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Calcium may play a role in the development of Parkinson's disease

Researchers have found that excess levels of calcium in brain cells may lead to the formation of toxic clusters that are the hallmark of Parkinson's disease.

The international team, led by the University of Cambridge, found that calcium can mediate the interaction between small membranous structures inside nerve endings, which are important for neuronal signalling in the brain, and alpha-synuclein, the protein associated with Parkinson's disease. Excess levels of either calcium or alpha-synuclein may be what starts the chain reaction that leads to the death of brain cells.

The findings, reported in the journal Nature Communications, represent another step towards understanding how and why people develop Parkinson's. According to the charity Parkinson's UK, one in every 350 adults in the UK - an estimated 145,000 in all - currently has the condition, but as yet it remains incurable.

Parkinson's disease is one of a number of neurodegenerative diseases caused when naturally occurring proteins fold into the wrong shape and stick together with other proteins, eventually forming thin filament-like structures called amyloid fibrils. These amyloid deposits of aggregated alpha-synuclein, also known as Lewy bodies, are the sign of Parkinson's disease.

Curiously, it hasn't been clear until now what alpha-synuclein actually does in the cell: why it's there and what it's meant to do. It is implicated in various processes, such as the smooth flow of chemical signals in the brain and the movement of molecules in and out of nerve endings, but exactly how it behaves is unclear.

"Alpha-synuclein is a very small protein with very little structure, and it needs to interact with other proteins or structures in order to become functional, which has made it difficult to study," said senior author Dr Gabriele Kaminski Schierle from Cambridge's Department of Chemical Engineering and Biotechnology.

Thanks to super-resolution microscopy techniques, it is now possible to look inside cells to observe the behaviour of alpha-synuclein. To do so, Kaminski Schierle and her colleagues isolated synaptic vesicles, part of the nerve cells that store the neurotransmitters which send signals from one nerve cell to another.

In neurons, calcium plays a role in the release of neurotransmitters. The researchers observed that when calcium levels in the nerve cell increase, such as upon neuronal signalling, the alpha-synuclein binds to synaptic vesicles at multiple points causing the vesicles to come together. This may indicate that the normal role of alpha-synuclein is to help the chemical transmission of information across nerve cells.

"This is the first time we've seen that calcium influences the way alpha-synuclein interacts with synaptic vesicles," said Dr Janin Lautenschläger, the paper's first author. "We think that alpha-synuclein is almost like a calcium sensor. In the presence of calcium, it changes its structure and how it interacts with its environment, which is likely very important for its normal function."

"There is a fine balance of calcium and alpha-synuclein in the cell, and when there is too much of one or the other, the balance is tipped and aggregation begins, leading to Parkinson's disease," said co-first author Dr Amberley Stephens.

The imbalance can be caused by a genetic doubling of the amount of alpha-synuclein (gene duplication), by an age-related slowing of the breakdown of excess protein, by an increased level of calcium in neurons that are sensitive to Parkinson's, or an associated lack of calcium buffering capacity in these neurons.

Understanding the role of alpha-synuclein in physiological or pathological processes may aid in the development of new treatments for Parkinson's disease. One possibility is that drug candidates developed to block calcium, for use in heart disease for instance, might also have potential against Parkinson's disease.

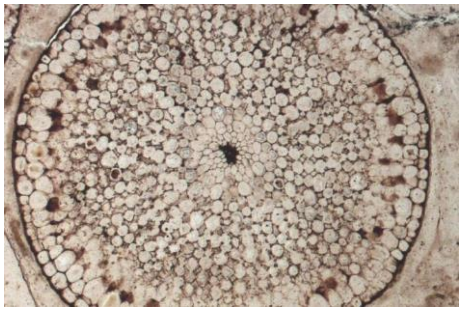
The research was funded in part by the Wellcome Trust, the Medical Research Council, Alzheimer's Research UK, and the Engineering and Physical Sciences Research Council.

http://bit.ly/2EQHRB9

Plants colonized the earth 100 million years earlier than previously thought

For the first four billion years of Earth's history, our planet's continents would have been devoid of all life except microbes.

All of this changed with the origin of land plants from their pond scum relatives, greening the continents and creating habitats that animals would later invade.



The timing of this episode has previously relied on the oldest fossil plants which are about 420 million years old.

***Rhynia gwynne-vaughanii** -- 400 million-year-old fossil plant stem from Aberdeenshire, Scotland.* **Image courtesy of The Natural History Museum, London.**

New research, published today in the journal Proceedings of the National Academy of Sciences USA, indicates that these events actually occurred a hundred million years earlier, changing perceptions of the evolution of the Earth's biosphere.

Plants are major contributors to the chemical weathering of continental rocks, a key process in the carbon cycle that regulates Earth's atmosphere and climate over millions of years.

The team used 'molecular clock' methodology, which combined evidence on the genetic differences between living species and fossil constraints on the age of their shared ancestors, to establish an evolutionary timescale that sees through the gaps in the fossil record.

Dr Jennifer Morris, from the University of Bristol's School of Earth Sciences and co-lead author on the study, explained: "The global spread of plants and their adaptations to life on land, led to an increase in continental weathering rates that ultimately resulted in a dramatic decrease the levels of the 'greenhouse gas' carbon dioxide in the atmosphere and global cooling.

"Previous attempts to model these changes in the atmosphere have accepted the plant fossil record at face value - our research shows that these fossil ages underestimate the origins of land plants, and so these models need to be revised."

Co-lead author Mark Puttick described the team's approach to produce the timescale.

He said: "The fossil record is too sparse and incomplete to be a reliable guide to date the origin of land plants. Instead of relying on the fossil record alone, we used a 'molecular clock' approach to compare differences in the make-up of genes of living species - these relative genetic differences were then converted into ages by using the fossil ages as a loose framework.

"Our results show the ancestor of land plants was alive in the middle Cambrian Period, which was similar to the age for the first known terrestrial animals."

One difficulty in the study is that the relationships between the earliest land plants are not known.

Therefore the team, which also includes members from Cardiff University and the Natural History Museum, London, explored if different relationships changed the estimated origin time for land plants.

Leaders of the overall study, Professor Philip Donoghue and Harald Schneider added: "We used different assumptions on the relationships between land plants and found this did not impact the age of the earliest land plants.

"Any future attempts to model atmospheric changes in deep-time must incorporate the full range of uncertainties we have used here."

Paper: 'Timescale of early land plant evolution' by JL Morris, MN Puttick, J Clark, D Edwards, P Kenrick, S Pressel, CH Wellman, Z Yang, H Schneider and PCJ Donoghue in Proceedings of the National Academy of Sciences USA.

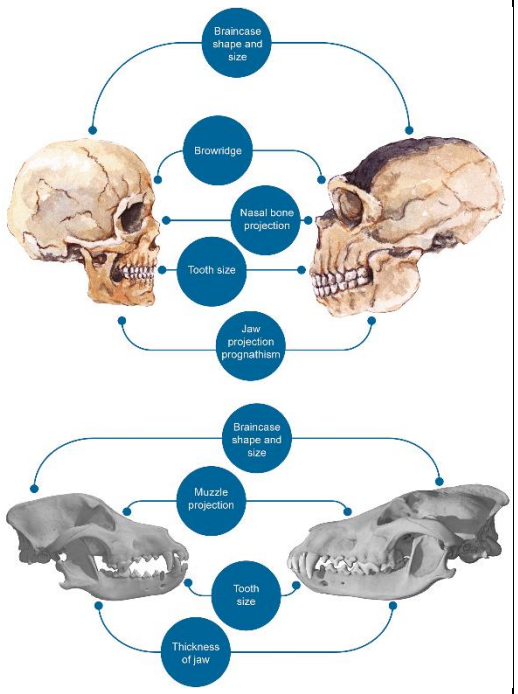
http://bit.ly/2FhPxKL

Did humans domesticate themselves?

New genetic evidence for this evolutionary process

Human self-domestication posits that among the driving forces of human evolution, humans selected their companions depending on who exhibited more pro-social behavior. Researchers from a team of the UB led by Cedric Boeckx, ICREA professor at the Department of Catalan Philology and General Linguistics and member of the Institute of Complex Systems of the University of Barcelona (UBICS), report new genetic evidence for this evolutionary process.

The study, published in PLOS ONE, compared the genomes of modern humans to those of several domesticated species and their wild animal types in order to find overlapping genes associated with domestication traits, such as docility or a gracile physiognomy. The results showed a statistically significant number of genes associated with domestication, which overlapped between domestic animals and modern humans, but not with their wild equals, like Neanderthals.



Craniofacial differences between modern humans and Neanderthals (top) and between dogs and wolves (bottom). **PLOS ONE**

According to the researchers, these results reinforce the human self-domestication hypothesis and "help to shed light on one aspect that makes us human, our social instinct."

A new type of evidence: the genomes of extinct human relatives

Self-domestication is proposed in species that display anatomical and behavioural features typical of the differences between domestic animals in comparison to their wild types. However, unlike the transition of wolves to dogs, self-domestication occurs without one species domesticating another. Several studies proposed the hypothesis, stating that humans (and other species such as bonobos) domesticated themselves. The aim of this study was to find biological evidence of this process by looking at the genomes of our extinct relatives, such as Neanderthals or Denisovans. This evidence was previously unavailable to biologists.

"One reason that scientists claim that humans are self-domesticated is our behavior: Modern humans are docile and tolerant, like domesticated species. Our cooperative abilities and pro-social behaviour are key features of modern cognition," says Cedric Boeckx. "The second reason is that modern humans, when compared to Neanderthals, present a more gracile phenotype that resembles that seen in domesticates when compared to their wild-type cousins."

To identify signs of a self-domestication process in humans, the researchers made a list of genes associated with domestication features in humans, out of the comparison with the genome in Neanderthals and Denisovans, extinct human species. Then they compared this list to the genome from some domesticated animals and their wild relatives, for instance, dogs compared to wolves, and cattle compared to wisents.

Results showed that this overlap was only relevant between domesticated species and humans. "Those modern humans' selected genes under selection may prove central to a relevant process of domestication, given that these interactions may provide significant data on relevant phenotypic traits," said Cedric.

Intersection between modern humans and domesticated species

Researchers also employed other statistical measures, including control species, to certify these results. Their aim was to rule randomly overlapped genes between humans and domesticated animals, so they compared the genomes among other great apes. "We found that

chimpanzees, orangutans and gorillas do not show a significant overlap of genes under positive selection with domesticates. Therefore, it seems there is a 'special' intersection between humans and domesticated species, and we take this to be evidence for self-domestication," Boeckx said.

Researchers note that more experimental work is required in order to determine the anatomical, cognitive and behavioural characteristics associated with these genes. "We suspect it will cover the anatomical, cognitive, and behavioral characteristics that researchers used to motivate the idea of self-domestication. We think that the overlap could help us explain our special mode of cognition and why we are strikingly cooperative, but this remains to be put to the test. In a sense, what we did is narrow down the set of genes to examine experimentally," concluded Cedric Boeckx.

More information: Constantina Theofanopoulou et al. Self-domestication in Homo sapiens: Insights from comparative genomics, PLOS ONE (2017). DOI: 10.1371/journal.pone.0185306
Journal reference: PLoS ONE search and more info website

http://bit.ly/2oo8uU3

Our discovery of how humans experience the smell of death may one day help save lives

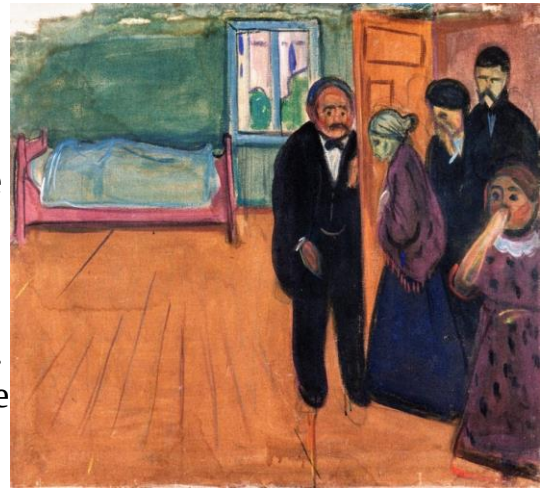
How do humans actually sense the smell of death?

Jean-Christophe Nebel*

And the sky was watching that superb cadaver
Blossom like a flower.
So frightful was the stench that you believed
You'd faint away upon the grass.
The blow-flies were buzzing round that putrid belly,
From which came forth black battalions
Of maggots, which oozed out like a heavy liquid
All along those living tatters.

This poem was written by Charles Baudelaire in 1857, when scientists didn't really know what the smell of death was. Perhaps Baudelaire's morbid curiosity inspired the work of the German physician Ludwig Brieger, who a couple of decades later for the first time described the main chemical compounds responsible for the "rotting flesh" smell – a mix putrescine and cadaverine.

But how do humans actually sense this terrifying smell? Our new study, published in PLOS Computational Biology, has now uncovered the biochemical details. Bizarrely, the findings may be able to help treat major mood disorders such as depression.



Edvard Munch's "The Smell of Death".

In recent years, the smell of death has become an important topic of investigation due to its potential of being used as a forensic tool. Its exact composition and intensity could help in distinguishing human from animal remains – and even determining the time of death. Such information could be used when training human remains detection dogs.

Our sense of smell relies on the detection of airborne molecules. Proteins belonging to a large family – G protein-coupled receptors (GPCRs) – do this by sensing molecules outside the cell and activating physiological responses. This includes not only smell, but also vision, taste and the regulation of behaviour and mood.

The interaction these proteins have with the outside world makes them major targets for drug development – around one-third of currently available drugs were designed to interact with them. Among the 800 human GPCRs, more than 100 are classified as "orphans" – meaning we don't know which molecules they are able to sense and how they would interact with them. As a consequence, their potential for developing new drugs is particularly difficult to exploit.

But our new research has recently established that two of these orphans – the human TAAR6 and TAAR8 receptors – are able to detect putrescine and cadaverine molecules. Using computational strategies

including modelling of the three-dimensional structure of the receptors, we revealed exactly how they interact with the chemicals of death.

There are many direct applications of this work. For example, we could design drugs to reduce the sensitivity to those odours for people either suffering from increased smell perception (hyperosmia) or working in environments where those compounds are present. They may also be useful for developing a new form of "tear gas" for riot control by creating artificial compounds activating those receptors.

Tackling depression

In the longer term, the findings could also help us tackle major mood disorders. Several specific variations in TAAR6 have previously been associated with conditions which affect a sizeable proportion of the world population: depression, bipolar and schizophrenic disorders. For example, one variant was found to affect how people respond to antidepressants, while another was linked to higher suicide risk.

Pig carcass in the smelliest stage of decomposition: the bloat stage. **Hbreton19 /wikimedia, CC BY-SA**

The research could therefore help us develop a new non-invasive method to support diagnosis. Patients with major mood disorders could be offered a "death smell test", where an abnormal response (experiencing it either more or less strongly than normal) to those odour stimuli could indicate that they carry one of the TAAR6 variants that increases susceptibility to specific mental conditions.

Once diagnosed, sufferers of these conditions could also get specific help from new drugs – the detected genetic variant could be targeted to alleviate symptoms of the psychiatric disorder. While we currently don't know the exact biochemical mechanisms by which a given variant causes a specific mental health condition, our study is a very useful starting point for uncovering that since it explains the biochemical mechanism involved in the interaction of TAAR6 with external compounds.

It would then be easy to estimate how the presence of a certain variant would affect that interaction. Establishing the link to its physiological response – helping us understand what compounds alter the mental state – would be more challenging. However, even if the detailed pathway between the drug and the final outcome remains unknown, simply testing them in animals and human clinical trials can often be sufficient to demonstrate that they work.

Baudelaire himself was affected by bipolar disorder: the great troubled poet wrote of his thoughts of suicide and even attempted to kill himself when his mistress and muse, Jeanne Duval, was rejected by his family. Could the poet have ever imagined that inside the rotting carcass that he described so vividly may have resided a remedy to his mental condition?

Associate Professor in Pattern Recognition, Kingston University

Disclosure statement

Jean-Christophe Nebel does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond their academic appointment.

Partners

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http://bit.ly/2C8UoyP

Loneliest tree in the world marks new age for our planet

An international research team, including Professor Christopher Fogwill from Keele University, has pinpointed a new geological age, the Anthropocene.

When humans first set foot on the moon in 1969, the people of that decade thought the world had changed forever. Little did they know the world had already laid down the precise marker of a far greater global change four years earlier, signalling our planet had entered an entirely new geological epoch, a time period defined by evidence in rock layers, the Anthropocene.

That new epoch began between October and December 1965 according to new research published today in Scientific Reports by members of

the Australasian Antarctic Expedition 2013-2014, which was co-led by co-author Professor Christopher Fogwill from Keele University.

The researchers were able to mark this profound change so precisely because of a "golden spike" found in the heartwood of a strange and singular tree, a Sitka Spruce found on Campbell Island, a World Heritage site in the middle of the Southern Ocean. The spruce is locally referred to as 'the loneliest tree in the world' with the next closest tree over 200km away on the Auckland Islands.

The radioactive carbon spike was created by the culmination of mostly Northern Hemisphere atmospheric thermonuclear bomb tests in the 1950s and 1960s. The signal was fixed in the wood of the Campbell Island Sitka spruce by photosynthesis.

Professor Fogwill, Head of the School of Geography, Geology and the Environment at Keele University, said: "The impact that humanity's nuclear weapons testing has had on the Earth's atmosphere provides a global signal that unambiguously demonstrates that humans have become the major agent of change on the planet. This is an important, yet worrying finding. The global atomic bomb signal, captured in the annual rings of this invasive tree species, represents a line in the sand, after which our collective actions have stamped an indelible mark, which will define this new geological epoch for generations to come."

Various researchers from around the world have been talking about declaring a new geological epoch called the Anthropocene, indicating the point where human influence on the planet fundamentally changed the natural world. However, for a new epoch to be officially declared there must be a clear and precise "global" signal that can be detected in the geological forming materials of the future. This radiocarbon spike is that signal.

Lead author Professor Chris Turney, from University of New South Wales, said: "We were incredibly excited to find this signal in the Southern Hemisphere on a remote island, because for the first time it gave us a well defined global signature for a new geological epoch that could be preserved in the geological record. Thousands of years from now this golden spike should still stand as a detectable marker for the transformation of the Earth by humankind."

In the Northern Hemisphere, the atmospheric radiocarbon peak occurred in 1964 where the signal is preserved in European trees. That same peak took until late 1965 to reach the Southern Hemisphere atmosphere. With that, the signal became global, precise and detectable in the geological record, meaning it fitted the requirements as a marker for a new epoch.

The 100-year-old tree itself is an anomaly in the Southern Ocean. It is naturally found along the North American Pacific Coast but it is credited with being planted on Campbell Island by the Governor of New Zealand in 1901. The oceanic climate has had an unusual effect on the spruce. Although it has grown to 10m tall, the tree has never produced cones, suggesting it has remained in a permanently juvenile state.

Co-author Professor Mark Maslin, from University College London, said: "It seems somehow apt that this extraordinary tree, planted far from its normal habitat by humans has also become a marker for the changes we have made to the planet, it is yet further evidence, if that was needed, that in this new epoch no part of our planet remains untouched by humans."

http://nyti.ms/2GufFBa

Doctors Said Immunotherapy Would Not Cure Her Cancer. They Were Wrong.

Scientists are struggling to understand why the drugs worked when they should not have

By GINA KOLATA FEB. 19, 2018

No one expected the four young women to live much longer. They had an extremely rare, aggressive and fatal form of ovarian cancer. There was no standard treatment.

The women, strangers to one another living in different countries, asked their doctors to try new immunotherapy drugs that had revolutionized treatment of cancer. At first, they were told the drugs were out of the question — they would not work against ovarian cancer.

Now it looks as if the doctors were wrong. The women managed to get immunotherapy, and their cancers went into remission. They returned to work; their lives returned to normalcy.

The tale has befuddled scientists, who are struggling to understand why the drugs worked when they should not have. If researchers can figure out what happened here, they may open the door to new treatments for a wide variety of other cancers thought not to respond to immunotherapy.

“What we are seeing here is that we have not yet learned the whole story of what it takes for tumors to be recognized by the immune system,” said Dr. Jedd Wolchok, chief of the melanoma and immunotherapeutics service at Memorial Sloan Kettering Cancer Center in New York.

“We need to study the people who have a biology that goes against the conventional generalizations.”

Four women hardly constitutes a clinical trial. Still, “it is the exceptions that give you the best insights,” said Dr. Drew Pardoll, who directs the Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins Medicine in Baltimore.

The cancer that struck the young women was hypercalcemic small cell ovarian cancer, which typically occurs in a woman’s teens or 20s. It is so rare that most oncologists never see a single patient with it.

But Dr. Douglas Levine, director of gynecologic oncology at New York University Langone Medical Center, specialized in this disease. A few years ago, he discovered that the cancer was driven by a single gene mutation. The finding was of little use to patients — there was no drug on the horizon that could help.

Women with this form of ovarian cancer were sharing news and tips online in a closed Yahoo group. Dr. Levine asked to become part of the group and began joining the discussions. There he discovered patients who had persuaded doctors to give them an immunotherapy drug, even though there was no reason to think it would work.

The women reported that their tumors shrank immediately.

The idea behind immunotherapy is to dismantle a molecular shield that some tumors use to avoid an attack by the body’s white blood cells.

The immune system sees these tumors as foreign — they are fueled by hundreds of genetic mutations, which drive their growth and are recognized by the body. But when white blood cells swarm in to attack the cancer cells, they bounce back, rebuffed.

Immunotherapy drugs pierce that protective shield, allowing the immune system to recognize and demolish tumor cells. But the new drugs do not work against many common cancers.

Those cancers are supported by fewer genetic mutations, and experts believe that the tumor cells just do not look threatening enough to the body to spur a response. So the immune system leaves them alone.

Lung cancer, a genetic type of colorectal cancer and melanoma have huge numbers of mutations, and immunotherapy drugs often are successful in treating them. Cancers of the prostate, pancreas, breast, ovaries — and most other tumors — carry few mutations.

“These are the cancers that rarely respond,” Dr. Pardoll said.

The idea that the drugs might work against something like hypercalcemic ovarian cancer, which is fueled by just one genetic mutation, just made no sense.

“For the vast majority of cancers, there is an amazingly clean correlation between response to therapy and mean mutational load,” Dr. Pardoll said.

But there were a few oddball exceptions. An unusual skin cancer called Merkel cell carcinoma responded to immunotherapy, scientists found. It is caused by a virus, and researchers suggested the infection itself draws the attention of the immune system.

Mesothelioma also responded, perhaps because the asbestos that caused it also inflames the immune system. And some kidney cancers responded to immunotherapy treatment; no one knows why.

And then came a handful of women with a rare ovarian cancer. Oriana Sousa, 28, a psychologist in Marinha Grande, Portugal, was one of them. She found out she had cancer in December 2011. She knew something was wrong — for several months she had been feeling tired, constipated and endlessly thirsty. She began vomiting and had abdominal cramps. But her doctors told her she was fine and not to worry.

Finally, her aunt, a nurse, suggested she see a different doctor, who performed a CT scan of her abdomen. It revealed a huge mass. The doctor operated to find out what it was. Two days later, he gave her the bad news: Cancer, and a really terrible form of it.

For the next four years, Ms. Sousa's doctors tried to control the cancer, giving her rounds of chemotherapy, radiotherapy and surgery. But every time, new tumors emerged.

"I suffered a lot, and I felt I had no life," she said.

Things are different now. In 2015, she finally persuaded a doctor to give her an immunotherapy drug, nivolumab. Immediately, her tumors shrank and continued shrinking as she continued with the drug — so much that her doctors now say she has no evidence of disease. Life has returned to normal.

"Generally after work, I go to the gym and do classes and work out," she said. "People who don't know what I have been through, they can't imagine I am an oncology patient."

What saved her? Dr. Eliezer M. Van Allen, a cancer researcher at Dana-Farber Cancer Institute, has come across one clue.

He found that a gene mutated in kidney cancer was sort of a master regulator of other genes, controlling which were turned on and when. But the regulated genes were normal and did not produce proteins that the immune system might recognize as abnormal.

Nonetheless, patients responding to immunotherapy were the ones with the master gene mutation. "We saw this result and weren't sure what to make of it," he said.

Dr. Levine and his colleagues found the same phenomenon in patients with hypercalcemic ovarian cancers. One explanation, he and Dr. Van Allen said, is that the immune system may recognize that cells in which genes are erratically turning on and off are dangerous and should be destroyed.

"That is strictly hypothesis," Dr. Levine cautioned.

One thing is clear, though: When pathologists examine these tumors, they find white blood cells in them — as if the immune system were trying to attack. And that finding has led both Dr. Pardoll and Dr. Padmanee Sharma of M.D. Anderson Cancer Center in Houston to plan new clinical trials.

They know that immunotherapy fails most patients, even those with cancers that are most likely to respond. So they have set out to create a test to determine who might respond to immunotherapy and then treat those patients — regardless of their cancer type.

Dr. Sharma's study, funded by the Parker Institute, is getting ready to enroll patients. The researchers will look at pathology slides of patients' tumors to see if white blood cells are worming their way into the cancers. If so, the patients will get an immunotherapy drug to help activate their white blood cells to attack the tumor.

If there are few white blood cells in the tumor tissue, patients will get a combination of two immunotherapy drugs to help move more white blood cells into the tumor and help them attack.

"The trial is written for all comers," Dr. Sharma said. "If we have learned anything, it is that it is not the tumor type we are treating — it is the immune system."

At Johns Hopkins, Dr. Pardoll and his colleagues are planning a similar trial. They will be looking for tumors — it does not matter what type — that have a protein, PD-L1, on the surface that repels the immune system. Any patient whose tumor fits that description will get an immunotherapy drug.

It's a shot in the dark. But sometimes such a shot finds the mark, as Ms. Sousa will tell you.

"Incredible things happen, and against all the odds," she said.

http://bit.ly/2GA1j2v

High blood pressure limits protection to vital organs and tissues in low- oxygen conditions

New research published in The Journal of Physiology sheds light on the effects of high blood pressure by considering the way the body responds to a lack of oxygen.

When a healthy person has a deficiency of oxygen in the blood (a state called 'hypoxia') caused by reduced oxygen pressure in the air (e.g. at high altitude) or when their upper airway is blocked during sleep (sleep apnoea) their body compensates by increasing blood flow to vital organs and tissues such as the brain and muscles in order to maintain oxygen supply to them. This is important to protect these organs and tissues.

To understand how high blood pressure impacts these compensatory responses to hypoxia, the study conducted by researches from the Fluminense Federal University, Brazil and The University of Copenhagen, Denmark, involved measuring the blood flow to the brain and the leg muscles whilst middle-aged men with normal and high blood pressure inhaled air with a low oxygen concentration for 5 minutes.

This research then showed that this increased blood supply response to hypoxia does not occur for middle-aged men with high blood pressure, and therefore when they are deprived of oxygen, oxygen delivery to parts of the brain and the leg skeletal muscles is limited. According to the study, this compromised response may be caused by the high blood pressure-induced impairment in the function of the blood vessels as well as increases in neural signals from the hypoxic brain to the circulation, increasing resistance to blood supply.

Importantly, this study only offers insights into the disturbances caused by high blood pressure during a short-term exposure (5 minutes) to low oxygen concentrations in a controlled environment (i.e. carbon dioxide concentration was kept constant and blood pressure to hypoxia did not change). Looking into these responses during a longer exposure to hypoxia in daily life situations such as high altitude exposure or sleep apnoea is also necessary to confirm these findings.

Dr Igor A Fernandes, the lead investigator of the project, also highlights the importance to understand the mechanisms that maintain brain and skeletal muscle oxygen supply of healthy individuals in hypoxic conditions and how high blood pressure affects them:

"We are interested in determining how high blood pressure impacts the mechanisms by which hypoxia increases brain and skeletal muscle blood supply and oxygen delivery. This will enable us to investigate how to prevent their deterioration or restore their adequate functioning."

http://bit.ly/2EGMtdO

Women once considered low risk for heart disease show evidence of previous heart attack scars

New study shows that women who complain of chest pain but don't have coronary artery blockages could have experienced undiagnosed heart attacks

LOS ANGELES -- Women who complain about chest pain often are reassured by their doctors that there is no reason to worry because their angiograms show that the women don't have blockages in the major heart arteries, a primary cause of heart attacks in men.

But a National Institutes of Health study led by investigators at the Barbra Streisand Women's Heart Center in the Smidt Heart Institute, shows that about 8% of those women actually have scars on their heart that indicate they experienced a heart attack. The findings were published today in Circulation, the American Heart Association's peer-reviewed medical journal.

"This study proves that women need to be taken seriously when they complain of chest pain, even if they don't have the typical symptoms we see in men," said Janet Wei, MD, the first author of the study. "Too often, these women are told they don't have a heart problem and they are sent home instead of receiving appropriate medical care."

The study is part of the ongoing Women's Ischemic Syndrome Evaluation (WISE) study, a multiyear, multicenter research project. Sponsored by the National Heart, Lung, and Blood Institute, the study began in 1997 and has brought to light gender-related differences in heart disease.

The study looked at women who had complained of chest pain and had no coronary artery blockages. Results include:

Of the 340 women who underwent cardiac magnetic resonance (CMR), a detailed imaging scan of the heart, 26, or 8%, were found to have myocardial scar, indicating the women had experienced prior heart muscle damage;

Approximately one-third of those 26 women were never diagnosed with a heart attack, even though their cardiac scans indicated they had heart muscle damage;

Of the 179 women who underwent a one-year follow-up CMR, 2 women, or 1% were found to have myocardial scar that wasn't there the year before; both of these women had interim hospitalizations for chest pain but were not diagnosed with heart attacks.

"Many women go to the hospital with chest pain but they often aren't tested for a heart attack because doctors felt they were low-risk," said Noel Bairey Merz, MD, director of the Barbra Streisand Women's Heart Center in the Smidt Heart Institute. "And they are considered low-risk because their heart disease symptoms are different than the symptoms men experience."

Bairey Merz, who also serves as the primary investigator of the WISE study, is a pioneer in uncovering the differences between men and women with heart disease.

Men with heart disease are more likely to have major plaque build-up in the major arteries bringing blood to the heart. A heart attack occurs when plaque causes blood flow to decrease or stop.

The WISE study has revealed that women who don't have blockages in their major heart arteries, but who experience chest pain might have microvascular dysfunction in the tiny vessels around the heart. That condition can go undetected because typical heart attack tests, such as an electrocardiogram, often don't detect microvascular dysfunction.

"We are finding that either these women are not being tested because doctors think they are at low-risk or that the tests doctors are ordering are not picking up these small heart attacks," Wei said.

As a result of the study, Wei and Bairey Merz are collaborating with Jennifer Van Eyk, PhD, a renowned expert in the study of proteins, including troponin, a protein that appears in the blood after a heart attack.

"By developing highly sensitive tests to detect previously unknown biomarkers, we may pinpoint and even prevent cardiovascular disease in women," Van Eyk said.

http://bit.ly/2ofUcFx

TSRI stroke drug demonstrates safety in clinical trial

A preliminary Phase 2 clinical trial has demonstrated that patients with acute ischemic stroke, the most common type of stroke, can safely tolerate high doses of 3K3A-APC

LA JOLLA, CA - Feb. 20, 2018 - A preliminary Phase 2 clinical trial has demonstrated that patients with acute ischemic stroke, the most common type of stroke, can safely tolerate high doses of 3K3A-APC, a promising anti-stroke drug invented at The Scripps Research Institute (TSRI). The trial results, announced by pharmaceutical company ZZ Biotech, also show that 3K3A-APC substantially reduced hemorrhage volume and hemorrhage incidence in patients.

"These results lay the groundwork for the next steps toward FDA approval," says John Griffin, PhD, professor at TSRI, whose team invented 3K3A-APC.

Stroke is the fifth leading cause of death in the United States and the number one cause of adult disability. Acute ischemic strokes occur when a clot blocks blood flow to the brain. To date, the FDA has approved only one drug treatment, called tissue plasminogen activator (tPA), to treat acute ischemic strokes. tPA helps break up blood clots if given within a 4.5-hour window after the stroke.

Unfortunately, tPA's use is limited due to this brief treatment window and its potential to cause bleeding in the brain and neuronal cell death. But studies so far show that 3K3A-APC could complement tPA administration. Griffin designed the experimental drug by modifying just three amino acids on a naturally occurring blood protein called protein C, which is both an anticoagulant and a cell protective agent.

"This is an extremely novel drug," says Griffin.

Preclinical testing in collaborative studies involving Griffin's lab and the lab of Berislav Zlokovic, MD, PhD, director of the Zilkha Neurogenetic Institute at the University of Southern California, showed that 3K3A-APC lessens the damage of stroke and protects brain cells from the side effects of tPA. The drug was licensed by TSRI to the pharmaceutical company ZZ Biotech, where Zlokovic was the scientific founder.

To find the maximally tolerated dose, the National Institutes of Health's National Institute of Neurological Disorders and Stroke (NINDS) funded the recent Phase 2 study, called RHAPSODY, through a grant to the principal investigator Patrick Lyden, MD, chair of the Department of Neurology at Cedars-Sinai in Los Angeles, and through a NeuroNEXT Infrastructure Resource Access grant to ZZ Biotech, where Kent Pryor, PhD, served as co-principal investigator. NINDS entered into a Cooperative Research and Development Agreement (CRADA) with ZZ Biotech.

For the placebo-controlled dose-escalation trial, the researchers evaluated 3K3A-APC in patients with acute ischemic stroke treated with intravenous tPA, intra-arterial thrombectomy, or both. The scientists evaluated four doses of the drug: 120, 240, 360 and 540 µg/kg. Study participants, aged 18 to 90, were followed for 90 days. All doses were deemed safe and well tolerated.

As a secondary endpoint, the researchers evaluated cerebral hemorrhage in these patients. They found that total hemorrhage volume and hemorrhage incidence were both substantially reduced in 3K3A-APC-treated patients. The incidence of any hemorrhage was reduced from 86.5 percent in placebo-treated patients to 67.4 percent in the combined treatment arms. Total hemorrhage volume was likewise reduced from an average of 2.1±5.8 mL on placebo to 0.8±2.1 mL in the combined treatment arms.

The next steps for the researchers are to confirm and extend the successful Phase 2 study results in larger clinical trials.

Griffin says the collaborative environment at TSRI made the development of 3K3A-APC possible. "I've been blessed by working with fantastic people. TSRI has been committed to basic research and discovery of new knowledge, especially with translational potential--and that's been my philosophy."

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UA study: Brain liquefaction after stroke is toxic to surviving brain

Liquefied, dying brain tissue is toxic and can slowly leak into the remaining healthy portion of the brain

Scientists have known for years that the brain liquefies after a stroke. If cut off from blood and oxygen for a long enough period, a portion of the brain will die, slowly morphing from a hard, rubbery substance into liquid goop.

Now, researchers at the University of Arizona College of Medicine - Tucson have discovered that this liquefied, dying brain tissue is toxic -- and can slowly leak into the remaining healthy portion of the brain, potentially causing harm. The new findings may open the door for developing new treatments to ward off dementia after stroke; they are described in the April 2018 issue of Neurobiology of Disease.

"Most people probably assume that the brain heals in the same way as other tissues," said Kristian Doyle, PhD, an assistant professor in the UA Department of Immunobiology. "But it doesn't; dead brain tissue doesn't just heal and go away like other bodily injuries. Instead it liquefies and remains in this liquefactive state for a long time."

To better understand this dying fluid, Dr. Doyle and his laboratory team studied mice that had experienced strokes. First, the researchers

extracted fluid from the area of liquefaction and tested its toxicity by placing it in a petri dish with living neurons. After four hours, more than 50 percent of the neurons in the dish had died, compared to neurons that were placed in a dish with regular, healthy brain fluid.

The researchers then evaluated how well this toxic fluid was sealed off from the surviving brain.

Normally, a scar forms around dying brain tissue after a stroke. This scar, known as a glial scar, creates a barrier around the injured area to protect the remaining brain; it's formation is critical to the healing process.

Using a high-powered microscope, the UA researchers imaged this barrier between the healthy and injured portions of the mouse brain. Up close, the glial scar looked like "a fence made of branches twisted tightly together," Dr. Doyle said.

Then they injected a dye into the injured portion of the brain. At seven weeks post-stroke, the dye was able to spread past the glial scar and into the healthy brain region. According to Dr. Doyle, this suggested that toxic substances present in the liquefied tissue also leak into the brain after a stroke, potentially killing healthy neurons.

"We found that the glial scar is a pretty decent barrier, but it's not perfect," Dr. Doyle said. "Imagine putting sandbags around your house; they will reduce flood damage, but not control everything."

Dr. Doyle suspects this slow, leaking fluid may be a cause of dementia after stroke. Of the 10 million people who survive a stroke each year, about one-third will develop dementia for unclear reasons, he said.

If the brain is injured near the hippocampus -- the portion of the brain responsible for memory -- perhaps this slow leak of toxic fluid causes neurodegeneration, the loss of neurons in the brain, and ultimately, memory problems.

"This work really challenges the old paradigms and breaks new ground critical for our understanding of stroke and its consequences," said Janko Nikolich-Zugich, MD, PhD, chair of the UA Department of Immunobiology. "We used to think that the glial scar forms a fool-proof barrier, and had no idea about the toxicity of the liquefied brain materials. Thanks to this research, we now will be able to consider new and different stroke therapies."

Nevertheless, further research is needed. The team hopes to verify its results in the future by showing that post-stroke memory problems can be curbed with a drug that makes the glial scar's barrier more robust.

Research also is needed to find out precisely how long the toxic fluid lasts. Liquefied brain tissue eventually will result in an empty cavity in which healthy brain tissue once existed. Dr. Doyle's lab believes that the liquefied tissue lasts for months in the brain before the process is complete.

The UA College of Medicine - Tucson research was funded by a grant from the National Institute of Neurological Disorders and Stroke under award No. R01NS096091.

http://bbc.in/2Cc3ETa

Roman boxing gloves unearthed by Vindolanda dig

Roman boxing gloves unearthed during an excavation near Hadrian's Wall have gone on public display.

Experts at Vindolanda, near Hexham, in Northumberland, believe they are "probably the only known surviving examples from the Roman period".

Dr Andrew Birley, Vindolanda Trust director of excavations, described the leather bands as an "astonishing" find.

The gloves were "skilfully made" about 2,000 years ago **Vindolanda Trust**

The gloves were discovered last summer along with a hoard of writing tablets, swords, shoes and bath clogs. Made of leather, they were designed to fit snugly over the knuckles and have the appearance of a protective guard.

'Hairs stand up'

Dr Birley said: "I have seen representations of Roman boxing gloves depicted on bronze statues, paintings and sculptures, but to have the privilege of finding two real leather examples is exceptionally special.

"The hairs stand up on the back of your neck when you realise you have discovered something as astonishing as these boxing gloves."
The larger of the two is filled with natural material, which would have acted as a shock absorber. The smaller glove, found "in near perfect condition", is filled with a coil of hard, twisted leather. It is understood they would have been used for sparring sessions as they do not have metal inserts used in ancient boxing bouts.

http://bbc.in/2sODvpn

Tool 'names and shames' hidden drug trials

Institutions that fail to report the results of their drug and medical trials will be named on a new website.

By Chris Foxx Technology reporter

Trials Tracker logs which clinical trials have missed deadlines for reporting their results in the US. Some pharmaceutical organisations have been accused of burying unfavourable drug and medical test results. Dr Ben Goldacre, who devised the website, told the BBC he hoped it would "nudge" institutions into properly disclosing data. "For many years, trials transparency has been neglected," he said.
"I'm not interested in naming and shaming people in order to criticise them. This project is being done to nudge institutions to prioritise trial reporting. "I think most institutions will want to comply with their legal obligations and their ethical obligations."

Deadlines

Some types of clinical trial involving US citizens must be registered on the clinicaltrials.gov website, following the introduction of the Food and Drug Administration Amendment Act (FDAAA) 2007. That law does not cover all types of clinical trial, but some - such as trials of existing approved treatments involving US citizens - must be registered. Results must be reported within 12 months of completion. Companies that miss the deadline can be fined $10,000 (£7,000) a day by the FDA.
"Nobody has ever been penalised for breaching those codes," explained Dr Goldacre. "I think accountability is a really important way of driving up standards."

Enforcement

The Trials Tracker website automatically takes data from clinicaltrials.gov to find trials that have missed the reporting deadline.
It also calculates how much the US government could have collected in fines, if the FDA pursued every missed deadline. It was created by a team of researchers at the University of Oxford's Evidence Based Medicine DataLab.
The FDA told the BBC it had not had time to fully review Trials Tracker. "It is often not possible to determine which parties may be non-compliant based solely on the information in the record that is publicly posted on clinicaltrials.gov," it said in a statement. "The FDA intends to assess compliance with the requirements on a case-by-case basis."
Imperial College London was among the first six institutions to be named on the website for missing a reporting deadline. It told the BBC it had investigated what happened and had updated clinicaltrials.gov with the missing results.
Dr Goldacre said he was developing further trial-tracking websites exploring different types of clinical trial. "Some people might say it's mean - but it is proportionate, reasonable and fair," he told the BBC.

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Want healthy teeth? Drink red wine

Surprising results show compounds in wine act against three major dental bugs.

Andrew Masterson reports.

Compounds present in red wine reduce the ability of three species of bacteria responsible for creating plaque, gum lesions and caries, scientists have discovered.
The findings, established experimentally using human gum cells called gingival fibroblasts, raises the possibility that quaffing a daily glass of wine might one day be considered part of a sensible oral health regime.

Research by a Spanish team, published in the *Journal of Agricultural and Food Chemistry*, found that two polyphenol metabolites common in red wine – known as caffeic and p-courmaric acids – effectively mount a multi-pronged attack against *Fusobacterium nucleatum*, responsible for gum lesions, *Porphyromonas gingivalis*, which is linked to periodontitis, and *Streptococcus mutans*, which catalyses caries disease.

The compounds produce an anti-adhesive response, making it more difficult for the bacteria to become part of the biofilm that coats teeth and gums. They also have an anti-microbial effect, killing the three species, and work as anti-inflammatories, mediating the body's local immune system response.

The scientists, led by Victoria Moreno-Arribas of the Instituto de Investigacion en Ciencias de la Alimentacion, in Madrid, found that the positive effects of caffeic and p-courmaric acids were evident whether they were applied in isolation, or in combination with other compounds in wine-based extracts.

In a slightly surprising result, the researchers found that the actions of the metabolites were boosted if they were applied in combination with another bacterial species, *Streptococcus dentisani*, which is thought to function as an oral probiotic.

Previous research has pointed to the benefits of red wine polyphenols in areas such as cardiovascular and neurological health. Several studies have indicated positive associations between consuming about 250 millilitres of wine a day and the management of diabetes and gut health. A major study published in 2017, for instance, talked up "promising dietary approaches linked to wine polyphenols".

Until now, however, little attention has been paid to the effects of red wine on the oral cavity, simply because it was assumed that the essential breakdown of polyphenols (and hence the creation of bioavailable molecules called phenols) didn't begin until the gut.

Moreno-Arribas and her colleagues, however, demonstrate that the compounds begin to break down in the mouth, because of the actions of salivary enzymes, oral microbes, and the mechanical action of teeth and jaws.

The scientists concede that the understanding of these processes is "still preliminary", but may well be key to uncovering the mechanisms that produce the antimicrobial effects observed.

The team now intend to continue with tissue-based tests to try to better understand the interaction of the polyphenols and tooth-destroying bacteria, as well as investigating the seemingly supportive role of *S. dentisani*.

After that, they write, they want to scale the whole enterprise up, and shift to human clinical trials. There would seem little doubt that a call for volunteers to drink two glasses of red wine a day in the name of science will be answered.

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New paper links ancient drawings and the origins of language

When and where did humans develop language? To find out, look deep inside caves, suggests an MIT professor.

by Peter Dizikes, Massachusetts Institute of Technology

More precisely, some specific features of cave art may provide clues about how our symbolic, multifaceted language capabilities evolved, according to a new paper co-authored by MIT linguist Shigeru Miyagawa.

A key to this idea is that cave art is often located in acoustic "hot spots," where sound echoes strongly, as some scholars have observed. Those drawings are located in deeper, harder-to-access parts of caves, indicating that acoustics was a principal reason for the placement of drawings within caves. The drawings, in turn, may represent the sounds that early humans generated in those spots.

In the new paper, this convergence of sound and drawing is what the authors call a "cross-modality information transfer," a convergence of auditory information and visual art that, the authors write, "allowed early humans to enhance their ability to convey symbolic thinking." The

combination of sounds and images is one of the things that characterizes human language today, along with its symbolic aspect and its ability to generate infinite new sentences.

"Cave art was part of the package deal in terms of how homo sapiens came to have this very high-level cognitive processing," says Miyagawa, a professor of linguistics and the Kochi-Manjiro Professor of Japanese Language and Culture at MIT. "You have this very concrete cognitive process that converts an acoustic signal into some mental representation and externalizes it as a visual."

While the world's best-known cave art exists in France and Spain, examples of it abound throughout the world. **stock image of a cave painting in South Africa**

Cave artists were thus not just early-day Monets, drawing impressions of the outdoors at their leisure. Rather, they may have been engaged in a process of communication. "I think it's very clear that these artists were talking to one another," Miyagawa says. "It's a communal effort."

The paper, "Cross-modality information transfer: A hypothesis about the relationship among prehistoric cave paintings, symbolic thinking, and the emergence of language," is being published in the journal *Frontiers in Psychology*. The authors are Miyagawa; Cora Lesure, a Ph.D. student in MIT's Department of Linguistics; and Vitor A. Nobrega, a Ph.D. student in linguistics at the University of Sao Paulo, in Brazil.

Re-enactments and rituals?

The advent of language in human history is unclear. Our species is estimated to be about 200,000 years old. Human language is often considered to be at least 100,000 years old.

"It's very difficult to try to understand how human language itself appeared in evolution," Miyagawa says, noting that "we don't know 99.9999 percent of what was going on back then." However, he adds, "There's this idea that language doesn't fossilize, and it's true, but maybe in these artifacts [cave drawings], we can see some of the beginnings of homo sapiens as symbolic beings."

While the world's best-known cave art exists in France and Spain, examples of it abound throughout the world. One form of cave art suggestive of symbolic thinking—geometric engravings on pieces of ochre, from the Blombos Cave in southern Africa—has been estimated to be at least 70,000 years old. Such symbolic art indicates a cognitive capacity that humans took with them to the rest of the world.

"Cave art is everywhere," Miyagawa says. "Every major continent inhabited by homo sapiens has cave art. … You find it in Europe, in the Middle East, in Asia, everywhere, just like human language." In recent years, for instance, scholars have catalogued Indonesian cave art they believe to be roughly 40,000 years old, older than the best-known examples of European cave art.

But what exactly was going on in caves where people made noise and rendered things on walls? Some scholars have suggested that acoustic "hot spots" in caves were used to make noises that replicate hoofbeats, for instance; some 90 percent of cave drawings involve hoofed animals. These drawings could represent stories or the accumulation of knowledge, or they could have been part of rituals.

In any of these scenarios, Miyagawa suggests, cave art displays properties of language in that "you have action, objects, and modification." This parallels some of the universal features of human language—verbs, nouns, and adjectives—and Miyagawa suggests that "acoustically based cave art must have had a hand in forming our cognitive symbolic mind."

Future research: More decoding needed

To be sure, the ideas proposed by Miyagawa, Lesure, and Nobrega merely outline a working hypothesis, which is intended to spur additional thinking about language's origins and point toward new research questions.

Regarding the cave art itself, that could mean further scrutiny of the syntax of the visual representations, as it were. "We've got to look at the content" more thoroughly, says Miyagawa. In his view, as a linguist who has looked at images of the famous Lascaux cave art from France, "you see a lot of language in it." But it remains an open question how much a re-interpretation of cave art images would yield in linguistics terms.

The long-term timeline of cave art is also subject to re-evaluation on the basis of any future discoveries. If cave art is implicated in the development of human language, finding and properly dating the oldest known such drawings would help us place the orgins of language in human history—which may have happened fairly early on in our development. "What we need is for someone to go and find in Africa cave art that is 120,000 years old," Miyagawa quips.

At a minimum, a further consideration of cave art as part of our cognitive development may reduce our tendency to regard art in terms of our own experience, in which it probably plays a more strictly decorative role for more people.

"If this is on the right track, it's quite possible that … cross-modality transfer helped develop a symbolic mind," Miyagawa says. In that case, he adds, "art is not just something that is marginal to our culture, but central to the formation of our cognitive abilities."

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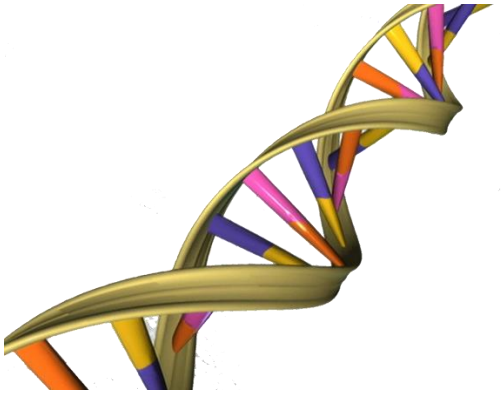
Genetic study suggests humans may be evolving in a way that prevents alcoholism

A pair of researchers with the University of Pennsylvania has found evidence suggesting humans may be evolving in a way that will prevent alcoholism in the future.

February 21, 2018 by Bob Yirka, Phys.org report

In their paper published in the journal *Nature Ecology & Evolution*, Kelsey Elizabeth Johnson and Benjamin Voight describe their study which involved analyzing data from the 1000 Genomes Project looking for emerging gene variants and what they found.

Humans are, of course, still evolving, which suggests studies looking into the ways we are evolving might be important. In this new effort, Johnson and Voight analyzed genetic data from the over 2,500 people whose DNA ended was used in the 1000 Genomes Project.



A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. **NHGRI**

More specifically, they looked for emerging variants in different population groups that might shed some light on the evolutionary changes that we are currently undergoing. They report that they were able to identify five genetic "hot spots"—resistance to malaria in African populations, an amino acid change in Europeans, two sections of DNA left over from interbreeding with Neanderthals, and finally, an ADH variant.

The ADH gene is responsible for inducing production of alcohol dehydrogenase, an enzyme that breaks down alcohol into acetaldehyde, which is then converted to acetate by another process. The researchers note that the variants seem to protect against alcoholism, though how that might happen is still unclear. They theorize that it might break down alcohol faster, causing drinkers to feel sick almost right away—a side-effect that would almost certainly deter drinkers from further consumption. They further theorize that it is possible that over the past 1000 years or so, people, particularly those in their reproductive years, who drank a lot wound up killing themselves off before reproducing—a trend still in evidence today as young people who drink and drive frequently wind up dead before they have a chance to make babies.

The researchers report that there was an anomaly in the data, however—ADH variants were not nearly as prevalent in European and American

populations as they were in others. They suggest this might have been due to overlooking the markers in the data.

Abstract

Signatures of recent positive selection often overlap across human populations, but the question of how often these overlaps represent a single ancestral event remains unresolved. If a single selective event spread across many populations, the same sweeping haplotype should appear in each population and the selective pressure could be common across populations and environments. Identifying such shared selective events could identify genomic loci and human traits important in recent history across the globe. In addition, genomic annotations that recently became available could help attach these signatures to a potential gene and molecular phenotype selected across populations. Here, we present a catalogue of selective sweeps in humans, and identify those that overlap and share a sweeping haplotype. We connect these sweep overlaps with potential biological mechanisms at several loci, including potential new sites of adaptive introgression, the glycophorin locus associated with malarial resistance and the alcohol dehydrogenase cluster associated with alcohol dependency.

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Animal study shows how to retrain the immune system to ease food allergies

Nanoparticles are used to deliver a therapeutic payload that quells an allergic reaction

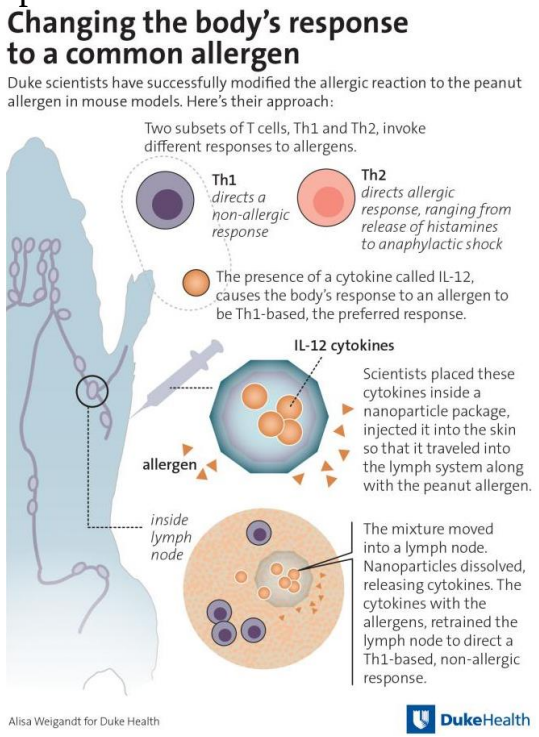
DURHAM, N.C. -- Treating food allergies might be a simple matter of teaching the immune system a new trick, researchers at Duke Health have found.

In a study using mice bred to have peanut allergies, the Duke researchers were able to reprogram the animals' immune systems using a nanoparticle delivery of molecules to the lymph nodes that switched off the life-threatening reactions to peanut exposures.

"This study in mice proves the concept of this approach, so tests in humans are not that far off," said Soman N. Abraham, Ph.D., professor in Duke's Department of Pathology. Abraham is senior author of a study published this month in the *Journal of Allergy and Clinical Immunology*.

Food allergies affect an estimated 4 percent of adults in the United States, and up to 6 percent of children. Peanuts are among the most common allergen and can trigger a life-threatening immune response, so people must learn to be vigilant about hidden exposures in everyday food choices.

In recent years, efforts have been made to desensitize allergic people to peanuts and other foods with a series of measured exposures that are gradually increased over time. Such treatments can be effective, but they're also risky and time-consuming.



Duke scientists have successfully modified the allergic reaction to the peanut allergen in mouse models. **Alisa Weigandt for Duke Health**

The approach -- planned by lead author Ashley St. John, Ph.D., an assistant professor at the Duke-NUS Medical School in Singapore -- appears to resolve those issues.

Starting with the observation that allergic reactions basically result from an imbalance of key messages between cells, called cytokines, the researchers set out to devise a way to restore order.

They focused on the Th2-type cytokine immune response, which is increasingly understood as a driver of the overactive immune responses in allergy attacks. In an appropriate immune response, Th2 works in tandem with Th1, but during allergic reactions, Th2 is overproduced and Th1 is diminished.

The solution appears simple enough: deliver more Th1-type cytokines ahead of an allergen exposure to restore balance. But it has proven

difficult. A test of this type was attempted as an asthma therapy, but it required a massive dose to the lungs and was ineffective.

In their experiment with the peanut-allergy mice, St. John and colleagues instead delivered antigen- and cytokine-loaded nanoparticles into the skin. The nanoparticles traveled to the lymph nodes, where they dissolved and dispensed their payload at the source of the immune response.

Animals that received this therapy no longer went into an acute allergic response called anaphylaxis when they were subsequently exposed to peanuts. The new-found tolerance was long-lasting, so did not need to be repeated ahead of each exposure to the allergen.

"The Th1 and Th2 sides of immunity balance each other," St. John said. "We reasoned that since we know Th2 immunity is over-produced during allergic responses, why not try to skew the immune response back the other direction? By delivering cytokines to the lymph nodes where immune responses are established, we were able to re-educate the immune system that an allergic response is not an appropriate one." The approach could theoretically be applied to other allergens, including environmental triggers such as dust and pollen. Additional experiments are underway to move the findings into human trials.

"We are encouraged by these findings, because it's a fairly simple way to reprogram the immune system," Abraham said.

In addition to Abraham and St. John, study authors include Gladys W. X. Ang and Abhay P. S. Rathore.

The study received funding support from the National Institutes of Health (R01 AI96305, R01 AI35678, R01 DK077159, R01 AI50021, R37 DK50814 and R21 AI056101).

http://bit.ly/2Gz5NGv

Ancient DNA tells tales of humans' migrant history

Scientists once could reconstruct humanity's distant past only from the mute testimony of ancient settlements, bones, and artifacts.

No longer. Now there's a powerful new approach for illuminating the world before the dawn of written history—reading the actual genetic code of our ancient ancestors. Two papers published in the journal *Nature* on February 21, 2018, more than double the number of ancient humans whose DNA has been analyzed and published to 1,336 individuals—up from just 10 in 2014.

The new flood of genetic information represents a "coming of age" for the nascent field of ancient DNA, says lead author David Reich, a Howard Hughes Medical Institute investigator at Harvard Medical School—and it upends cherished archeological orthodoxy. "When we look at the data, we see surprises again and again and again," says Reich. Together with his lab's previous work and that of other pioneers of ancient DNA, the Big Picture message is that our prehistoric ancestors were not nearly as homebound as once thought. "There was a view that migration is a very rare process in human evolution," Reich explains. Not so, says the ancient DNA. Actually, Reich says, "the orthodoxy—the assumption that present-day people are directly descended from the people who always lived in that same area—is wrong almost everywhere."

Instead, "the view that's emerging—for which David is an eloquent advocate—is that human populations are moving and mixing all the time," says John Novembre, a computational biologist at the University of Chicago.

Stonehenge's Builders Largely Vanish

In one of the new papers, Reich and a cast of dozens of collaborators chart the spread of an ancient culture known by its stylized bell-shaped pots, the so-called Bell Beaker phenomenon. This culture first spread between Iberia and central Europe beginning about 4,700 years ago. By analyzing DNA from several hundred samples of human bones, Reich's team shows that only the ideas—not the people who originated them—made the move initially. That's because the genes of the Iberian population remain distinct from those of the central Europeans who adopted the characteristic pots and other artifacts.

But the story changes when the Bell Beaker culture expanded to Britain after 4,500 years ago. Then, it was brought by migrants who almost completely supplanted the island's existing inhabitants—the mysterious people who had built Stonehenge—within a few hundred years. "There

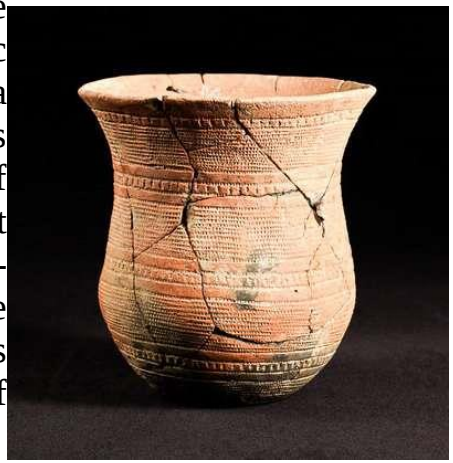
was a sudden change in the population of Britain," says Reich. "It was an almost complete replacement."

For archeologists, these and other findings from the study of ancient DNA are "absolutely sort of mind-blowing," says archaeologist Barry Cunliffe, a professor emeritus at the University of Oxford. "They are going to upset people, but that is part of the excitement of it."

Vast Migration from the Steppe

Consider the unexpected movement of people who originally lived on the steppes of Central Asia, north of the Black and Caspian seas. About 5,300 years ago, the local hunter-gatherer cultures were replaced in many places by nomadic herders, dubbed the Yamnaya, who were able to expand rapidly by exploiting horses and the new invention of the cart, and who left behind big, rich burial sites.

Archeologists have long known that some of the technologies used by the Yamnaya later spread to Europe. But the startling revelation from the ancient DNA was that the people moved, too—all the way to the Atlantic coast of Europe in the west to Mongolia in the east and India in the south. This vast migration helps explain the spread of Indo-European languages. And it significantly replaced the local hunter-gatherer genes across Europe with the indelible stamp of steppe DNA, as happened in Britain with the migration of the Bell Beaker people to the island.



The use of stylized bell-shaped pots like this one from Sierentz, France spread across Europe beginning about 4,700 years ago. DNA analysis show that this so-called Bell Beaker culture was brought to Britain by people who largely replaced the island's existing inhabitants. **Anthony Denaire**

"This whole phenomenon of the steppe expansion is an amazing example of what ancient DNA can show," says Reich. And, adds Cunliffe, "no one, not even archeologists in their wildest dreams, had expected such a high steppe genetic content in the populations of northern Europe in the third millennium B.C."

This ancient DNA finding also explains the "strange result" of a genetic connection that had been hinted at in the genomes of modern-day Europeans and Native Americans, adds Chicago's Novembre. The link is evidence from people who lived in Siberia 24,000 years ago, whose telltale DNA is found both in Native Americans, and in the Yamnaya steppe populations and their European descendants.

New Insights from Southeastern Europe

Reich's second new *Nature* paper, on the genomic history of southeastern Europe, reveals an additional migration as farming spread across Europe, based on data from 255 individuals who lived between 14,000 and 2,500 years ago. It also adds a fascinating new nugget—the first compelling evidence that the genetic mixing of populations in Europe was biased toward one sex.

Hunter-gatherer genes remaining in northern Europeans after the influx of migrating farmers came more from males than females, Reich's team found. "Archaeological evidence shows that when farmers first spread into northern Europe, they stopped at a latitude where their crops didn't grow well," he says. "As a result, there were persistent boundaries between the farmers and the hunter-gatherers for a couple of thousand years." This gave the hunter-gatherers and farmers a long time to interact. According to Reich, one speculative scenario is that during this long, drawn-out interaction, there was a social or power dynamic in which farmer women tended to be integrated into hunter-gatherer communities.

So far that's only a guess, but the fact that ancient DNA provides clues about the different social roles and fates of men and women in ancient society "is another way, I think, that these data are so extraordinary," says Reich.

Advanced Machines

These scientific leaps forward have been fueled by three key developments. One is the dramatic cost reduction (and speed increase)

in gene sequencing made possible by advanced machines from Illumina and other companies. The second is a discovery spearheaded by Ron Pinhasi, an archaeologist at University College Dublin. His group showed that the petrous bone, containing the tiny inner ear, harbors 100 times more DNA than other ancient human remains, offering a huge increase in the amount of genetic material available for analysis. The third is a method implemented by Reich for reading the genetic codes of 1.2 million carefully chosen variable parts of DNA (known as single nucleotide polymorphisms) rather than having to sequence entire genomes. That speeds the analysis and reduces its cost even further.

The new field made a splash when Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology, working with Reich and many other colleagues, used ancient DNA to prove that Neanderthals and humans interbred. Since then, the number of ancient humans whose DNA Reich has analyzed has risen exponentially. His lab has generated about three-quarters of the world's published data and, included unpublished data, has now reached 3,700 genomes. "Every time we jump an order of magnitude in the number of individuals, we can answer questions that we couldn't even have asked before," says Reich.

Now, with hundreds of thousands of ancient skeletons (and their petrous bones) still to be analyzed, the field of ancient DNA is poised to both pin down current questions and tackle new ones. For example, Reich's team is working with Cunliffe and others to study more than 1,000 samples from Britain to more accurately measure the replacement of the island's existing gene pool by the steppe-related DNA from the Bell Beaker people. "The evidence we have for a 90 percent replacement is very, very suggestive, but we need to test it a bit more to see how much of the pre-Beaker population really survived," explains Cunliffe.

Beyond that, ancient DNA offers the promise of studying not only the movements of our distant ancestors, but also the evolution of traits and susceptibilities to diseases. "This is a new scientific instrument that, like the microscope when it was invented in the seventeenth century, makes it possible to study aspects of biology that simply were not possible to examine before," explains Reich. In one example, scientists at the University of Copenhagen found DNA from plague in the steppe populations. If the groups that migrated to Britain after 4,500 years ago brought the disease with them, that could help explain why the existing population shrank so quickly.

With the possibility of many such discoveries still ahead, "it is a very exciting time," says Cunliffe. "Ancient DNA is going to revitalize archeology in a way that few of us could have guessed even ten years ago."

More information: *Iain Mathieson et al., "The genomic history of southeastern Europe." Nature. Published online February 21, 2018. DOI: 10.1038/nature25778*

Iñigo Olalde et al., "The Beaker phenomenon and the genomic transformation of northwest Europe." Nature. Published online February 21, 2018. DOI: 10.1038/nature25738

http://bit.ly/2EN14ka

Here's What Happens When You Leave Surgical Sponges in a Person's Body for Years

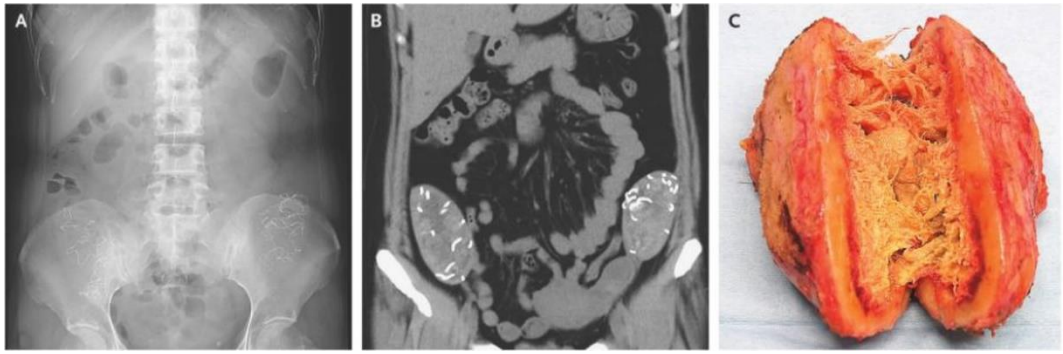
Abdominal bloating turned out to be caused by surgical sponges that were left in for years

By Rachael Rettner, Senior Writer

Sometimes, a bloated stomach is just gas or the result of something you ate. But for one woman in Japan, her abdominal bloating turned out to be caused by two surgical sponges that were left in her body years earlier, according to a new report of the case.

The 42-year-old woman told her doctors that she'd had symptoms of bloating in her lower abdomen for three years, the report said. Previously, she'd had two cesarean sections — one six years ago, and one nine years ago.

When doctors examined the women, they felt two masses near her right and left hip bones. She was sent for a CT scan of her abdomen, which revealed two masses filled with "hyperdense, stringy structures," according to the report, which was published today (Feb. 21) in The New England Journal of Medicine.



A woman in Japan had two surgical sponges left in her body. Images show an X-ray (left) and CT scan (middle) of the woman's abdomen; the sponges appear on either side of the abdominal cavity as masses with white, squiggly lines. On the right, an image of one of the sponges after it was removed and sliced open.
The New England Journal of Medicine ©2018.

To remove the masses, the woman needed to have surgery. During the operation, the doctors found the two masses in an area called the paracolic gutters, which are the spaces (on each side of the body) between the colon and the abdominal wall. After the masses were removed, the doctors cut them open, revealing gauze sponges that were encased in "thick, fibrous walls," the report said.

These sponges turned out to have been left behind after one of the woman's C-sections, but it's not clear whether the error occurred during the woman's first operation, which was nine years ago, or her second, which was six years ago, said lead case-report author Dr. Takeshi Kondo, of the Department of General Medicine at Chiba University Hospital in Japan, who treated the patient for her abdominal pain. Still, Kondo suspects that both sponges were left during a single operation, rather than one from each operation.

During a C-section, an obstetrician may put surgical sponges in the paracolic gutters to prevent the intestines from getting in the way during surgery, Kondo told Live Science.

Leaving a surgical instrument inside a patient's body is considered a "never event" in medicine — in other words, an event that should never happen — according to a 2013 review article on the topic.

These events are rare: The 2013 review found that the incidence of "retained foreign bodies" after surgery ranges from 1 in 5,500 operations to 1 in 18,760 operations.

But gynecological surgeries may come with a greater risk of these events, compared with other surgeries. A 2010 study found that girls under 18 who underwent gynecological surgeries, such as the removal of ovarian cysts, had four times the risk of coming out of surgery with a foreign object inside them as other children who'd had surgery.

This may be because areas of the pelvis are more difficult to reach and have more recesses to lose a sponge or small instrument, Dr. Fizan Abdullah, a pediatric surgeon now at the Ann & Robert H. Lurie Children's Hospital of Chicago, told Live Science in a 2010 interview.

Kondo said a surgical checklist, in which surgeons count and recount the objects placed in and removed from a patient's body, may help prevent these errors.

The woman recovered from her surgery, and her bloating symptoms completely went away, the report said. She went home from the hospital five days after her surgery.

http://bit.ly/2EZsZQX

Debunking claims about medical marijuana: More teen recreational use, fewer opioid deaths

In 1996, California became the first US state to legalise marijuana use for medical purposes. Medical marijuana is now legal in 29 states.

Opponents of medical marijuana argue that such laws increase recreational marijuana use among adolescents, while advocates contend that medical marijuana helps to address the US opioid crisis by reducing overdose deaths.

Two papers published today in the scientific journal Addiction look at the current evidence of the effects of medical marijuana laws and conclude that there is little support for either claim.

The first claim, that legalizing medical marijuana increases recreational use among adolescents, is addressed by a new meta-analysis that pooled

the results of eleven separate studies of data from four large-scale US surveys dating back as far as 1991.

Results of the meta-analysis indicate that no significant changes (increases or decreases) occurred in adolescent recreational use following enactment of medical marijuana laws. Far fewer studies examined the effects of medical marijuana laws among adults, although existing evidence suggests that adult recreational use may increase after medical marijuana laws are passed

Senior author Professor Deborah Hasin says, "Although we found no significant effect on adolescent marijuana use, we may find that the situation changes as commercialized markets for medical marijuana develop and expand, and as states legalize recreational marijuana use. However, for now, there appears to be no basis for the argument that legalising medical marijuana increases teens' use of the drug."

The second claim, that legalising medical marijuana reduces opioid overdose deaths by offering a less risky method of pain management, is addressed in an editorial co-authored by several members of Addiction's editorial board. Here, the evidence is clear but weak, being rooted in ecological studies whose results have not been confirmed through more rigorous methods.

Although those studies show a correlation over time between the passage of medical marijuana laws and opioid overdose death rates, they do not provide any evidence that the laws caused the reduction in deaths.

In fact, several recent studies have shown that chronic pain patients who use cannabis do not use lower doses of opioids. There are more plausible reasons for the reduction in opioid deaths that ought to be investigated.

Sarvet AL, Wall MM, Fink DS, Greene E, Le A, Boustead AE, Pacula RL, Keyes KM, Cerda M, Galea S, and Hasin DS (2018) Medical marijuana laws and adolescent marijuana use in the United States: A systematic review and meta-analysis. Addiction, doi: 10.1111/add.14136.

Hall W, West R, Marsden J, Humphreys K, Neale J, and Petry N (2018) It is premature to expand access to medicinal cannabis in hopes of solving the US opioid crisis. Addiction, doi: 10.1111/add.14139.

http://bit.ly/2EXH9lF

"Neanderthals and early modern humans were cognitively indistinguishable"

Spanish evidence shows Neanderthals were painting and decorating at least 20,000 years before humans arrived.

Andrew Masterson reports.

Paintings found in Spanish caves have been found to be at least 68,000 years old, meaning they were made 20,000 years before the entry of modern humans into Europe.

120,000 year-old painted and pierced shells, fashioned by Neanderthals – proof, say researchers, that our distant cousins developed symbolic thought well before modern humans arrived in Europe. **J. Zihao**

The artists, therefore, say a team led by Dirk Hoffmann from the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, were Neanderthals. The paintings – located in caves called La Pasiega, Maltravieso, and Ardales – are the subject of a paper published in the journal *Science*.

Hoffman is also lead author of a second study, published in the journal *Science Advances*, analysing a collection of 120,000-year-old painted and perforated seashells found in another Spanish location, called Cueva de los Aviones.

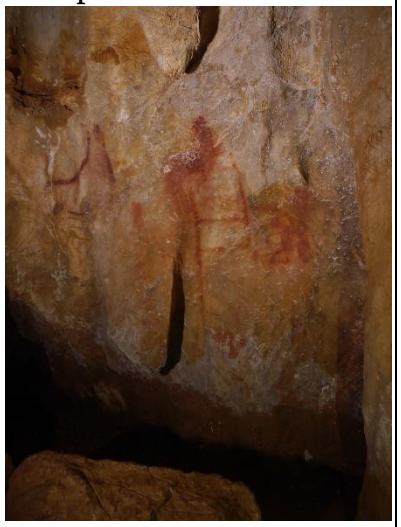
Dating evidence reveals that the artefacts, like the paintings, were fashioned many millennia before the arrival of *Homo sapiens*, meaning that they, too, were the work of Neanderthals.

Hoffman and colleagues note that similar finds in Africa, attributed to modern humans, have been uncontroversially accepted as proxies for symbolic behaviour.

With only a few contested exceptions, symbols – artefacts and paintings, for instance – have not previously been discovered in Europe dating to any earlier than about 45,000 years ago. Thus, it has been assumed that

symbolic thought and language were the exclusive province of humanity.

The caves of Spain, argue the researchers, give the lie to such cosy assumptions. Symbolic thought seems to have been present among our distant cousins, too. This, they suggest, makes it "possible that the roots of symbolic material culture may be found among the common ancestor of Neanderthals and modern humans, more than half-a-million years ago."



A symbolic painting done by Neanderthal hand in a Spanish cave 68,000 years ago. **CD Standish, AWG Pike and DL Hoffman**

The cave paintings comprise red and black depictions of animals, linear signs, ladder-like designs and hand stencils. To establish their age, Hoffman and his team used a method known as uranium-thorium dating, which establishes age based on the fixed decay rates between two radioactive isotopes: thorium-230 and uranium-234.

The team used carbonates recovered from directly underneath and directly on top of the paintings, thus uncovering the earliest and latest possible dates for when the pigment was laid down. Across all three locations, the most recent date revealed was approximately 68,000 years ago. Other paintings stretched as far back as another 25,000 years, showing that symbolic painting for the Neanderthals wasn't a short-term fad, but a long and established tradition.

The dating of the marine shells over at Cueva de los Aviones presented some problems, largely because they were embedded in a rock system that had been subject to subsidence many thousands of years ago.

Some of the shells had been uncovered in 1985, and largely left in place. A 2010 study led by João Zilhão of the University of Barcelona in Spain (a co-author of the current study), identified them as Neanderthal in origin, but dated them to only about 50,000 years ago.

By carefully teasing out the relationship between the sediment layers at the site, then applying thorium-uranium dating techniques, Hoffman's team came up with a much more reliable – and much earlier – date. The shells all dated to within a 5000-year period, between 115,000 and 200,000 years ago.

The date range is significant on more than one level. It clearly shows that the artefacts were made before the arrival of modern humans in the area. Also, however, it makes them older than the earliest human symbolic material found anywhere in the world.

Hoffman and colleagues note that the earliest South African artefacts so far discovered date to about 79,000 years ago. A shell bead found at Grotte des Pigeons, Morocco, is estimated to be 82,000 years old, and perforated shells found at Qafzeh Cave in Israel are thought to be 92,000 years old.

The Spanish find, say the researchers, "substantially predates … anything comparable known in Africa or western Asia to date".

This, combined with the painting evidence, they conclude, "leaves no doubt that Neanderthals shared symbolic thinking with early modern humans and that, as far as we can infer from material culture, Neanderthals and early modern humans were cognitively indistinguishable."

http://bit.ly/2ormQ5T

Younger age at diabetes diagnosis is linked to higher risk of death from heart disease

Yet lower risk of cancer death

While type 2 diabetes (T2D) was once considered a disease largely confined to older people, the global epidemic of obesity and overweight has seen diagnoses rocket in young adults, adolescents and even appear in young children. New research published in Diabetologia (the journal of the European Association for the Study of Diabetes [EASD]) shows that the earlier a person is diagnosed with T2D, the higher their risk of death from heart disease and stroke, but, unusually, the lower their risk of death from cancer.

In almost all countries of the world, diabetes rates are increasing substantially in younger adults, aged 20-45 years. Rates are also continuing to increase in adults over 45 years old, however not as sharply as in younger adults. The increase in the younger adults means there is a steadily growing pool of diabetes patients who are exposed to diabetes for a longer period in their lives.

The study by Professor Dianna Magliano and Professor Jonathan Shaw (Baker Heart and Diabetes Institute, Melbourne, Australia) and colleagues analysed the data of 743,709 Australians with T2D who were registered on Australia's National Diabetes Services Scheme (NDSS) over a 15-year period between 1997 and 2011. All-cause mortality and mortality due to cardiovascular disease (CVD), cancer and all other causes were identified.

The average (median) age at T2D diagnosis was 59 years, and a total of 115,363 deaths occurred during the study period. The authors say: "An earlier diagnosis of type 2 diabetes -- and thus a longer duration of disease -- was associated with a higher risk of all-cause mortality, primarily driven by cardiovascular disease (CVD) mortality."

The data showed that for two people of the same age, the one with a 10-year earlier diagnosis (equivalent to 10 years' longer duration of diabetes) had a 20% to 30% increased risk of all-cause mortality and about a 60% increased risk of CVD mortality. The effects were similar in men and women.

authors say: "Evidence is accumulating to suggest that earlier onset of type 2 diabetes is associated with an increased risk of complications and comorbidities compared with later onset, and that the development and progression of complications might be more aggressive in those with earlier onset."

They add: "As such, increased clinical attention is imperative for individuals with earlier-onset type 2 diabetes. Efforts should focus on timely optimisation of individuals' self-management skills and medical treatment to prevent or reduce the onset of complications and comorbidities. Additionally, there is a need to identify and screen those at high risk of developing diabetes so that individuals can make lifestyle changes that will prevent or delay the onset of diabetes."

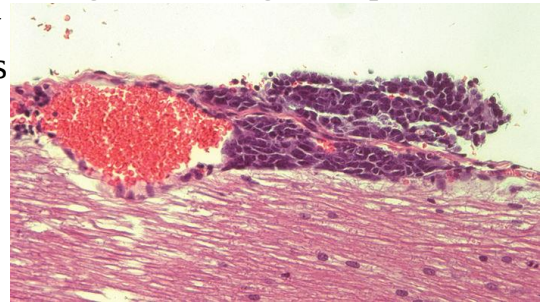
Other interesting findings from the study by Professors Magliano, Shaw and colleagues include that for mortality due to cancer (all cancers and colorectal and lung cancers), earlier diagnosis of type 2 diabetes was associated with lower mortality compared with diagnosis at an older age. While this may appear unusual, the authors point out that "it is possible that following a diagnosis of diabetes, people have more frequent contact with the healthcare system, which may increase the likelihood of any present but undiagnosed cancer being detected."

http://go.nature.com/2GEaFtQ

Deadly brain tumour in children spreads through surprising route

Dogma had it that the cancer cells travel through the brain fluid.

A deadly childhood brain cancer has long been thought to spread through fluid in the brain. But new findings show that the tumour cells can travel through the blood. Medulloblastoma, which forms at the base of the skull, is the most common type of malignant brain tumour in children.



A tumour (purple) on a mouse's spinal cord (pink) originated in the animals' brain and spread through the blood (red). **L. Gazia et al./Cell**

When it spreads, or metastasizes, it is nearly always to the leptomeninges — inner membranes that envelop the brain and spinal cord. Scientists had assumed that medulloblastoma cells migrate there through the cerebrospinal fluid, the clear liquid that bathes the leptomeninges and cushions the brain.

But Michael Taylor of the Hospital for Sick Children, in Toronto, Canada, and his colleagues found tumour-specific DNA in patients' bloodstreams. The team also found tumour cells circulating in the blood of three separate individuals. When the researchers grafted tumours into

mice on the animals' flanks, far from the cerebrospinal fluid, the mice developed metastases in the leptomeninges, confirming that the cancer can spread through the blood. *Cell* (2018)

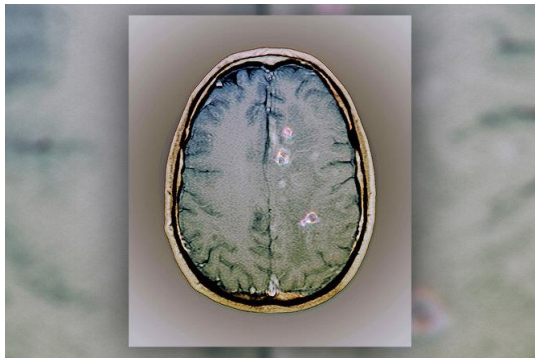
http://bit.ly/2BMqPcn

This Parasite Is a Surprising Cause of Seizures in the US

The idea of tapeworm larvae traveling to your brain and forming life-threatening cysts sounds horrifying.

By Rachael Rettner, Senior Writer | February 22, 2018 03:24pm ET

But for many people around the world — including a surprising number in the United States - this condition is a reality. Now, U.S. doctors are releasing new guidelines on how to identify and treat this condition, called neurocysticercosis, to help tackle the disease in this country.



A brain scan reveals several tapeworm cysts, which appear as bright spots.
Science Photo Library/Alamy

"Neurocysticercosis is an important problem in the United States, and the right diagnosis and treatment are critical," Dr. A. Clinton White, lead author of the guidelines and professor of infectious diseases at the University of Texas Medical Branch in Galveston, said in a statement.

The guidelines, which were developed by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH), were published today in the journal Clinical Infectious Diseases.

Neurocysticercosis occurs when a person ingests microscopic eggs from a pork tapeworm (*Taenia solium).* This can happen when a person eats infected pork that's undercooked, according to the Centers for Disease Control and Prevention. If the tapeworm's eggs hatch in a person's intestine, the larvae can travel throughout the individual's body, including to the brain, where they form cysts, resulting in neurocysticercosis.

Symptoms of the disease depend on the location of the brain cysts and can range from harmless to life-threatening, according to the IDSA. The most common symptoms are headaches and seizures; in fact, neurocysticercosis is one of the most common causes of seizures around the world, the IDSA said.

Other symptoms may include nausea, vomiting, dizziness and altered mental status. The condition may also lead to stroke, meningitis (swelling of the membranes that cover the brain and spinal cord) or blindness, according to the World Health Organization.

In the U.S., more than 2,000 people are hospitalized with neurocysticercosis each year, according to the IDSA. Most U.S. cases occur in people who have traveled to this country from developing nations in Latin America, Africa or Asia, where the tapeworm, called *Taenia solium*, is common, the IDSA said. There are about twice as many hospitalizations for neurocysticercosis in the U.S. each year than there are for malaria, according to a 2015 study.

If doctors suspect that a person has neurocysticercosis, the patient should have both a CT scan and an MRI — two types of brain scans — according to the new guidelines. And to confirm the diagnosis, the patient should have a special blood test called an enzyme-linked immunotransfer blot, or EITB.

Treatments include anti-epileptic medications for people experiencing seizures, as well as steroids and anti-parasitic drugs. In some cases, the brain cysts can block a ventricle, or a fluid-filled cavity in the brain, and this complication can be life-threatening. In these cases, the cysts need to be surgically removed, the guidelines said.

"Neurocysticercosis is a serious problem, but with optimal diagnosis and treatment, patients can be managed effectively," White said.

http://bit.ly/2CqN8Bj

Want to Boost Reproducibility? Get Another Lab Involved

Including as few as two labs in a study improved the odds of getting the true effect size by as much as 23 percent, according to a replication model.

By Jim Daley | February 22, 2018

According to a study published today (February 22) in *PLOS Biology*, the current design of some preclinical studies may be undermining their reproducibility. Including just a few additional laboratories in each preclinical trial could improve the replicability of study results, the authors find.

A clinical trial would never be designed that only drew one cohort of participants from a single tiny village, but preclinical trials are typically designed in precisely that manner, study coauthor Hanno Würbel, a zoologist at the University of Bern, tells *The Scientist*. "If you want generally valid conclusions that apply to a whole range of conditions or individuals in a population, then you need to address this heterogeneity," he says. "That leads to larger variation within your study cohort, but that is just an image of reality."

In 1999, a report in *Science* found individual laboratories had unique differences that could yield "idiosyncratic" results, even when study protocols and housing conditions for animal models were rigorously standardized. That prompted Würbel, who was then studying how different environments affect behavior and brain function in mice and rats, to begin investigating the effect of various lab conditions on study outcomes. "If you run a highly standardized study—all animals with the same genotype, all exposed to the same conditions—you may obtain a highly precise result," he says. "But it may only be valid under the specific conditions [of the study]." He concluded that perhaps by including multiple laboratories in a study, the problem could be mitigated.

To test this idea, Würbel and his colleagues simulated single- and multi-laboratory experiments with published results from preclinical studies. They included 440 preclinical studies across 13 animal models of stroke, myocardial infarction, and breast cancer.

To model several laboratories collaborating on a single study, the team combined data from multiple independent studies. They found that including just two to four laboratories in a study was enough to produce more-consistent results than single-laboratory studies, which had high variation between their findings. They first conducted a meta-analysis of 50 independent studies on the effect of hypothermia on stroke severity in rodents, and found that it reduces severity by 50 percent. They used this number as a benchmark, comparing it to single- and multi-lab simulations' predictions of the reduction in severity. Single-lab studies successfully predicted it 50 percent of the time. Adding a second lab to the simulation increased prediction success by 23 percent, and adding a third and fourth lab increased it by 33 and 37 percent, respectively.

"What [the study is] recommending makes sense, and would certainly improve the field," says oncologist Glenn Begley, the CEO of BioCurate, an Australian public-private biopharmaceutical partnership that was not involved in this study. "There is no doubt in my view that if the recommendations presented in this paper were adopted, we would be much better off." Begley coauthored a letter to *Nature* in 2012 that advocated, in part, for improving preclinical trials by "[raising] the bar for reproducibility."

Using multiple labs for preclinical research may not always be necessary to improve reproducibility, says Würbel—for example, when establishing a proof of concept. "[Researchers] may well run initial studies under highly standardized conditions," he says, but as soon as you want to generalize your findings, heterogeneity becomes important. "If your hypothesis doesn't stand the test of a heterogenized preclinical setting, then there is probably little hope that under clinical conditions it will work."

Tim Errington, metascience manager at the Center for Open Science's Reproducibility Project, says including multiple labs in preclinical studies could lead to a more efficient use of resources. "These types of suggestions are exactly the way we can move forward on that front," he says. But he adds that such progress requires changing the culture of how research is conducted. "People are slowly starting to move on this, and I think doing studies like this is a great way to allow us to see the benefits of moving the way that we conduct our research," he says. "I think that what I'd like to see now is more groups doing this and reporting [their findings]."

The researchers acknowledge that it may be logistically difficult to include multiple labs in every new preclinical study, and to address this they recommended varying experimental conditions within labs to mimic multi-laboratory studies. The problem, says Würbel, is that a method for doing so still needs to be developed. He is currently investigating how best to do so.

Würbel says that if a study cannot reproduce an observation, "then strictly speaking, you have no evidence for it. I think objectivity is always based on multiple independent observations."

http://bbc.in/2EWDZyN

Mutation 'gives bats edge over deadly viruses'

A single mutation in an immunity gene called Sting might be one reason why bats can resist the worst effects of harmful viruses such as Ebola.

By Jonathan Ball Science writer

Chinese scientists have shown that bat Sting triggers production of lower levels of interferon, the proteins that signal when the body is under attack. Too much interferon is associated with the serious symptoms seen in many virus infections. But bats, through their mutation, have evolved a means to dampen the response.

The researchers also think that the Sting gene has evolved to cope with the potentially harmful effects of flight. Their study is published in the Journal Cell Host and Microbe.

Bats carry lots of deadly viruses, like Nipah, Marburg, Sars and Ebola, without suffering from ill-effects. And Prof Peng Zhou, from the Wuhan Institute of Virology, was intrigued by this resilience. "We were interested why and how bats' immune systems could deal with so many deadly viruses," he told BBC News.

Usually when we think of immunity to viruses we tend to think about antibodies and a set of T cells called killer T cells. These recognise and destroy specific viruses that they have been trained to see, either through past infection or vaccination.

But an important arm of our immune system, and one that Prof Zhou and his colleagues focussed on, is able to fend off viral invaders without ever seeing them before – so called innate immunity.

Sensing danger

When a virus infects a cell it leaves a variety of tell-tale signs and these rogue virus molecules are detected by sensor proteins that switch on production of interferon.

The early symptoms that we associate with a virus infection – fever, aches and tiredness – are all caused by the effects of interferon.

When interferon is produced, it triggers creation of other molecules that have a direct antiviral effect.

We can think of innate immunity as a cascade of powerful virus killing effects. But too much interferon can be damaging and is thought to be one of the reasons why some viruses, like Ebola and Sars, cause really serious illness.

"At the start, we thought that the bat might have a super-strong innate immune system which meant that their interferon could kill all the virus, but later on after the bat genome and a number of other studies, we started to think that there might be something special, and that they were in balance with the virus," Prof Zhou explained.

He said that this previous work had hinted that whilst some parts of the anti-virus cascade were ramped up, others were dampened down.

One of the genes that might be diminished is called Sting.

Flight of fancy

Sting is an important defence against the invasion of DNA viruses and it does this by detecting DNA in the place where it should not normally be found – in the cytoplasm of the cell. Some studies have also suggested it can detect RNA too – an alternative genetic material often used by viruses.

An animal cell can be divided into two main compartments: the nucleus and the cytoplasm. Inside the sea of cytoplasm is a range of specialist factories including the power plants of the cell known as the mitochondria. In a healthy cell, DNA is locked away in the nucleus and mitochondria, but the scientist had a hunch that the exertion of flight would damage DNA, which might leak into the cytoplasm.

And Prof Zhou thought that this might help shape evolution of the bat Sting protein: "We believed that this free DNA as well as DNA viruses may shape the bat genome so that it shifts the Sting pathway in bats so that less interferon is produced, because too much interferon production is not good," he said.

Their initial experiments confirmed that switching on bat Sting resulted in lower levels of interferon than the human version. Then, by comparing Sting gene sequences between bats and other mammals, the Chinese team was able to identify a single difference in the protein's amino-acid building blocks. At a key location – called S358 - all the non-bat species had a serine amino acid, whilst the bats did not.

Further work

When Prof Zhou and his team mutated bat Sting to contain a serine at S358, interferon production increased. But, when they replaced the serine in the human protein to a different amino acid then lower amounts of interferon were produced. This was true if interferon production was switched on using chemicals or when the cells were infected with a DNA-containing virus called herpes simplex.

Commenting on the findings, Prof Victor DeFilippis from the Oregon Health and Science University, US, said "I'm not sure that you can draw broad conclusions that a dampened Sting-dependent interferon response is allowing bats to harbour a large array of viruses.

"For one thing, this pre-supposes that Sting-mediated anti-viral activity is detrimental to the host. But an opposite case could just as easily be made – that optimal Sting function is necessary to protect against pathogenic viruses. "Importantly, there are no 'smoking-gun' mechanistic studies that indicate Sting is a direct or indirect factor in increased viral occupation of bat species."

And Prof Alexander Bukreyev, who is based at the University of Texas Medical Branch, wondered if the findings would be relevant for viruses that have an RNA genome.

He told the BBC: "This is an important step toward understanding why bats harbour multiple viral pathogens. But some published studies demonstrate that treatment of bat cells with various stimuli or infection with viral pathogens such as Ebola and Marburg... do produce quite robust interferon response. This apparent discrepancy can be explained by multiple redundant pathways triggering the interferon response.

"Clearly, more studies are required to better understand the ability of bats to harbour viral pathogens."

And Prof Zhou agrees that more work is needed: "What we see may be an adaptation to flight or to allow the bats to carry more DNA or RNA viruses. In this study, we focussed on DNA sensing and whilst RNA sensing is likely to be dampened, we have to prove that in future studies."

http://bit.ly/2olL2HM

Japan confirms oil from wrecked tanker hitting its beaches

Oil that has washed ashore on several southern Japanese islands is likely from an Iranian tanker that sank in the East China Sea last month, Japan's coastguard said Friday.

Analysis of samples of heavy fuel that began washing up on remote Okinoerabu and Yoron islands this month found similar components to the fuel used by the Sanchi tanker, coastguard spokesman Takuya Matsumoto said. "We are not aware of any other maritime accident in the region that resulted in oil leaks," he told AFP. "So we have

concluded that it is highly likely that the oil that reached (the two islands) is connected with Sanchi," he said.

The sunken ship—carrying 111,000 tonnes of light crude oil—went down in a ball of flames on January 14 in Japan's economic waters in the East China Sea, sparking concerns it could lead to a massive environmental catastrophe.

Late January, greasy sludge began to wash up on remote Japanese islands, known for seafood and pristine shores that lure holidaymakers. The oil washing ashore differs from the light crude that was the ship's cargo and is likely to be the fuel that was powering the vessel.

At least 16 islands in the area saw oil reach their shores, and residents have collected a total of 90 tonnes of oil in their cleanup efforts, according to the local government.

Tokyo has launched detailed studies of the accident's impact on the regional environment, although coastguard officials believe the leaking light crude oil is gradually dissipating. Oil samples from other islands showed different characteristics, but the tanker could have used various kinds of heavy oil in different tanks and equipment, Matsumoto added. "We are continuing our analysis. We believe it is premature to reach any conclusion about the oil coming to other islands," he said. Reviews of water samples collected in the region have not shown elevated levels of contamination, the coastguard said.

The government has launched studies to analyse the accident's impact on the region's fisheries as well as ecosystems, including impacts on birds and coral reefs.

The Sanchi caught fire after colliding with a bulk freighter in early January, setting off a desperate rescue mission by authorities. The bodies of only three of its 32 crew have been found so far.

Environmental campaign group Greenpeace has urged authorities to boost clean up efforts and monitoring of regional waters.

The type of condensate oil carried by the Sanchi does not form a traditional surface slick when spilt, but is nonetheless highly toxic to marine life and much harder to separate from water.

http://go.nature.com/2BM0aFU

Researchers have finally created a tool to spot duplicated images across thousands of papers

Publishers would need to join forces to apply image-checking software across the literature.

Declan Butler

Computer software can now quickly detect duplicate images across large swathes of the research literature, three scientists say.

In a paper published on 22 February on the bioRxiv preprint server[1] , a team led by Daniel Acuna, a machine-learning researcher at Syracuse University in New York, report using an algorithm to crunch through hundreds of thousands of biomedical papers, searching for duplicate images. If journal editors adopted similar methods, they might be able to more easily screen images before publication — something that currently requires considerable effort and is done by only a few publications.

The work shows that it is possible to use technology to detect duplicates, says Acuna. He isn't making the algorithm public, but he has discussed it with Lauran Qualkenbush, director of the Office for Research Integrity at Northwestern University in Chicago, Illinois, and vice-president of the US Association of Research Integrity Officers. “It would be extremely helpful for a research-integrity office,” she says. “I am very hopeful my office will be a test site to figure out how to use Daniel’s tool this year.”

In early 2015, Acuna and two colleagues used an algorithm to extract more than 2.6 million images from the 760,000 articles then in the open-access subset of the PubMed database of biomedical literature, which is run by the US National Institutes of Health. These included micrographs of cells and tissues, and gel blots. The algorithm then zoomed in on the most feature-rich areas — where colour and greyscales vary most — to extract a characteristic digital ‘fingerprint’ of each image.

After eliminating features such as arrows or flow-chart components, the team ended up with around 2 million images. The researchers only compared images across papers from the same first and corresponding authors, to avoid the computational load of comparing every image against every other one. But the system could pick up potential duplicates even if they had been rotated, resized or had their contrast or colours changed.

The trio then manually examined a sample of around 3,750 of the flagged images to judge whether they thought the duplicates were suspicious or potentially fraudulent. On the basis of their results, they predict that 1.5% of the papers in the database would contain suspicious images, and that 0.6% of the papers would contain fraudulent images.

The researchers haven't been able to benchmark the accuracy of their algorithm, says Hany Farid, a computer scientist at Dartmouth College in Hanover, New Hampshire — because there isn't any database of known duplicate or non-duplicate scientific images against which they could test the tool. But he applauds the trio for applying existing techniques to real-world images and for working to put tools in the hands of journal editors.

Laborious process

At present, many journals check some images but relatively few have automated processes. For instance, *Nature* runs random spot checks on images in submitted manuscripts and also requires authors to submit unedited gel images for reference. It is currently reviewing its image-checking procedures. (*Nature*'s news team is editorially independent of its journal team.)

Some journals are following the lead of publications such as the *Journal of Cell Biology* and *The EMBO Journal* in manually screening most images in submitted manuscripts. But the process is time-consuming, and a routine, automated screen to streamline the process is long overdue, says Bernd Pulverer, chief editor of *The EMBO Journal*.

In order to spot image re-use across the literature, publishers would need to create a shared database of all published images against which articles submitted for publication could be compared, says IJsbrand Jan Aalbersberg, head of research integrity at the Dutch publishing giant Elsevier.

There is a precedent for such co-operation. In 2010, scholarly publishers worked together on an industry-wide service to tackle plagiarism. Crossref, a non-profit collaboration of around 10,000 commercial and learned society publishers, created CrossCheck, a service that collates full-text articles from its member publishers and makes use of the iThenticate plagiarism detection software made by Turnitin, a company in Oakland, California. The service, since renamed Similarity Check', has helped to make it routine practice in publishing to screen submitted manuscripts for plagiarism.

There are currently no plans for a publisher-wide system for image checking, but that is partly because the technologies are not yet mature, says Ed Pentz, executive director of Crossref. But Crossref watches developments in the area with interest, he says.

Elsevier says it would support an initiative such as Similarity Check for images. Two years ago, the company set up a 3-year, €1-million (US$1.2-million) partnership with Humboldt University in Berlin to research article mining and to identify research misconduct. On 25 January, the project announced that it intends to create a database of images from retracted publications. Such a data set would provide a bank of test images for researchers developing automated screening of images in publications.

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http://bit.ly/2opMybF

Short-term use of IV devices is common -- and risky -- study shows

Intravenous devices known as PICCs should be reserved for long-term use, but a new study shows 1 in 4 are used for 5 days or less

Many hospital patients get medicine or nutrition delivered straight into their bloodstream through a tiny device called a PICC. In just a decade,

it's become the go-to device for intravenous care. But a new study finds that one in every four times a PICC gets inserted, the patient didn't need it long enough to justify the risks that it can also pose.

In fact, in just the five days or less that they had a PICC implanted in their vein, nearly one in ten of these patients suffered a blocked line, an infection, a blood clot or another complication linked to the device.

One in three short-term PICC patients also had serious kidney problems that could make them potential dialysis candidates, the study also shows. They face special risks from the devices, which can harm blood vessels and jeopardize a patient's ability to receive dialysis later, if their kidneys fail.

The study, published in the February issue of the *Journal of Hospital Medicine*, is based on data from 52 hospitals around the state of Michigan taking part in a massive quality improvement and patient safety effort. It's a detailed analysis of records from 15,397 PICC placements over a two-year period from 2014 to 2016, just before and after guidelines for safe and appropriate PICC use made their debut.

The study is a large-scale examination of real-world use of PICCs, or peripherally inserted central catheters, and the factors associated with their short-term use.

It highlights the need for efforts to reduce short-term use of PICCs and help medical care teams understand current practice and consider other alternatives for short-term IV access that pose less risk.

"When PICCs first came out, they became an 'easy button' for vascular access, and the safety issues weren't recognized," says David Paje, M.D., M.P.H., the University of Michigan hospitalist who led the research team. "Now the dynamics have changed, and we need to be more thoughtful with their use."

Paje, an assistant professor of internal medicine, also helps lead the Medical Short Stay Unit at Michigan Medicine, U-M's academic medical center.

For the new study, he worked with senior author and Division of Hospital Medicine chief Vineet Chopra, M.D., M.Sc., and co-author Scott Flanders, M.D., who directs the Michigan Hospital Medicine Safety Consortium that provided the data for the study. Colleagues from several Michigan hospitals are co-authors.

Moving to MAGIC

Based on previous studies of PICC-associated risks, the team assembled an expert panel that developed a guideline for choosing IV devices appropriately, called MAGIC. They unveiled it in 2015, and turned into a mobile and web app in 2017.

Hospitals in the Michigan consortium, which is funded by Blue Cross Blue Shield of Michigan, began receiving training in MAGIC during the study period, but were still implementing it.

MAGIC guides clinicians to the appropriate option for the individual patient they're treating. For instance, instead of a PICC, it recommends that patients who will need intravenous access for less than five days should receive a different form of IV device, such as a midline or peripheral IV.

"This study helps illustrate how medical devices such as PICCs can be both helpful and harmful," says Chopra, who led the development of MAGIC and is a member of the U-M Institute for Healthcare Policy and Innovation. "Understanding how best to balance appropriate use - using tools like MAGIC - is the way to safe and better patient care."

Factoring into PICC use

As part of the study, Paje and his colleagues looked at which patients were more likely to receive a PICC for short-term use.

The strongest factor was difficult vascular access - a catch-all phrase that means it had been hard to start an IV in the patient in previous visits or earlier in the hospital stay.

Clinicians may default to choosing a PICC in these patients in order to keep an intravenous access point open, rather than having to find a vein each time, Paje says. Or, some experienced patients may even ask for a PICC to avoid so many "pokes."

Patients whose physicians ordered a multilumen IV device, to avoid contact between different medications or nutrition solutions, were also

more common among short-term PICCs. But Paje notes that few of the patients' records actually said that they were receiving multiple IV substances that had to be kept separate. And patients who had a short-term multilumen PICC were much more likely to suffer a complication. Interestingly, patients treated in teaching hospitals were more likely to receive a short-term PICC than those treated in non-teaching hospitals. This could actually be seen as an opportunity to address the issue of inappropriate short-term PICC, if hospitals make a plan to teach their residents about the risks and benefits of PICCs and other IV devices.

A recent paper by members of the consortium showed that at one hospital that implemented MAGIC, inappropriate PICC use decreased compared with hospitals that didn't implement it, and PICC-related complications also decreased modestly.

Paje notes that the body's own reaction to foreign material, and the mechanical stress put on veins when a PICC is inserted, can combine to damage veins and increase the risk of clots or scarring. The damage can keep a dialysis candidate from being able to successfully establish a vascular fistula, which would have been the preferred way to receive long-term dialysis.

In all, 9.6 percent of the short-term PICC patients experienced a complication, including 2.5 percent who experienced a blood clot forming in their vein that could have broken off and caused more serious consequences, and 0.4 percent developing a CLABSI, or central line associated blood stream infection.

"The use of PICCs exploded because the safety issues were not initially recognized, including those associated with clots and infections," says Paje. "Now we're coming back full circle, and we need to adapt and implement quality improvement processes to be more judicious with their use. We need to recognize that PICCs are not without any consequence, even for short-term use."

He notes that most of the reasons cited for PICC use in the patient records used in the study - such as delivering antibiotics -- do not require the deep access to the central bloodstream that PICC provides.

Even as clinicians get the word about the MAGIC guidelines and implement measures to right-size PICC uses, Paje calls on patients and family members to speak up and ask questions before a PICC gets placed. "Patients or their representatives should be actively engaged, and informed," he says. "Find out what lines they're putting in, and ask questions."

Reference: J. Hosp. Med 2018;2;76-82. doi:10.12788/jhm.2847
https://www.journalofhospitalmedicine.com/jhospmed/article/157107/hospital-medicine/patterns-and-predictors-short-term-peripherally-inserted

http://bit.ly/2BPuyyT

Ice chips only? Study questions restrictions on oral intake for women in labor

No increase in risks for women who are allowed to eat and drink during labor

At most US maternity units, women in labor are put on nil per os (NPO) status--they're not allowed to eat or drink anything, except ice chips. But new nursing research questions that policy, showing no increase in risks for women who are allowed to eat and drink during labor. The study appears in the March issue of the *American Journal of Nursing*, published by Wolters Kluwer.

"The findings of this study support relaxing the restrictions on oral intake in cases of uncomplicated labor," write Anne Shea-Lewis, BSN, RN, of St. Charles Hospital, Port Jefferson, N.Y., and colleagues. Adding to the findings of previous reports, these results suggest that allowing laboring women to eat and drink "ad lib" doesn't adversely affect maternal and neonatal outcomes.

No Increase in Complications with 'Ad lib' Oral Intake During Labor

The researchers analyzed the medical records of nearly 2,800 women in labor admitted to one hospital from 2008 through 2012. At the study hospital, one practice group of nurses and doctors had a policy of allowing laboring women to eat and drink ad lib (ad libitum, or "as they please"). Another four practice groups kept all patients NPO (nil per os, or "nothing by mouth").

Recommendations to restrict oral intake during labor reflect concerns over the risk of vomiting and aspiration (inhalation) in case general anesthesia and surgery are needed. However, with advances in epidural and spinal anesthesia, the use of general anesthesia during labor has become rare (and, if needed, much safer than before).

The study compared maternal and child outcomes in about 1,600 women who were kept NPO (except for ice chips) with 1,200 who were allowed to eat and drink ad lib during labor. The two groups were "sufficiently equivalent" for comparison. The women's average age was 31 years. Before delivery, a "preexisting medical condition" complicating pregnancy was identified in 14 percent of the NPO group compared with 20 percent of the ad lib group.

Even though the women in the NPO group started out with fewer medical problems, they had a significantly higher incidence of complications during labor and birth, compared with the ad lib group. The women in the NPO group were also significantly more likely to give birth via unplanned cesarean section.

Other outcomes--including requiring a higher level of care after delivery and the newborns' condition as measured by Apgar score--were not significantly different between groups. Analysis using a technique called propensity score matching, comparing groups of women with similar risk factors, yielded similar results.

The findings add to those of previous studies suggesting that restrictions on eating and drinking during labor could be safely relaxed in uncomplicated cases. "Yet in keeping with current guidelines, most obstetricians and anesthesiologists in the United States continue to recommend restrictions on oral intake for laboring women," Anne Shea-Lewis and colleagues write.

"Our findings support permitting women who are at low risk for an operative birth to self-regulate their intake of both solid food and liquids during labor," the researchers add. They note some limitations of their study, especially the fact that the women weren't randomly assigned to NPO or ad lib groups.

The authors hope their study will lead to reconsideration of current recommendations to keep women NPO during the "often long and grueling" process of labor and delivery. "Restricting oral intake to a laboring woman who is hungry or thirsty may intensify her stress," Anne Shea-Lewis and colleagues conclude. "Conversely, allowing her to eat and drink ad lib during labor can contribute to both her comfort and her sense of autonomy."

Click here to read "Original Research An Investigation into the Safety of Oral Intake During Labor." DOI: 10.1097/01.NAJ.0000530913.80349.53

http://bit.ly/2Fx3OU1

Wine Tied to Healthier Arteries for Some Diabetics

Some diabetics with plaque buildup in their arteries might have less debris in these blood vessels after adding wine to their diets, a recent study suggests.

For the study, researchers examined data on 224 people with type 2 diabetes who normally didn’t drink alcohol, but were randomly assigned to follow a Mediterranean diet and drink approximately one glass of red wine, white wine or water for daily. Among the subset of 174 people with ultrasound images of their arteries, 45 percent had detectable plaque at the start of the study.

Two years later, researchers didn’t see any significant increase in plaque for any of the participants with ultrasounds, regardless of whether they drank wine or water.

However, among the people who started out with the most plaque in their arteries, there was a small but statistically meaningful reduction in these deposits by the end of the study, researchers report in the European Journal of Clinical Nutrition.

“Among patients with well-controlled diabetes and a low risk for alcohol abuse, initiating moderate alcohol consumption in the context of a healthy diet is apparently safe and may modestly reduce cardiometabolic risk,” said lead study author Rachel Golan, a public health researcher at Ben-Gurion University of the Negev in Beer Sheva, Israel.

"Our study is not a call for all patients with type 2 diabetes to start drinking," Golan said by email.

Cardio-metabolic risk factors can increase the chances of having diabetes, heart disease or a stroke. In addition to plaque in the arteries, other risk factors include high blood pressure, elevated blood sugar, high cholesterol, smoking and having poor diet and exercise habits.

Previous research

Some previous research has linked drinking moderate amounts of wine or other alcohol to a lower risk of cardiovascular disease in otherwise healthy people as well as diabetics.

In the current study, all of the participants had the most common form of the disease, known as type 2 diabetes, which is linked to obesity and aging and occurs when the body can no longer produce or use the hormone insulin to convert sugars in the blood into energy.

Participants were part of a larger study looking at people with cardiovascular disease and diabetes.

They were typically in their late 50s or early 60s and most of them were overweight or obese. Roughly 65 to 70 percent of them took medications to lower cholesterol or other blood fats and the majority of them also took diabetes drugs to control blood sugar.

Mediterranean diet

Patients were told to follow a Mediterranean diet, which typically includes lots of fruits, vegetables, whole grains, legumes and olive oil. This diet also tends to favor lean sources of protein like chicken or fish over red meat, which contains more saturated fat. Participants were provided with wine or mineral water throughout the study period along with a 150-milliliter (5.07-ounce) glass to measure their daily dose of their assigned beverage, which was consumed with dinner.

Some previous research has linked a Mediterranean diet to weight loss and a reduced risk of heart disease and some cancers as well as better management of blood sugar in people with diabetes.

One limitation of the current study is the potential for the apparent beneficial effect of the wine to have been at least partially caused by the Mediterranean diet. Another drawback is that researchers only had ultrasound images of plaque buildup for a small proportion of patients, and the two-year follow up period might not be long enough to detect meaningful differences in plaque accumulation.

There is a risk

Alcohol may help, but it also isn't risk free, noted Dr. Gregory Marcus, a researcher at the University of California, San Francisco, who wasn't involved in the study. It can increase the risk of heart rhythm problems, which can cause stroke, Marcus said by email.

Even though alcohol might help reduce the risk of cardiovascular disease in some circumstances, there isn't enough evidence yet to suggest that people who avoid alcohol should start drinking, Marcus said.

"I would certainly recommend against starting to drink alcohol in the hopes of obtaining beneficial health effects among anyone that currently abstains," Marcus said. "And among those who drink, these sorts of positive results should never be used to consume more alcohol, particularly beyond drinking in moderation."

http://bit.ly/2F3VCN1

Switching from smoking to glo significantly reduces exposure to toxicants

Clinical study results reveal that when smokers switched completely from conventional cigarettes to glo, their exposure to certain harmful chemicals was significantly reduced

A clinical study conducted by scientists at British American Tobacco have revealed that when smokers switch completely from cigarettes to glo, their exposure to certain cigarette smoke toxicants is significantly reduced, in some cases to levels comparable to those seen in smokers who quit smoking completely.

These results add to evidence suggesting that glo may have the potential to be substantially reduced risk compared to smoking conventional cigarettes. glo is a tobacco heating product (THP) designed to heat rather than burn tobacco. This means it does not produce smoke and

certain toxicants associated with tobacco combustion are substantially reduced. Previous studies revealed toxicant levels in the heated tobacco vapour from glo to be around 90-95% less than in cigarette smoke.

'Products like glo are very new and consumers and regulators alike understandably want as much information as possible about them. Understanding how vapour from glo compares to cigarette smoke is, therefore, a core component of our scientific research,' said Dr James Murphy, Head of Reduced Risk Substantiation at British American Tobacco. 'Clinical studies, which are studies involving real people, are an extremely important component of that,' he said.

Because glo vapour has lower levels of toxicants than cigarette smoke, it should in principle expose consumers to much less toxicants. The results of this study indicate that this is indeed the case. The results are presented today at the annual conference of the Society for Nicotine and Tobacco Research in Baltimore, Maryland, USA.

Clinical Study

This clinical study was conducted in Japan because THPs like glo are popular there. One hundred and eighty people participated in the study, which was conducted over a period of eight days in a clinic. They were all smokers for at least three years prior to enrolment.

For the first two days, study participants continued to smoke as normal and their urine was collected to measure levels of chemicals. Blood and breath were also collected for analysis.

For the next five days, participants were randomly allocated to either continue smoking, switch to using a THP or quit smoking. Urine, blood and breath samples were again collected for analysis.

Exposure to certain smoke toxicants was determined by measuring the levels of certain chemicals in the urine. These could be the toxicants themselves or their metabolites - which is what the body breaks it down into - called biomarkers of exposure. Toxicants measured included those identified by the World Health Organisation as being of concern in cigarette smoke.

The results show that the concentration of certain chemicals in the urine was reduced in smokers who switched to glo. In some cases, these reductions were the same as those in smokers who quit (Figure 1). This suggests that smokers who switched to glo were exposed to less toxicants - in some cases, their exposure was the same as smokers who quit altogether.

'These results are very encouraging,' explains Murphy. 'The next step will be to determine whether this reduction in exposure translates to a reduced biological effect, and in turn a reduction in adverse health effects for those smokers who switch completely to glo,' he said.

Future clinical studies will test for markers of biological effect, like cholesterol levels or heart rate (i.e. measurements that give an indication of general health). A reduction in biomarkers of biological effect could suggest that a reduction in exposure is having a positive impact on reducing the adverse health risks of smokers who switch completely.

'The results of one test are important,' said Murphy, 'but it is the combination of the results of many different tests that start to give us a real feel for the bigger picture and the potential for glo to be reduced risk compared to a conventional cigarette.'

British American Tobacco's Commitment to NGPs

British American Tobacco has invested more than US$2.5 billion over the last six years in developing and commercialising a world-leading portfolio of products in the Next Generation Products (NGPs) category. British American Tobacco currently has NGPs in 17 markets with plans to be double the amount of markets we're in by the end of 2018. BAT has a bold ambition to realise revenue of more than £5bn from NGPs by 2022.

https://usat.ly/2outzvT

Vaping? You could be inhaling lead and arsenic, a new study says

A new study found toxic levels of metals, including lead, in e-cigarette vapors.

Potentially unsafe levels of toxic chemicals were found in e-cigarette vapers, according to a recently released study. Researchers at Johns Hopkins Bloomberg School of Public Health tested e-liquids in vapers'

refilling dispensers from 56 Baltimore-area daily e-cigarette users for a study published Wednesday in the peer-reviewed journal *Environmental Health Perspectives*.

After testing for the presence of 15 metals, researchers found significant levels of highly toxic arsenic in 10 of the samples. Significant levels (nearing or exceeding current health-based limits) of chromium, manganese, nickel and lead were found in about half of the samples. Aerosol metal concentrations were also highest for e-cigarettes with more frequently changed coils, study authors found.

"It's important for the FDA, the e-cigarette companies and vapers themselves to know that these heating coils, as currently made, seem to be leaking toxic metals — which then get into the aerosols that vapers inhale," said study senior author Ana María Rule, assistant scientist in the Bloomberg School's Department of Environmental Health and Engineering.

The Food and Drug Administration has the authority to regulate e-cigarettes and e-liquids. The Johns Hopkins team is planning future studies on vaping and metal exposures. More research must be done to determine possible health affects.

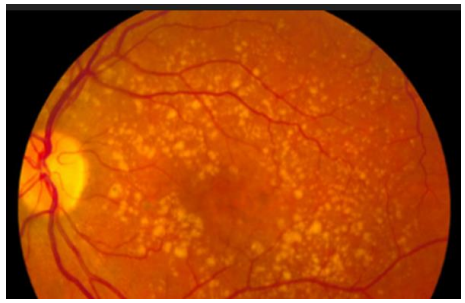
http://bit.ly/2oq377r

AI trained to spot heart disease risks using retina scan

The blood vessels in the eye reflect the state of the whole circulatory system.

John Timmer - 2/25/2018, 1:00 AM

The idea behind using a neural network for image recognition is that you don't have to tell it what to look for in an image. You don't even need to care about what it looks for. With enough training, the neural network should be able to pick out details that allow it to make accurate identifications.



The yellow spots in this image are sites of retinal degeneration. NIH

For things like figuring out whether there's a cat in an image, neural networks don't provide much, if any, advantages over the actual neurons in our visual system. But where they can potentially shine are cases where we don't know what to look for. There are cases where images may provide subtle information that a human doesn't understand how to read, but a neural network could pick up on with the appropriate training.

Now, researchers have done just that, getting a deep-learning algorithm to identify risks of heart disease using an image of a patient's retina.

The idea isn't quite as nuts as it might sound. The retina has a rich collection of blood vessels, and it's possible to detect issues in those that also effect the circulatory system as a whole; things like high levels of cholesterol or elevated blood pressure leave a mark on the eye. So, a research team consisting of people at Google and Verily Life Sciences decided to see just how well a deep-learning network could do at figuring those out from retinal images.

To train the network, they used a total of nearly 300,000 patient images tagged with information relevant to heart disease like age, smoking status, blood pressure, and BMI. Once trained, the system was set loose on another 13,000 images to see how it did.

Simply by looking at the retinal images, the algorithm was typically able to get within 3.5 years of a patient's actual age. It also did well at estimating the patient's blood pressure and body mass index. Given those successes, the team then trained a similar network to use the images to estimate the risk of a major cardiac problem within the next five years. It ended up having similar performance to a calculation that used many of the factors mentioned above to estimate cardiac risk—but the algorithm did it all from an image, rather than some tests and a detailed questionnaire.

The neat thing about this work is that the algorithm was set up so it could report back what it was focusing on in order to make its diagnoses. For things like age, smoking status, and blood pressure, the software focused on features of the blood vessels. Training it to predict gender

ended up causing it to focus on specific features scattered throughout the eye, while body mass index ended up without any obvious focus, suggesting there are signals of BMI spread throughout the retina.

The researchers say that even a 300,000-image training set is small for a deep-learning algorithm, so they think they could do better if given more data to work with. And the improvement is needed, as they note that performance similar to the diagnostic calculation isn't all that great, since the calculation has a large uncertainty. With some improvement, the algorithm could be a useful diagnostic tool, since retinal images are often taken to screen for eye problems associated with diabetes—which, in turn, is often associated with cardiac disease.

Nature Biomedical Engineering, *2018. DOI: 10.1038/s41551-018-0195-0 (About DOIs).*

http://nyti.ms/2ETC8Ye

Why Your Pharmacist Can't Tell You That $20 Prescription Could Cost Only $8

"Gag clauses" prohibit pharmacists from telling customers they could save money by paying cash for prescription drugs rather than using their health insurance

By ROBERT PEAR FEB. 24, 2018

WASHINGTON — As consumers face rapidly rising drug costs, states across the country are moving to block "gag clauses" that prohibit pharmacists from telling customers that they could save money by paying cash for prescription drugs rather than using their health insurance.

Many pharmacists have expressed frustration about such provisions in their contracts with the powerful companies that manage drug benefits for insurers and employers. The clauses force the pharmacists to remain silent as, for example, a consumer pays $125 under her insurance plan for an influenza drug that would have cost $100 if purchased with cash. Much of the difference often goes to the drug benefit managers.

Federal and state officials say they share the pharmacists' concerns, and they have started taking action. At least five states have adopted laws to make sure pharmacists can inform patients about less costly ways to obtain their medicines, and at least a dozen others are considering legislation to prohibit gag clauses, according to the National Conference of State Legislatures.

Senator Susan Collins, Republican of Maine, said that after meeting recently with a group of pharmacists in her state, she was "outraged" to learn about the gag orders.

"I can't tell you how frustrated these pharmacists were that they were unable to give that information to their customers, who they knew were struggling to pay a high co-pay," Ms. Collins said.

Alex M. Azar II, the new secretary of health and human services, who was a top executive at the drugmaker Eli Lilly for nearly 10 years, echoed that concern. "That shouldn't be happening," he said.

Pharmacy benefit managers say they hold down costs for consumers by negotiating prices with drug manufacturers and retail drugstores, but their practices have come under intense scrutiny.

The White House Council of Economic Advisers said in a report this month that large pharmacy benefit managers "exercise undue market power" and generate "outsized profits for themselves."

Steven F. Moore, whose family owns Condo Pharmacy in Plattsburgh, N.Y., said the restrictions on pharmacists' ability to discuss prices with patients were "incredibly frustrating."

Mr. Moore offered this example of how the pricing works: A consumer filling a prescription for a drug to treat diabetes or high blood pressure may owe $20 if he uses insurance coverage. By contrast, a consumer paying cash might have to pay $8 to $15.

Mark Merritt, the president and chief executive of the Pharmaceutical Care Management Association, which represents benefit managers, said he agreed that consumers should pay the lower amount.

As for the use of gag clauses, he said: "It's not condoned by the industry. We don't defend it. It has occurred on rare occasions, but it's an outlier practice that we oppose."

However, Thomas E. Menighan, the chief executive of the American Pharmacists Association, said that such clauses were "not an outlier," but instead a relatively common practice. Under many contracts, he said,

"the pharmacist cannot volunteer the fact that a medicine is less expensive if you pay the cash price and we don't run it through your health plan."

A bipartisan measure that took effect in Connecticut this year prohibits the gag clauses. It was introduced by the top Democrat in the Connecticut Senate, Martin M. Looney, and the top Republican, Len Fasano.

"This is information that consumers should have," Mr. Looney said in an interview, "but that they were denied under the somewhat arbitrary and capricious contracts that pharmacists were required to abide by."

Mr. Fasano said that consumers were sometimes paying three or four times as much when they used their insurance as they would have paid without it. "That's price gouging," he said in an interview.

The legislation, Mr. Fasano said, encountered "a lot of resistance" from large pharmacy benefit managers and some insurance companies.

In North Carolina, a new law says that pharmacists "shall have the right" to provide insured customers with information about their insurance co-payments and less costly alternatives.

A new Georgia law says that a pharmacist may not be penalized for disclosing such information to a customer. Maine has adopted a similar law.

In North Dakota, a new law explicitly bans gag orders. It says that a pharmacy or pharmacist may provide information that "may include the cost and clinical efficacy of a more affordable alternative drug if one is available."

The North Dakota law also says that a pharmacy benefit manager or insurer may not charge a co-payment that exceeds the actual cost of a medication.

The lobby for drug benefit companies, the Pharmaceutical Care Management Association, has filed suit in federal court to block the North Dakota law, saying it imposes "onerous new restrictions on pharmacy benefit managers."

Specifically, it says, the North Dakota law could require the disclosure of "proprietary trade secrets," including information about how drug prices are set. "P.B.M.–pharmacy contracts typically preclude a pharmacy from disclosing to the patient the amount of a reimbursement," the lawsuit says.

Gov. Asa Hutchinson of Arkansas, a Republican, said this past week that he would call a special session of the State Legislature to authorize the regulation of pharmacy benefit managers by the state's Insurance Department.

He said he feared that some independent pharmacists receiving "inadequate reimbursement" from the benefit managers might go out of business, reducing patients' access to care, especially in rural areas.

http://bit.ly/2CqVrgq

One-dose flu drug Xofluza gets nod from health ministry

Osaka-based drugmaker Shionogi & Co. has announced that the health ministry gave it approval to manufacture and market its new flu drug Xofluza, which requires only a single dose regardless of age.

by Tomoko Otake

The drug, which has been approved in tablet form for use against the type A and B influenza viruses, "is highly convenient as it only requires just one dose. It is expected to . . . raise the quality of life for flu patients," Shionogi said in a statement released Friday. Xofluza will go on sale as soon as its price is decided by the government, the company said.

Xofluza works by inhibiting an enzyme that flu viruses need to replicate. Tamiflu, a popular flu drug also known by the name of its main ingredient, oseltamivir, usually needs to be taken twice a day for five consecutive days.

Shionogi sought government approval for Xofluza in October. The drug was approved in just four months by the Health, Labor and Welfare Ministry, which introduced the so-called sakigake (fast-track) drug review system in 2015 to allow medicine with high potential to be launched in Japan before other countries.

The new medicine will give doctors more options to fight a disease that kills as many as 650,000 people worldwide annually.

The flu season is currently in full swing in Japan. According to the latest statistics from the ministry, the number of people who visited hospitals and clinics in the week through Feb. 18 was estimated at 1.67 million, which is still high despite leveling off from the weekly peak of 2.83 million logged in mid-January.