corticosteroid in the placebo group.

Fezakinumab: An Anti-IL-22 Monoclonal Antibody

IL-22 promotes epidermal hyperplasia, inhibits keratinocyte differentiation, impairs skin barrier formation, and induces proinflammatory cytokines. Hence, IL-22 blockade may have a therapeutic benefit in at least some subsets of AD. Still in early clinical trials, Guttman-Yassky and colleagues[6] recently concluded a randomized, double-blind, phase 2a trial of fezakinumab, administered intravenously every 2 weeks for 10 weeks, versus placebo. The primary outcome measure was the change in severity scoring of AD (SCORAD), an AD clinical severity index, from baseline to 12 weeks. Findings included the following:

- At 12 weeks, the mean reduction in SCORAD was 13.8 ± 2.7 in the fezakinumab group versus 8.0 ± 3.1 in the placebo group.
- SCORAD improvement was strongest in patients with severe AD treated with fezakinumab versus placebo, measured at 12 and 20 weeks.
- Rates of adverse events were similar in the fezakinumab and placebo groups.
- Because fezakinumab targets a novel inflammatory pathway (IL-22) independent of IL-4 and IL-13, it may help patients with moderate to severe AD that is refractory to dupilumab therapy.

Nemolizumab: An Anti-IL-31 Receptor A Monoclonal Antibody

IL-31 is a pruritogenic cytokine expressed in peripheral nerves and keratinocytes. A pilot placebo-controlled clinical trial[7] of nemolizumab injected subcutaneously every 4 or 8 weeks for the treatment of moderate to severe AD (n = 264) had the following findings:

- Pruritus, EASI scores, and sleep disruption improved during a 12-week period.
- The greatest improvement was seen in patients who received 0.5 mg/kg nemolizumab every 4 weeks.
- The study included a 52-week double-blind extension, during which improvement in pruritus and EASI scores was maintained or increased.
- No new safety concerns were identified during long-term use.

Small Molecules

Biologics are not the only story when it comes to promising new therapies for AD. The topical phosphodiesterase-4 inhibitor crisaborole received FDA approval in 2016 for the treatment of mild to moderate AD in adults and children aged 2 years or older, with modest efficacy and an excellent safety profile.[8]

Small molecules that are in clinical trials for AD include a Janus kinase 1/3 inhibitor (tofacitinib); an oral phosphodiesterase-4

inhibitor (apremilast); and drugs targeting the thymic stromal lymphopoietin (TSLP)-OX40 ligand pathway, which is thought to play a key role in Th2 immune activation.[9]

Viewpoint

Over the past decade, patients with moderate to severe AD had to watch in frustration as one new biologic after another received FDA approval for the treatment of psoriasis. Last spring, AD sufferers finally got their own highly effective biologic with the FDA approval of dupilumab.

Fortunately, this is only the beginning. An improved understanding of the complex immunology of AD has inspired a "gold rush" of targeted therapies to suppress the cytokines and T-cell subsets at the root of AD. Studies are under way to investigate the safety and efficacy of these Th2-axis-inhibiting biologics and small molecules in atopic adults and children. Over the next decade, patients struggling with AD can finally expect some well-deserved and durable relief.

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Mysterious interstellar visitor is a comet — not an asteroid

Quirks in 'Oumuamua's path through the Solar System helped researchers solve a case of mistaken identity.

Alexandra Witze

The first-known visitor from outside the Solar System, an object dubbed 'Oumuamua, is an icy comet rather than a rocky asteroid. New measurements help to confirm early guesses as to the composition of the interstellar interloper, and could also aid researchers in their hunt for similar objects in our Solar System.

The cigar-shaped 'Oumuamua probably has a cold, icy heart. **ESO/M. Kornmesser**

Careful observations of 'Oumuamua's orbit showed that as the object flew through space, something continually nudged it a tiny bit farther from the Sun than expected. That something was probably ice that warmed up and sprayed gas into space. This process is characteristic of a comet, rather than an asteroid, even though 'Oumuamua never displayed the glorious tail of gas and dust that accompanies most comets.

"It's an unusual comet, and that's pretty exciting," says Karen Meech, an astronomer at the University of Hawaii in Honolulu. She and her

colleagues, led by astronomer Marco Micheli of the European Space Agency in Frascati, Italy, report the discovery on 27 June in *Nature*[1]. The finding supports earlier hints[2] that ‘Oumuamua resembles a ‘baked Alaska’ dessert, with a frozen heart and warm exterior, says Michele Bannister, a planetary astronomer at Queen’s University Belfast in Northern Ireland.

Going, going, gone

Astronomers discovered ‘Oumuamua on 19 October 2017 using the PanSTARRS-1 telescope on the Hawaiian island of Maui. Within hours, they could tell its trajectory was unlike that of any other known celestial object, suggesting that the interloper must have come from beyond the Solar System. In Hawaiian, ‘Oumuamua means “a messenger from afar arriving first”.

But by the time scientists spotted it, the visitor had already flown past the Sun and was on its way out of the Solar System. Telescopes around the world strained to follow ‘Oumuamua as it grew fainter and disappeared among the stars. Since astronomers couldn’t see a characteristic comet-like tail extending from it, most categorized it as an interstellar asteroid[3]. Other observations, however, hinted that the object could have an icy interior beneath its desiccated surface[2].

Using the Canada–France–Hawaii Telescope in Hawaii, the Very Large Telescope in Chile and the Hubble Space Telescope, Micheli and his colleagues traced the visitor’s path from late October until early January 2018.

A little push

By plotting ‘Oumuamua’s position against the stars, the scientists saw that it was travelling in ways that could not be accounted for by the gravitational tug of the Sun, the planets, the Moon and other major bodies in the Solar System. “As it moved away from the Sun, it was slowing down a little bit less than we would have expected,” says Meech. The magnitude of whatever was affecting it was tiny — just one-thousandth as strong as the pull of the Sun’s gravity.

After considering other possible explanations, the researchers concluded that the effect comes from comet-like outgassing. As ‘Oumuamua approached the Sun, it began to heat up, and its icy heart started to melt. This released gas that made its way to the comet’s surface and shot outward, giving the object a little push.

The outgassing rate is small compared to what typical comets experience, says Jessica Agarwal, an astronomer at the Max Planck Institute for Solar System Research in Göttingen, Germany. ‘Oumuamua also emits relatively little debris, perhaps because its dust particles are too large and heavy for the weak outgassing to carry aloft. That could explain why ‘Oumuamua never developed a visually stunning, comet-like tail.

This invisible outgassing could inspire researchers to look for similar objects in our own Solar System, says Henry Hsieh, who studies asteroids and comets with the Planetary Science Institute in Honolulu, Hawaii. When it comes online in 2022, the Large Synoptic Survey Telescope in Chile might be able to spot some of these stealth comets. “That’s going to be a powerhouse of discovery and the most sensitive instrument we’ll have for detecting interstellar objects,” says Alan Fitzsimmons, an astronomer at Queen’s University Belfast. “It’s going to be fun.”

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http://bit.ly/2lGCVDM

Immunotherapy drug for skin disease could boost hormone treatment for prostate cancer

Researchers believe combination with established treatment could improve outcomes in prostate cancer

A new form of immunotherapy reactivates the response to hormone treatment in advanced prostate cancer, a study in mice and human prostate cancer cells has found.

Hormone therapy is a mainstay of prostate cancer treatment - but tumour cells can grow resistant, leading to a hard-to-treat, advanced form of the disease.

The new study found that blocking a protein produced by a type of immune cell - known as granulocytic myeloid-derived suppressor cells - restored sensitivity to hormone therapy.

Drugs that block this protein, called IL-23, already exist and are used for autoimmune diseases such as the skin condition psoriasis.

Clinical trials are now planned to assess the possible benefit of this new form of immunotherapy alongside the next-generation hormone therapy enzalutamide, in men with advanced prostate cancer.

Scientists at The Institute of Cancer Research, London, worked with colleagues at the Institute of Oncology Research in Switzerland on the study, which was published in the prestigious journal Nature today (Wednesday). The research was supported by funders including the Prostate Cancer Foundation in the US, Prostate Cancer UK, the Movember Foundation and Cancer Research UK.

The researchers studied mice, along with tumour and blood samples from prostate cancer patients treated at The Royal Marsden NHS Foundation Trust, to unpick the role of myeloid-derived suppressor cells in prostate cancer.

They found that blood and tumour samples from men with resistant prostate cancer contained higher levels of these suppressor immune cells and IL-23 than those from men whose cancer still responded to hormone therapy. When they studied mice with prostate cancer that no longer produced IL-23, they found their tumours shrank considerably, and cancer cells grew more slowly.

It also took longer for the prostate tumours to become resistant to hormone therapy, and the mice survived for a longer period of time.

Both blocking IL-23 and stopping suppressor cells from moving into the tumour led to an improved response to hormone therapy, giving the researchers confidence that they identified a key mechanism that drives hormone therapy resistance in prostate cancer.

The researchers believe that IL-23 allows prostate cancer cells to sidestep the need for androgen hormones to fuel their growth.

Other immunotherapies, which work by reactivating the immune system's ability to recognise and kill cancer cells, have shown some promise in prostate cancer, but only a subset of men respond well.

As myeloid-derived suppressor cells are present in many prostate tumours, the researchers believe that this immunotherapy approach could work in a large proportion of men with the disease.

Professor Johann de Bono, Regius Professor of Cancer Research at The Institute of Cancer Research, London, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust, said:

"Hormone therapy works well in men with prostate cancer, but when cancer evolves to become resistant to treatment, other options are greatly reduced.

"Our study found an important interaction between hormone signalling and the immune system. We believe we could exploit this to reverse hormone resistance in prostate cancer, and boost the effect of widely used prostate cancer drugs such as enzalutamide. "We are keen to start clinical trials to investigate how we can combine this new form of immunotherapy with existing hormone therapies, to improve treatment for men with advanced prostate cancer."

Professor Andrea Alimonti, Professor of Oncology at the University of Italian Switzerland and Institute of Oncology Research (IOR), Bellinzona, Switzerland, said:

"When we discovered that IL23 producing-MDSCs were the main immune subset infiltrating prostate tumors that have acquired resistance to hormone-treatment, we immediately realised that these cells could be one of the cause behind the emergence of castration-resistant prostate cancer.

"This study describes a new unexpected mechanism by which the tumor immune response supports the growth of prostate cancer and it opens the way for future novel therapeutic applications for the treatment of metastatic prostate cancer patients."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"Immunotherapies have shown great promise in many cancer types, but so far their benefit in prostate cancer has been limited to a small subset of men. "This new study has uncovered a completely new way to modify the immune system to combat prostate cancer.

"A combination of hormone therapy with this new form of immunotherapy could be a really exciting new avenue of treatment for advanced prostate cancer, and it's important this approach is tested in clinical trials."

Howard Soule, Ph.D., executive vice president and chief science officer of the Prostate Cancer Foundation, said:

"This important study identifies an immune protein that enables resistance to anti-androgen therapy, and suggests that targeting this protein may be effective in the treatment of men with castrate-resistant prostate cancer."

http://bit.ly/2KoO773

Rethinking the orangutan

How 70,000 years of human interaction have shaped an icon of wild nature

The critically endangered orangutan--one of human's closet living relatives--has become a symbol of wild nature's vulnerability in the face of human actions and an icon of rainforest conservation.

New research published June 27 in the journal Science Advances indicates this view overlooks how humans, over thousands of years, fundamentally shaped the orangutan known today.

Ignoring this obscures understanding of orangutans and impacts conservation efforts, said lead author Stephanie Spehar, an associate professor of anthropology at the University of Wisconsin Oshkosh.

"It was often assumed that environmental factors like fruit availability were primarily responsible for most features of modern-day orangutans, such as the fact that they usually live at low densities and have a restricted geographic distribution," Spehar said.

"However, the orangutan that existed before modern humans arrived in Southeast Asia 70,000 years ago may have been quite different. Our synthesis of fossil, archeological, genetic and behavioral evidence indicates that long-term interactions with humans shaped orangutans in some pretty profound ways."

The study shows that orangutans were once far more widespread and abundant, with orangutan teeth among the most common animal remains in deposits in China, Thailand and Vietnam. These orangutans weathered many environmental changes and may even have lived in a wider range of environments than their modern counterparts.

A widespread reduction in orangutan numbers, which occurred around 20,000 years ago, appears to be closely correlated with indicators of human impact, especially the appearance of projectile weapons that make hunting tree-living prey easier, Spehar said. "It suggests that Paleolithic humans were probably hunting orangutans regularly--and as orangutans reproduce very slowly, it doesn't take much to put a dent in their populations."

Today, orangutans are only found on the islands of Borneo and Sumatra. The ecology and behavior of modern orangutans probably represents an adaptation to environmental factors and long-term human pressures, especially hunting.

"Acknowledging how orangutans were affected by humans in the past can help us better understand how they respond to human threats now," said research lead Erik Meijaard, co-director of NGO Borneo Futures and a co-author on the paper.

Recent behavioral studies indicate that orangutan adaptability may be greater than previously thought, he said.

"For example, we always thought that orangutans were mostly arboreal, but when we started putting camera traps in the forest, it

turned out that they also walk extensively on the ground in some areas," Meijaard said.

Emerging research on orangutans living in heavily human-impacted habitat, such as oil palm and forestry plantations, also highlights that the apes can adjust their behavior to survive in such areas, at least in the short term. "These insights are important, because they show us how even well-studied species can be misunderstood due to our preconceptions," said Douglas Sheil, a tropical ecologist at the Norwegian University of Life Science and a co-author on the paper. "This also is a crucial realization for orangutan conservation. If we had known sooner that orangutans survive in selectively logged forests, we could have developed conservation strategies that incorporate these habitats much earlier. This could have saved many thousands of orangutans."

The good news is that orangutans can be conserved in a much larger part of the landscape than previously thought.

"We urgently need to explore these opportunities," Sheil said.

Serge Wich, another coauthor on the paper and a professor at Liverpool John Moores University, said this is especially important for the Tapanuli orangutan, a new species just described in 2017. "There are only 800 left in fragmented forest areas, so these findings must be applied immediately."

The researchers call for a multifaceted approach to orangutan conservation that incorporates human-dominated landscapes but reduces hunting and increases habitat quality and connectivity.

Such an approach requires developing sound policies, enforcing existing laws and promoting cooperation among stakeholders.

This research demonstrates that orangutans can be resilient in the face of some human interactions, said Marc Ancrenaz, director of French NGO Hutan and coauthor on the paper. "This offers hope. If we humans manage things correctly, there can be room for the orangutan in the Anthropocene," he said.

http://bit.ly/2MvNMM4

Recorded penicillin allergy linked to increased risk of 'superbug' infections

Risk largely due to use of 'broad spectrum' antibiotics as alternative to penicillin

Patients who have a penicillin allergy recorded in their medical records are at an increased risk of developing the drug resistant 'superbug' infection MRSA and healthcare-associated infection C difficile, finds a study published by *The BMJ* today.

The risk is largely due to the use of more 'broad spectrum' antibiotics as alternatives to penicillin, which may be fuelling the development of drug resistant bacteria.

The researchers argue that addressing penicillin allergies "may be an important public health strategy to reduce the incidence of MRSA and C difficile among patients with a penicillin allergy label."

Penicillin allergy is the most commonly documented drug allergy, reported by about 10% of patients. However, previous studies have shown that more than 90% of patients with listed penicillin allergies can be safely treated with penicillins.

To evaluate the public health consequences of a penicillin allergy label, researchers at Massachusetts General Hospital in Boston examined the relation between penicillin allergy and development of MRSA and C difficile.

Using data from the Health Improvement Network (THIN), an electronic medical record database of 11 million UK patients, they identified 64,141 adults with a documented penicillin allergy and 237,258 matched adults of similar age and sex, with recent penicillin exposure but without a penicillin allergy.

None of the participants had any history of MRSA and C difficile infection, and were followed up for an average of six years, during which time use of antibiotics and cases of doctor diagnosed MRSA and C difficile were recorded.

A total of 1,345 participants developed MRSA and 1,688 developed *C. difficile* over the follow-up period.

After adjusting for several known risk factors, the researchers found that a penicillin allergy label was associated with a 69% increased risk of MRSA and a 26% increased risk of C difficile.

Once documented, a penicillin allergy was associated with increased use of alternative 'broad spectrum' antibiotics, which act against a wider range of bacteria. The results show that increased use of broad spectrum antibiotics accounted for more than half (55%) of the increased MRSA risk and more than one third (35%) of the increased C difficile risk among patients with a listed penicillin allergy.

This is an observational study, so no firm conclusions can be drawn about cause and effect, and the researchers cannot rule out the possibility that other, unmeasured factors may have affected their results. However, they point out that this was a large, representative sample and the findings remained consistent after further analyses to test the strength of the results.

As such, they conclude that patients with a documented penicillin allergy "have an increased risk of new MRSA and C difficile that may be modifiable, to some degree, through changes in antibiotic prescribing." As infections with resistant organisms increase, "systematic efforts to confirm or rule out the presence of true penicillin allergy may be an important public health strategy to reduce the incidence of MRSA and *C. difficile*," they add.

http://bit.ly/2NczMrZ

Beer. Soup. Barley's next great use? A medical imaging drink

Study finds the grain an ideal and safe contrast agent for diagnosing swallowing disorders

BUFFALO, N.Y. -- Before launching their latest science experiment, University at Buffalo researchers bought more than 200 types of tea, chocolate, herbs and other foodstuffs.

The goal wasn't to stock up for long hours in the lab, but rather to find an elusive, edible contrast agent to show doctors what's happening inside our bodies.

The search culminated with a winner: barley. Turns out that a roasted version of the grain, when struck by a common laser beam, can illuminate the throat and the gastrointestinal track.

The discovery could improve our ability to diagnose swallowing disorders, which affect more than 15 million Americans, as well as gut disorders.

What's more, because many human diets already include barley, it could be fast-tracked for medical use.

"It's really incredible. Here you have this common grain -- it has been grown all over the world for thousands of years, and used to make tea, bread, beer -- and we're just now finding another use for it as a contrast agent for medical imaging," says Jun Xia, PhD, assistant professor in the University at Buffalo Department of Biomedical Engineering.

Xia and 10 other UB co-authors described the experiment and its results in a study published in May in the journal Biomaterials.

An alternative to barium

Swallowing disorders, also known as dysphagia, can be an indication of a serious medical problem.

They are caused by everything from cancer and Alzheimer's disease to missing teeth and neck injuries.

To test for dysphagia, doctors typically have patients drink a thick, chalky liquid called barium.

Doctors then use X-rays, MRIs or ultrasounds to look inside the throat. Each technique is limited with respect to safety, high-cost and lack of adequate contrast, respectively.

Photoacoustic computed tomography (PACT) is an emerging alternative.

Like barium, patients drink or are injected with a contrast agent -- often newly developed nanoparticles made of metals, polymers and other materials.

A laser strikes the nanoparticles, generating pressure waves that can provide nuanced and real-time views inside the body. One drawback to contrast-enhanced PACT is the often lengthy and expensive regulatory process for new contrast agents.

"That's what led us to search for edible alternatives. Because we've been eating or drinking these products, we know they're safe for most people," says study co-author Jonathan Lovell, PhD, associate professor in the Department of Biomedical Engineering, which is a joint program of UB's School of Engineering and Applied Sciences and the Jacobs School of Medicine and Biomedical Sciences at UB.

Swallowing and GI disorders

The researchers focused on dark foods and beverages because the darker the color, the more the foodstuff will absorb wavelengths from the laser and, theoretically, produce a clearer image.

Roasted barley, a grain used to produce beer, bread and other products, provided the best results.

Researchers were able to detect individual particles of it through 3.5 centimeters of chicken breast tissue, as well as through human hands.

Roasted barley tea -- a drink common in Japan, Korea and China -- was detectable through 2.5 centimeters of chicken breast.

It worked in human subjects as well, providing visualizations inside the human throat when swallowing.

In addition to swallowing imaging, researchers say roasted barley could potentially be used to diagnose gastrointestinal tract disorders.

The research was supported by grants from the National Institutes of Health, the Clinical and Translational Science Institute at UB, and the UB Office of the Vice President for Research and Economic Development.

http://bit.ly/2KDmfru

Research identifies barley beer in Bronze Age Mesopotamian drinking vessels

People living some 3500 years ago in Mesopotamia, which now is modern-day Iraq, enjoyed a pint as much as we do today **June 27, 2018**

A paper published in the *Journal of Archaeological Science* shows that Mesopotamia's Late Bronze Age inhabitants enjoyed drinking barley beer not unlike today's popular craft brews from a variety of drinking vessels.

Chemical compounds indicative of a barley-based fermented drink were discovered in numerous pottery vessels at the Bronze Age Site of Khani Masi located in the Upper Diyala River valley of north-eastern Iraq.

Drinking Cup And Faience Bucket excavated from Khani Masi. **Credit: University of Glasgow**

An international team led by Dr. Claudia Glatz (University of Glasgow) and Professor Jesse Casana (Dartmouth College, USA) has been carrying out large-scale excavations at Khani Masi since 2016 as part of the Sirwan Regional Project.

Beer was both a staple of the Mesopotamian diet and an important component of rituals and feasting—and has been studied mainly through cuneiform sources and iconography.

Traditionally, scholars have assumed that beer in Mesopotamia was consumed communally from large jars using long, bendy straws.

However, the paper entitled Revealing invisible brews: A new approach to the chemical identification of ancient beer says: "Our analytical results also allow us, for the first time and with confidence,

to ascribe a diverse range of drinking equipment to the consumption of beers and in so doing track a significant transformation in Mesopotamian drinking practices."

The new research shows that by 1400 BC beer drinking had become an individual experience using drinking cups and goblets ranging in size from a modern-day equivalent of a small glass of wine up to just over a pint glass of beer.

Kassite Goblet Being Excavated at Khani Masi

Dr. Claudia Glatz, a Senior Lecturer in Archaeology at the University of Glasgow, said "Our results present a significant advance in the study of ancient Near Eastern beer brewing and consumption practices.

"They also provide us with unprecedented new insights into Mesopotamia's cultural relationships with the Upper Diyala River valley, a strategic communication corridor between Mesopotamia and the Zagros mountains that formed part of the later Silk Roads and that we have only recently begun to explore systematically."

For this research, the Glasgow academics developed a new analytical method that has allowed them for the first time to chemically identify beer in drinking vessels.

Dr. Jaime Toney, a Senior Lecturer in Organic Geochemistry at the University's School of Geographical and Earth Sciences, said: "Using gas chromatography we were able to detect and measure a suite of co-occurring fossil compounds that are diagnostic of beer.

"We show that this suite of fossil compounds match those found in modern barley beer—identifying for the first time an important method for revealing the presence of beer, even when there is no visible evidence such as beerstone." Beerstone is a white crystalline substance that forms on the inner surface of fermentation and storage vats used in beer brewing.

The academics have now laid out a protocol for field-based sampling of vessels for archaeologists.

Elsa Perruchini, the University's Lord Kelvin Adam Smith Scholarship funded Ph.D. student on the project, carried out the chemical analysis and devised the new sampling method.

She said: "Our novel, multi-stage methodology, provides an easy-to-implement field-sampling and analytical approach that significantly enhances the reliably of organic residue analysis results in archaeology.

"Simply put, with our new on-site sampling strategy, we avoid sample contamination from things like human skin oils or modern products such as sunscreen by using cotton gloves and sterilised tweezers to handle sample vessels, which are then immediately wrapped in sterilised aluminium foil.

"The use of control samples as well as comparison with modern day food items is also crucial in our methodology."

More information: *E. Perruchini et al. Revealing invisible brews: A new approach to the chemical identification of ancient beer, Journal of Archaeological Science (2018).* DOI: 10.1016/j.jas.2018.05.010

https://wb.md/2tWB55E

An Unrecognized Suicide Risk Factor

The relatively common neurologic movement disorder known as restless leg syndrome is poorly understood

Arefa Cassoobhoy, MD, MPH

Hello. I'm Dr Arefa Cassoobhoy, a practicing internist, Medscape advisor, and senior medical director for WebMD. Welcome to Morning Report, our 1-minute news story for primary care.

The relatively common neurologic movement disorder known as restless leg syndrome is poorly understood.

Patients describe uncomfortable sensations in their legs that often are worse at night, having a huge impact on their ability to sleep and overall quality of life.

It now appears that severe restless leg syndrome is a risk factor for suicidal ideation and attempts. The risk correlates with history of

depression, and it is independent of the severity of restless leg symptoms and demographic factors.

Is this related to chronic sleep deprivation, stress, or pain? Experts speculate that patients with restless leg syndrome, like those with unrelieved chronic pain, might feel hopeless, leading to suicidal thoughts and actions.

Although evaluating restless leg syndrome and finding effective treatments is challenging, this study suggests that it's important to assess not only the impact of restless leg syndrome on the patient's life, but also the presence of suicidal thoughts.

http://bit.ly/2IJesHe

What makes dogs man's best friend?

A comparison of dog and wolf DNA reveals interesting genetics behind domestication. The new study is a step toward a deeper understanding of evolution for dogs and humans alike

ANN ARBOR, Mich. -- From pugs to labradoodles to huskies, dogs are our faithful companions. They live with us, play with us and even sleep with us. But how did a once nocturnal, fearsome wolf-like animal evolve over tens of thousands of years to become beloved members of our family? And what can dogs tell us about human health? Through the power of genomics, scientists have been comparing dog and wolf DNA to try and identify the genes involved in domestication.

Amanda Pendleton, Ph.D., a postdoctoral research fellow in the Michigan Medicine Department of Human Genetics, has been reviewing current domestication research and noticed something peculiar about the DNA of modern dogs: at some places it didn't appear to match DNA from ancient dogs.

Pendleton and her colleagues in assistant professor Jeffrey Kidd, Ph.D.'s laboratory are working to understand the dog genome to answer questions in genome biology, evolution and disease.

"We convinced ourselves that previous studies found many genes not associated with being a dog but with being a breed dog," says Pendleton.

Breed dogs, which mostly arose around 300 years ago, are not fully reflective of the genetic diversity in dogs around the world, she explains.

Three-quarters of the world's dogs are so-called village dogs, who roam, scavenge for food near human populations and are able to mate freely. In order to get a fuller picture of the genetic changes at play in dog evolution, the team looked at 43 village dogs from places such as India, Portugal and Vietnam.

Armed with DNA from village dogs, ancient dogs found at burial sites from around 5,000 years ago, and wolves, they used statistical methods to tease out genetic changes that resulted from humans' first efforts at domestication from those associated with the development of specific breeds.

This new genetic review revealed 246 candidate domestication sites, most of them identified for the first time by their lab.

Now that they'd identified the candidate genes the question remained: What do those genes do?

'A good entry point'

Upon closer inspection, the researchers noticed that these genes influenced brain function, development and behavior. Moreover, the genes they found appeared to support what is known as the neural crest hypothesis of domestication.

"The neural crest hypothesis posits that the phenotypes we see in domesticated animals over and over again -- floppy ears, changes to the jaw, coloration, tame behavior -- can be explained by genetic changes that act in a certain type of cell during development called neural crest cells, which are incredibly important and contribute to all kinds of adult tissues," explains Pendleton.

Many of the genetic sites they identified contained genes that are active in the development and migration of neural crest cells.

One gene in particular stuck out, called RAI1, which was the study's highest ranked gene. In a different lab within the Department of Human Genetics, Michigan Medicine assistant professor of human genetics Shigeki Iwase, Ph.D., has been studying this gene's function and role in neurodevelopmental disorders.

He notes that in humans, changes to the RAI1 gene result in one of two syndromes -- Smith-Magensis syndrome if RAI1 is missing or Potocki-Lupski syndrome if RAI1 is duplicated.

"RAI1 is a good entry point into studying brain function because its mutation results in a brain disorder," he says. "Studies suggest that this protein controls the expression of several genes involved in circadian rhythms.

One of the unique features in these conditions is the problem these patients have with sleep." In dogs, changes to this gene may help explain why domesticated dogs are awake during the day rather than nocturnal like most wolves.

Other genes Kidd's lab identified in dogs have overlap with human syndromes resulting from improper development of neural crest cells, including facial deformities and hypersociability. These parallels between dogs and humans are what make understanding dog genetics valuable.

Kidd explains, "We are using these changes that were selected for by humans for thousands of years as a way to understand the natural function and gene regulatory environment of the neural crest in all vertebrates."

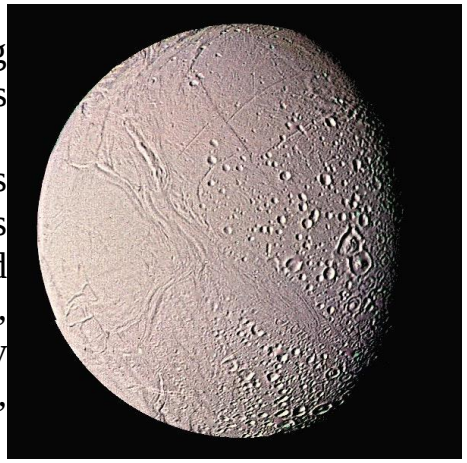
This work was supported by the National Institutes of Health (NIH) (R01GM103961 and T32HG00040).

http://bit.ly/2KAqY4a

Large molecules show Enceladus "clearly is habitable for life"

New findings support, but do not prove, the idea that life may exist on Saturn's icy moon.

Richard A Lovett reports.



What lives beneath? New findings bolster the case for life on Enceladus.
CORBIS/Corbis via Getty Images

Large organic molecules are spewing into space from the depths of Saturn's icy moon Enceladus, scientists say.

Exactly what these molecules are is unclear, but they contain at least as many as 15 carbon atoms, and possibly as much as 10 times more, says Nozair Khawaja, a planetary scientist at Heidelberg University, Germany.

Several years ago, scientists detected organic molecules containing up to four or five carbon atoms in the vicinity of Enceladus and in Saturn's tenuous "E ring", created by Enceladus's emissions.

"But we were completely shocked [to find] organic compounds much more complex than we had previously imagined," says study team member Christopher Glein, a planetary scientist at the Southwest Research Institute in San Antonio, Texas, US, who specialises in the oceanography of outer moons.

The new work, Glein says, came from collaboration between scientists using two different instruments on the Cassini spacecraft.

One, the Ion and Neutral Mass Spectrometer, was designed to analyse the molecular composition of gases. The other, the Cosmic Dust Analyser, examined dust particles. These particles hit its target plate at speeds of between three and 20 kilometres per second — fast

enough not only to vaporise them but to break large molecules into fragments. The fragments were then "weighed" by a "time of flight" spectrometer, in which large, heavy molecules move more slowly than small ones.

When the two teams compared notes, they realised they were seeing different aspects of the same thing: fragments of organic-rich dust grains that crashed into their instruments and broke into smaller pieces. Some of these pieces were the small molecules detected by the Ion and Neutral Mass Spectrometer. Others were larger fragments detected by the Cosmic Dust Analyser.

Putting it all together, the scientists concluded that the Cassini spacecraft was encountering dust particles rich in carbon in large, complex "macromolecular structures". The only place this material could have come from was the interior of Enceladus, from which ice, dust and gas is jetting out in geyser-like plumes. These plumes are fed by vapours escaping from a sub-surface ocean.

"So this is a direct sample of the Enceladus ocean," Khawaja says.

What exactly the newly discovered organic materials are is open for debate, although Khawaja believes they most likely are made of large numbers of ring-like structures cross-linked by hydrocarbon chains.

An important hint comes from the fact that the organic-rich grains don't contain much water, implying that the materials in them don't easily mix with water. Khawaja hypothesises that they formed deep inside Enceladus, then rose to the top of its underwater ocean, where they formed a thin film akin to an earthly oil slick.

Gas bubbles rising from the interior then lifted tiny blobs of the material into the vents that feed Enceladus's jets. There they solidified into flakes that become the cores of the organic-rich dust grains detected by Cassini. But that only explains how the dust grains are formed. The origin of the organic materials within them is entirely different.

One possibility is that they were created by reactions between hot water and matter in the rocky core of Enceladus. But it's also possible they were created by life. "This could come from abiotic processes and biotic processes," Khawaja notes. They could also have found their way to Enceladus via meteorites or comets, both of which are known to contain abiotically produced organics.

Other scientists are enthusiastic. Carolyn Porco, a planetary scientist at the Space Science Institute in Boulder, Colorado, and a visiting scholar at the University of California, Berkeley, US, is skeptical about the oil-slick theory, but excited about everything else.

Organic-rich flakes, she says, could also be created by bubbles rising from the ocean's depth. These bubbles could collect organics on their way up, then eject them when they reach the surface and pop.

"[That] can likely explain the results without the need for a thin film," she says. But that's a fairly minor quibble. The big news, she says, is the discovery of organic molecules with masses at least 200 times that of hydrogen, or 200 atomic mass units (amu). "The average weight of the 22 amino acids used by terrestrial life is about 110 amu," she explains.

Astrobiologist Chris McKay, of NASA's Ames Research Center in Moffett Field, California, agrees. "[This] further indicates that the ocean of Enceladus is an organic-rich soup and clearly is habitable for life," he says.

For the moment, however, there is no way to determine if the chemicals are produced by abiotic processes, or by life. And even if the Cassini spacecraft carried instruments capable of making the distinction (which it didn't), the mission ended last September, when the spacecraft ran out of manoeuvring fuel and made a final, fiery plunge into Saturn's upper atmosphere.

What's needed, the scientists agree, is a return to Enceladus with a new spacecraft equipped with instruments capable of studying

molecular structures in greater detail, thereby distinguishing biologically produced molecules from abiotically produced ones.

Not that this will happen in the near future. “It takes a long time to plan,” says Glein, who adds that the earliest we could get there is around 2035. “But we have quite a few people who are actively working toward this, so it’s very exciting,” he says.

In the meantime, NASA’s Europa Clipper mission is now being designed and built to visit Jupiter’s icy moon, Europa. Like Enceladus, Europa is known to have a subsurface ocean. Like Enceladus, it might be venting materials from that ocean into space, through cracks in its icy surface. The Europa Clipper’s launch date is not yet set, but if it is heavily prioritised, it could get to its destination as early as 2024, Glein says, though he suspects it will be a few years later.

Regardless of when it is launched, however, that spacecraft will contain the same types of instruments that Cassini did. “So, if Europa is spewing organic materials,” he says, the scientists on its instruments will be able to team up again. “[And] these instruments will be much more capable than the ones on Cassini because they are modern instruments with 20 years of advancements.” Glein and colleagues have reported their results in the journal *Nature*.

https://bbc.in/2Kl9lm1

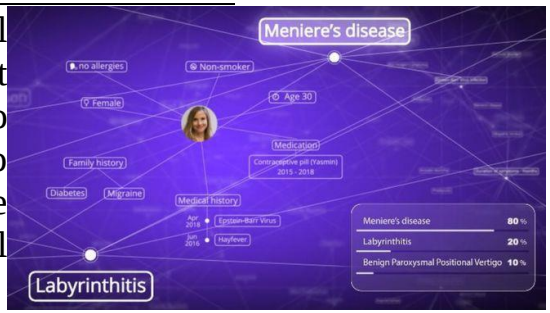
Babylon claims its chatbot beats GPs at medical exam

Claims that a chatbot can diagnose medical conditions as accurately as a GP have sparked a row between the software's creators and UK doctors.

By Jen Copestake BBC Click

Babylon, the company behind the NHS GP at Hand app, says its follow-up software achieves medical exam scores that are on-par with human doctors. It revealed the artificial intelligence bot at an event held at the Royal College of Physicians.

But another medical professional body said it doubted the AI's abilities. "No app or algorithm will be able to do what a GP does," said the Royal College of General Practitioners.



The artificial intelligence software provides what it determines to be the most likely diagnoses **Babylon**

"An app might be able to pass an automated clinical knowledge test - but the answer to a clinical scenario isn't always cut and dried. "There are many factors to take into account, a great deal of risk to manage, and the emotional impact a diagnosis might have on a patient to consider."

But NHS England chairman Sir Malcolm Grant - who attended the unveil - appeared to be more receptive. "It is difficult to imagine the historical model of a general practitioner, which is after all the foundation stone of the NHS and medicine, not evolving," he said.

"We are at a tipping point of how we provide care. "This is why we are paying very close attention to what you've been doing and what other companies are doing."

Higher score

The chatbot AI has been tested on what Babylon said was a representative set of questions from the Membership of the Royal College of General Practitioners exam. The MRCGP is the final test set for trainee GPs to be accredited by the organisation. Babylon said that the first time its AI sat the exam, it achieved a score of 81%. It added that the average mark for human doctors was 72%, based on results logged between 2012 and 2017.

But the RCGP said it had not provided Babylon with the test's questions and had no way to verify the claim. "The college examination questions that we actually use aren't available in the

public domain," added Prof Martin Marshall, one of the RCGP's vice-chairs.

Babylon said it had used example questions published directly by the college and that some had indeed been made publicly available.

"We would be delighted if they could formally share with us their examination papers so I could replicate the exam exactly. That would be great," Babylon chief executive Ali Parsa told the BBC.

To further test the AI, Babylon partnered with doctors at two US organisations - Stanford Primary Care and Yale New Haven Health - as well as doctors from the Royal College of Physicians.

It said they had developed 100 real-life scenarios to test the AI.

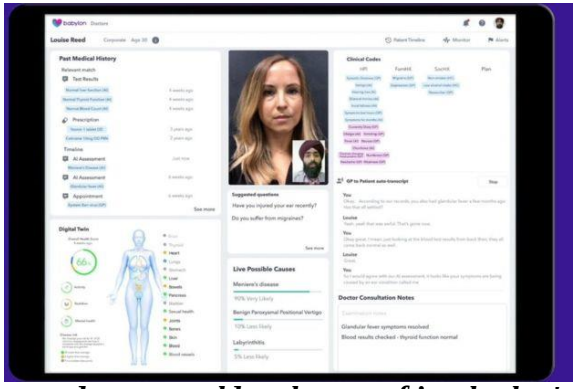
The company added that it expected its chatbot's diagnostic skills would further improve as a consequence.

Probable causes

Babylon has demonstrated its chatbot being used as a voice-controlled "skill" on Amazon's Alexa platform.

While Babylon's existing GP at Hand service refers users to a human doctor if the app suspects a medical problem, the new chatbot makes a diagnosis itself - offering several possible scenarios along with a percentage-based estimate of each one being correct.

"The suggestion that this can replace doctors is the key issue for us,' said Prof Marshall.



Babylon envisages that a human doctor would make use of its chatbot's diagnosis within a follow-up video chat **Babylon**

But Mr Parsa disputed the idea that doctors would be left out in the cold, explaining that the intention was still for a medic to follow up the AI's diagnoses. "We are fully aware that an artificial intelligence on its own cannot look after a patient. And that is why we complement it with physicians," he said. "It is never going to replace a doctor, but just to help."

Rwandan connection

Babylon's stated ambition is to deliver affordable health care to people all over the world. Since 2016, it has been working in partnership with the government of Rwanda. The country's health care service was decimated after the genocide in 1994, in which more than 800,000 people were killed.

Babylon has two million registered users in Rwanda and has conducted tens of thousands of consultations. Since smartphone use is not widespread in the country, people currently call nurses who follow symptom-checking prompts that appear to them via computer screens. Information gathered as a result has been used to improve the chatbot.

http://bit.ly/2KzlZKc

This novel, one-and-done flu drug could be available soon in the US

The FDA is expected to make a decision by December 24, 2018.

Beth Mole - 6/28/2018, 5:02 AM

A fast-acting drug that shortens influenza infections with a single dose has earned a priority review from the US Food and Drug Administration and—if approved—has the chance of hitting the market in 2019 amid the upcoming flu season. That’s all according to Genentech, the Roche-based company that is developing the drug, baloxavir marboxil, for the US market.

Baloxavir marboxil is garnering attention in part because of its timing. It’s arriving in the wake of a “high-severity” flu season for the US and a sub-optimal seasonal vaccine. The Centers for Disease Control and Prevention logged record-level rates of hospitalizations for the 2017-2018 flu season and a high tally of 171 pediatric deaths. But the new flu drug also has notable advantages over the small

number of other medications currently on the market for the seasonal affliction.

First, baloxavir marboxil is effective as a single dose. Genetech's other flu drug, Tamiflu (oseltamivir phosphate), needs to be taken twice a day for five days within 48 hours of the onset of flu symptoms. Baloxavir marboxil, on the other hand, is taken in one bout in the same timeframe.

In a randomized, placebo-controlled phase III clinical trial of 1,436 people, baloxavir marboxil knocked back how long flu symptoms lasted by about a day, getting the illness to last for only about 54 hours instead of the 80 or so it lasted with a placebo. That about matches what Tamiflu can muster. But in the same trial, baloxavir marboxil proved better than Tamiflu at reining in viral shedding from infected peoples' noses and throats. Snotty patients only spewed infectious particles for 24 hours after baloxavir marboxil, while Tamiflu-treated patients remained viral fountains for 72 hours after starting meds. The shorter shedding time could mean less infection all around.

A new weapon

Baloxavir marboxil uses a unique method to take out influenza virus. It targets an enzyme called cap-dependent endonuclease protein, which is critical for the virus' ability to churn out copies of its genetic material to make the infectious clone army it assembles within infected human cells. Tamiflu and a few other flu drugs are neuraminidase inhibitors. They work by targeting the viral enzyme neuraminidase, which the germ uses to bust out of human cells—unleashing its clone armies to storm more cells.

Because baloxavir marboxil uses a novel flu-crippling method, it could be useful for treating flu strains that have become resistant to neuraminidase inhibitors, such as certain strains of avian H5N1 and H7N9. The FDA is eager to add such new drugs to its coffers. As FiercePharma pointed out, FDA Commissioner Scott Gottlieb stated in a congressional hearing on flu preparedness in March that "I think the bottom-line message is that we are very interested in having a spectrum of antiviral drugs that act differently, at different points in the virus. In case the virus itself becomes resistant to one approach at targeting the virus, we have backups and we have alternative approaches."

Genentech said that it expects the FDA will make a decision on baloxavir marboxil's approval by December 24, 2018. In an interview with Stat, Mark Eisner, a vice president of product development for Genentech, said that the company is "working very hard to make it available as soon as possible after approval. And we will work with FDA to do everything we can to expedite" the process.

The drug is already available in Japan by Roche-partner Shionogi & Co., Ltd., which discovered the drug and still holds rights to it in Japan and Taiwan. Shionogi got approval in Japan this past February and markets baloxavir marboxil under the name Xofluza. That version sells for the equivalent of $43.50, Stat points out. Roche, meanwhile holds worldwide rights elsewhere and hasn't announced a US brand name or potential list price for the drug to be sold by Genentech.

https://go.nature.com/2NaJLOq

There's no limit to longevity, says study that revives human lifespan debate

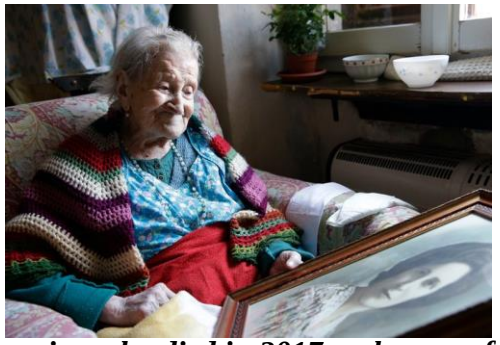
Death rates in later life flatten out and suggest there may be no fixed limit on human longevity, countering some previous work.

Elie Dolgin

There might be no natural limit to how long humans can live — at least not one yet in sight — contrary to the claims of some demographers and biologists.

That's according to a statistical analysis published Thursday in *Science*[1] on the survival probabilities of nearly 4,000 'super-elderly' people in Italy, all aged 105 and older.

A team led by Sapienza University demographer Elisabetta Barbi and University of Roma Tre statistician Francesco Lagona, both based in Rome, found that the risk of death — which, throughout most of life, seems to increase as people age — levels off after age 105, creating a 'mortality plateau'. At that point, the researchers say, the odds of someone dying from one birthday to the next are roughly 50:50 (see 'Longevity unlimited').



Emma Morano, an Italian supercentenarian who died in 2017 at the age of 117, was the world's last surviving person born in the 19th century. **Antonio Calanni/AP/REX/Shutterstock**

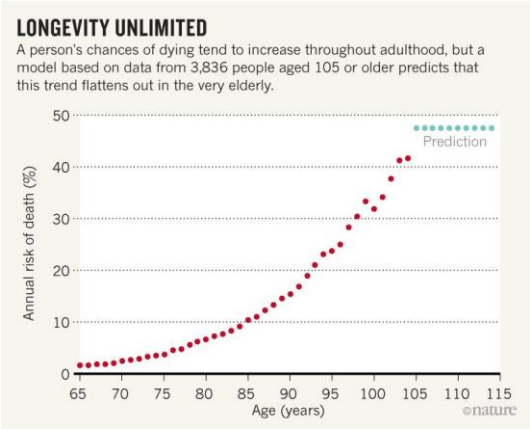
"If there is a mortality plateau, then there is no limit to human longevity," says Jean-Marie Robine, a demographer at the French Institute of Health and Medical Research in Montpellier, who was not involved in the study.

That would mean that someone like Chiyo Miyako, the Japanese great-great-great-grandmother who, at 117, is the world's oldest known person, could live for years to come — or even forever, at least hypothetically.

Researchers have long debated whether humans have an upper age limit. The consensus holds that the risk of death steadily increases in adulthood, up to about age 80 or so. But there's vehement disagreement about what happens as people enter their 90s and 100s. Some scientists have examined demographic data and concluded that there is a fixed, natural 'shelf-life' for our species and that mortality rates keep increasing. Others have looked at the same data and concluded that the death risk flattens out in one's ultra-golden years, and therefore that human lifespan does not have an upper threshold.

Age rage

In 2016, geneticist Jan Vijg and his colleagues at Albert Einstein College of Medicine in New York City rekindled the debate when they analysed the reported ages at death for the world's oldest individuals over a half-century. They estimated that human longevity hit a ceiling at about 115 years — 125 tops.



Vijg and his team argued[2] that with few, if any, gains in maximum lifespan since the mid-1990s, human ageing had reached its natural limit. The longest known lifespan belongs to Jeanne Calment, a French super-centenarian who died in 1997 at age 122.

Experts challenged the statistical methods in the 2016 study, setting off a firestorm into which now step Barbi and Lagona. Working with colleagues at the Italian National Institute of Statistics, the researchers collected records on every Italian aged 105 years and older between 2009 and 2015 — gathering certificates of death, birth and survival in an effort to minimize the chances of 'age exaggeration', a common problem among the oldest old.

They also tracked individual survival trajectories from one year to the next, rather than lump people into age intervals as previous studies that combine data sets have done. And by focusing just on Italy, which has one of the highest rates of centenarians per capita in the world, they avoided the issue of variation in data collection among different jurisdictions.

As such, says Kenneth Howse, a health-policy researcher at the Oxford Institute of Population Ageing in the United Kingdom, "these data provide the best evidence to date of extreme-age mortality plateaus in humans".

Ken Wachter, a mathematical demographer at the University of California, Berkeley, and an author of the latest study, suspects that prior disputes over the patterns of late-life mortality have largely stemmed from bad records and statistics. “We have the advantage of better data,” he says. “If we can get data of this quality for other countries, I expect we’re going to see much the same pattern.”

Robine is not so sure. He says that unpublished data from France, Japan and Canada suggest that evidence for a mortality plateau is “not as clear cut”. A global analysis is still needed to determine whether the findings from Italy reflect a universal feature of human ageing, he says.

Off limits

The world is home to around 500,000 people aged 100 and up — a number that’s predicted to nearly double with each coming decade. Even if the risk of late-life mortality remains constant at 50:50, the swelling global membership in the 100-plus club should translate into a creep upwards in the oldest person alive by about one year per decade, says Joop de Beer, a longevity researcher at the Netherlands Interdisciplinary Demographic Institute in The Hague.

Many researchers say they hope to better understand what’s behind the levelling off of mortality rates in later life. Siegfried Hekimi, a geneticist at McGill University in Montreal, Canada, speculates that the body’s cells eventually reach a point where repair mechanisms can offset further damage to keep mortality rates level.

“Why this plateaus out and what it means about the process of ageing — I don’t think we have any idea,” Hekimi says.

For James Kirkland, a geriatrician at the Mayo Clinic in Rochester, Minnesota, the strong evidence for a mortality plateau points to the possibility of forestalling death at any age. Some experts think that the very frail are beyond repair. But if the odds of dying don’t increase over time, he says, interventions that slow ageing are likely to make a difference, even in the extremely old.

Not everyone buys that argument — or the conclusions of the latest paper.

Brandon Milholland, a co-author of the 2016 *Nature* paper, says that the evidence for a mortality plateau is “marginal”, as the study included fewer than 100 people who lived to 110 or beyond. Leonid Gavrilov, a longevity researcher at the University of Chicago in Illinois, notes that even small inaccuracies in the Italian longevity records could lead to a spurious conclusion.

Others say the conclusions of the study are biologically implausible. “You run into basic limitations imposed by body design,” says Jay Olshansky, a bio-demographer at the University of Illinois at Chicago, noting that cells that do not replicate, such as neurons, will continue to wither and die as a person ages, placing upper boundaries on humans' natural lifespan.

This study is thus unlikely to be the last word on the age-limit dispute, says Haim Cohen, a molecular biologist at Bar-Ilan University in Ramat-Gan, Israel. “I’m sure that the debate is going to continue.”

doi: 10.1038/d41586-018-05582-3

http://bit.ly/2tXNOoG

Seeing the same doctor is a matter of life and death

Systematic review concludes that finds lower mortality rates in patients who see the same doctor over time

A ground-breaking study has concluded that patients who see the same doctor over time have lower death rates.

The study, a collaboration between St Leonard's Practice in Exeter and the University of Exeter Medical School, is published today in BMJ Open. It is the first ever systematic review of the relationship between death rates and continuity of care - seeing the same doctor over time. The study analyses all the available evidence in the field to draw its conclusions.

Sir Denis Pereira Gray, of St Leonard's Practice, said: "Patients have long known that it matters which doctor they see and how well they can communicate with them.

Until now arranging for patients to see the doctor of their choice has been considered a matter of convenience or courtesy: now it is clear it is about the quality of medical practice and is literally 'a matter of life and death'."

Professor Philip Evans, of the University of Exeter Medical School, said: "Continuity of care happens when a patient and a doctor see each other repeatedly and get to know each other. This leads to better communication, patient satisfaction, adherence to medical advice and much lower use of hospital services.

"As medical technology and new treatments dominate the medical news, the human aspect of medical practice has been neglected. Our study shows it is potentially life-saving and should be prioritised."

The study found that repeated patient-doctor contact is linked to fewer deaths.

The effect applied across different cultures, and was true not just for family doctors, but for specialists including psychiatrists and surgeons as well.

The review analysed the results of 22 eligible high-quality studies with varying time frames.

The studies were from nine countries with very different cultures and health systems.

Of those, 18 (82%) found that repeated contact with the same doctor over time meant significantly fewer deaths over the study periods compared with those without continuity.

The review, Continuity of care with doctors - a matter of life and death? A systematic review of continuity of care and mortality, is published in BMJ Open. Authors were Denis J Pereira Gray, Kate Sidaway-Lee, Eleanor White, Angus Thorne, and Philip H Evans.

http://bit.ly/2KlvY9P

Study suggests branching networks on surface of Mars due to heavy rainfall

Evidence suggests narrow channel networks on Mars' surface are due to heavy rainfall runoff

June 28, 2018 by Bob Yirka, Phys.org report

A trio of researchers with ETH Zurich and the University of Chicago has found evidence that suggests narrow channel networks seen on the surface of Mars are due to heavy rainfall runoff. In their paper published on the open access site *Science Advances*, Hansjoerg Seybold, Edwin Kite and James Kirchner describe their study of the channel networks and comparisons they made with similar formations found here on Earth.

The central portion of Osuga Valles, which has a total length of 164 km. In some places, it is 20 km wide and plunges to a depth of 900 m. **Photograph: ESA/DLR/FU Berlin, CC BY-SA 3.0 IGO**

As the study notes, prior study of narrow channel networks on Mars has led researchers to believe they were likely created by a standing body of water. Other possibilities include groundwater sapping, fluvial runoff or even ice melting. Lack of direct evidence supporting any of the theories, however, has led to continuing debates. The researchers with this new effort have jumped into the fray by suggesting an alternative theory based on observations of Earth geography. They suggest work done by other researchers studying channel networks here on planet Earth offers a blueprint for the origins of channels on Mars. In that prior effort, other researchers had discovered a connection between the dryness of an area and the branching angles characteristic of some channel networks. Those in

more arid areas, they found, tended to branch at narrower angles than did those in places exposed to more rainfall.

To find out if such evidence might be applicable to Mars, the researchers studied datasets containing information regarding the channel branching seen on Mars. In comparing two datasets from separate studies, they found similarities in descriptions of branching angles on Mars, both of which were compatible with the findings by the team studying channel networks on Earth—namely, that they had narrow angles. This, the researchers suggest, indicates a similar process was involved.

On Earth, the narrow channels resulted from infrequent rainfall runoff. Successive rainfalls led to deepening of the channels to their current depth. The researchers suggest the same is likely true for the branching networks on Mars. Rather than being formed by subtle movements of groundwater, they were likely carved into the ground by rushing water. Such an occurrence, they further note, would suggest that Mars had a very active hydrologic cycle.

Hansjoerg J. Seybold et al. Branching geometry of valley networks on Mars and Earth and its implications for early Martian climate, Science Advances (2018). DOI: 10.1126/sciadv.aar6692

Abstract

Mars' surface bears the imprint of valley networks formed billions of years ago. Whether these networks were formed by groundwater sapping, ice melt, or fluvial runoff has been debated for decades. These different scenarios have profoundly different implications for Mars' climatic history and thus for its habitability in the distant past. Recent studies on Earth revealed that valley networks in arid landscapes with more surface runoff branch at narrower angles, while in humid environments with more groundwater flow, branching angles are much wider. We find that valley networks on Mars generally tend to branch at narrow angles similar to those found in arid landscapes on Earth. This result supports the inference that Mars once had an active hydrologic cycle and that Mars' valley networks were formed primarily by overland flow erosion, with groundwater seepage playing only a minor role.