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Experimental vaccine may reduce post-stroke blood clot risk

Hypertension journal report

DALLAS - A vaccine may one day be able to replace oral blood thinners to reduce the risk of secondary strokes caused by blood clots, without increasing the risk of serious bleeding or triggering an autoimmune response, according to new research in the American Heart Association's journal *Hypertension*.

People who have had a stroke caused by a blood clot (ischemic strokes) often need to take medications that make their blood less likely to clot, which helps prevent another stroke.

Japanese researchers successfully tested an experimental vaccine in mice and found that it provided protection against blood clots for more than two months without increasing the risk of bleeding or causing an autoimmune response. The lack of an autoimmune response is important, because it means the mice's immune system did not perceive the vaccine as an "intruder" that needed to be attacked, which would have caused a reaction to the vaccine.

The vaccine, S100A9, inhibits blood clot formation and, during the study, protected the arteries of treated mice from forming new clots for more than two months, and additionally, worked as well as the oral blood thinner clopidogrel in a major artery, according to Hironori Nakagami, M.D., Ph.D., study co-author and professor at Osaka University, in Japan.

Developing a vaccine to replace and/or compliment daily, oral medications might save many lives and help prevent both secondary strokes and possibly heart attacks, according to Nakagami.

"Many stroke patients don't take their blood thinning drugs as prescribed, which makes it more likely they will have another stroke. This vaccine might one day help solve this issue since it would only need to be injected periodically," Nakagami said.

"We are continuing our research in hopes of being able to start clinical trials between five and ten years from now, but there are differences between mice and humans in how the vaccine will be recognized by the immune system," he said. "We should be able to overcome such problems and believe this vaccine provides a very promising strategy in secondary prevention of stroke."

Co-authors are Tomohiro Kawano, M.D.; Munehisa Shimamura, M.D., Ph.D.; Tatsuya Iso, M.D., Ph.D.; Hiroshi Koriyama, M.D., Ph.D.; Shuko Takeda; Tsutomu Sasaki, M.D., Ph.D.; Manabu Sakaguchi, M.D., Ph.D.; Ryuichi Morishita, M.D., Ph.D.; and Hideki Mochizuki, M.D., Ph.D. Author disclosures are on the manuscript.

The Mochida Memorial Foundation for Medical and Pharmaceutical Research, the Japan Cardiovascular Research Foundation, and the Japan Agency for Medical Research and Development funded the study.

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Obese mice lose a third of their fat using a natural protein

Protein investigated for possible role in cancer turned out to be powerful regulator of metabolism

WASHINGTON -- To the great surprise of cancer researchers, a protein they investigated for its possible role in cancer turned out to be a powerful regulator of metabolism. The Georgetown University-led study found that forced expression of this protein in a laboratory strain of obese mice showed a remarkable reduction of their fat mass despite a genetic predisposition to eat all the time.

The study, published in *Scientific Reports*, suggests that the protein FGFBP3 (BP3 for short) might offer novel therapy to reverse disorders associated with metabolic syndrome, such as type 2 diabetes and fatty liver disease.

Because BP3 is a natural protein and not an artificial drug, clinical trials of recombinant human BP3 could begin after a final round of preclinical studies, investigators say.

"We found that eight BP3 treatments over 18 days was enough to reduce the fat in obese mice by over a third," says the study's senior

investigator, Anton Wellstein, MD, PhD, a professor of oncology and pharmacology at Georgetown Lombardi Comprehensive Cancer Center.

The treatments also reduced a number of obesity-related disorders in the mice, such as hyperglycemia -- excess blood sugar that is often linked to diabetes -- and eliminated the fat in their once fatty livers. Clinical as well as microscopic examination of the mice showed no side effects, researchers say.

Obesity, which affects more than 650 million people worldwide, is the major driver for metabolic syndromes, which includes disorders such as insulin resistance, glucose intolerance, hypertension and elevated lipids in the blood.

BP3 belongs to the family of fibroblast growth factor (FGF) binding proteins (BP). FGFs are found in organisms ranging from worms to humans and are involved in a wide range of biological processes, such as regulating cell growth, wound healing and response to injury. Some FGFs act like hormones.

BP1, 2, and 3 are "chaperone" proteins that latch on to FGF proteins and enhance their activities in the body. Wellstein has long researched the BP1 gene because its production is elevated in a range of cancers, suggesting that growth of some cancers is linked to the excess delivery of FGFs. Only recently has Wellstein turned his attention, and that of his lab and colleagues, to BP3 to understand its role.

The researchers found that this chaperone binds to three FGF proteins (19, 21, and 23) that are involved in the control of metabolism. FGF19 and FGF 21 signaling regulates the storage and use of carbohydrates (sugars) and lipids (fats). FGF23 controls phosphate metabolism.

"We found that BP3 exerts a striking contribution to metabolic control," Wellstein says. "When you have more BP3 chaperone available, FGF19 and FGF21 effect is increased through the increase of their signaling. That makes BP3 a strong driver of carbohydrate and lipid metabolism. It's like having a lot more taxis available in New York City to pick up all the people who need a ride."

"With metabolism revved up, sugar in the blood, and fat processed in the liver are used for energy and is not stored," Wellstein says. "And warehouses of fat are tapped as well. For example, the job of FGF21 is to control break down of fat, whether it is stored or just eaten."

While the study results are exciting, additional research is required before BP3 protein can be investigated as a human therapy for metabolic syndromes, he says.

Contributing investigators include Elena Tassi, PhD, and Khalid A. Garman, MD, PhD, from Georgetown Lombardi, both co-lead authors; Marcel O. Schmidt, PhD, Xiating Ma, medical student Khaled W. Kabbara, Aykut Uren, MD, York Tomita, PhD, and Anna T. Riegel, PhD, from Georgetown Lombardi; Christopher S. Wilcox, MD, PhD, from Georgetown University School of Medicine; Mattias Carlstrom, PharmD, PhD, from the Karolinska Institute in Stockholm and Regina Goetz, PhD, and Moosa Mohammadi, PhD, from New York University School of Medicine.

Wellstein is named as an inventor on a patent application that has been filed by Georgetown University related to the technology described in this manuscript.

This research was supported by Georgetown University institutional funds, NIH grants (P01 HL068686, R01 CA71508, and P30 CA51008) and by the Swedish Research Council (2016-01381).

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Cancer's most deadly assassin exists in every cell

Scientists discover new kill code embedded in each cell to extinguish cancer

- ***Kill code is triggered by chemotherapy***
- ***Potential to trigger kill code without using chemotherapy, avoiding side effects***
- ***'I want to utilize a mechanism that nature developed,' lead author said***
- ***Cancer can't become resistant to kill code mechanism***

CHICAGO --- A kill code is embedded in every cell in the body whose function may be to cause the self-destruction of cells that become cancerous, reports a new Northwestern Medicine study. As soon as

the cell's inner bodyguards sense it is mutating into cancer, they punch in the kill code to extinguish the mutating cell.

The code is embedded in large protein-coding ribonucleic acids (RNAs) and in small RNAs, called microRNAs, which scientists estimate evolved more than 800 million years ago in part to protect the body from cancer. The toxic small RNA molecules also are triggered by chemotherapy, Northwestern scientists report.

Cancer can't adapt or become resistant to the toxic RNAs, making it a potentially bulletproof treatment if the kill code can be synthetically duplicated. The inability of cancer cells to develop resistance to the molecules is a first, the scientists said.

"Now that we know the kill code, we can trigger the mechanism without having to use chemotherapy and without messing with the genome. We can use these small RNAs directly, introduce them into cells and trigger the kill switch," said lead author Marcus E. Peter, the Tomas D. Spies Professor of Cancer Metabolism at Northwestern University Feinberg School of Medicine.

Chemotherapy has numerous side effects, some of which cause secondary cancers, because it attacks and alters the genome, Peter said.

"We found weapons that are downstream of chemotherapy," noted Peter, also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The paper describing the kill code and identifying how the cancer-fighting microRNAs use the code to kill tumor cells will be published Oct. 29 in *Nature Communications*. The paper describing that protein-coding large RNAs can be converted into toxic small RNAs was published Oct. 16 in eLife.

"My goal was not to come up with a new artificial toxic substance," Peter said. "I wanted to follow nature's lead. I want to utilize a mechanism that nature developed."

In published research in 2017, Peter showed cancer cells die when he introduced certain small RNA molecules. He also discovered cancer cells treated with the RNA molecules never become resistant because the molecules simultaneously eliminate multiple genes cancer cells need for survival.

At the time, Peter said, "It's like committing suicide by stabbing yourself, shooting yourself and jumping off a building all at the same time. You cannot survive."

But he didn't know what mechanism caused the cells to self-destruct. What he knew was a sequence of just six nucleotides (6mers) present in small RNAs made them toxic to cancer cells. Nucleotides are organic molecules that are the building blocks of DNA and RNA. They are G, C, A or T (in DNA), or U (in RNA).

In the first of the new studies, Peter then tested all 4,096 different combinations of nucleotide bases in the 6mers until he found the most toxic combination, which happens to be G-rich, and discovered microRNAs expressed in the body to fight cancer use this 6mer to kill cancer cells.

In the second new study, Peter showed the cells chop a gene (Fas ligand) involved in cancer cell growth into small pieces that then act like microRNAs and are highly toxic to cancer. Peter's group found about three percent of all protein-coding large RNAs in the genome can be processed in this way.

"Based on what we have learned in these two studies, we can now design artificial microRNAs that are much more powerful in killing cancer cells than even the ones developed by nature," Peter said.

The next step? "We absolutely need to turn this into a novel form of therapy," Peter said. He is exploring multiple ways to trigger the embedded kill code to kill cancer cells, but stressed a potential therapy is many years off.

Other Northwestern authors are Quan Q. Gao, William E. Putzbach and Andrea E. Murmann.

http://bit.ly/2zmkfQk

Secrets of mighty cancer killing virus unlocked by Otago researchers

University of Otago researchers have used high-resolution electron microscopy images to reveal how an anti-cancer virus interacts with tumor cells, increasing its potential to save lives.

Seneca Valley Virus (SVV), a newly discovered virus which infects cancer cells but not normal tissue, has become a main research project in the New Zealand laboratory of Dr Mihnea Bostina, Academic Director of Otago's OMNI Electron Microscopy unit and senior lecturer in the Department of Microbiology and Immunology.

He hopes the results from this latest study, published in *Proceedings of the National Academy of Sciences*, will help to develop the virus for clinical use.

Working with researchers from Japan's Okinawa Institute of Science and Technology, the group used cryo-electron microscopy to capture thousands of images of the virus bound to its receptor, using them to reconstruct a high resolution structure of the complex.

The structure demonstrates how SVV discriminates between its preferred receptor (cancer cells) and other similar proteins (healthy tissue). "We can see exactly how the virus breaks into the cancer cells, while leaving other cells untouched," Dr Bostina says.

The virus is a strong contender for effective virotherapy because it selectively targets a receptor found only in tumor cells in more than 60 per cent of human cancers.

The receptor, a protein called ANTXR1, is expressed on tumors, but it has a cousin, ANTXR2, that only appears on healthy tissues. SVV doesn't bind with the similar receptor on healthy cells - it only shows strong affinity for ANTXR1.

SVV has already demonstrated its cancer-fighting abilities in clinical trials, but there is one problem - the body builds up immunity to the virus within a couple of weeks.

"This structure teaches us which part of the virus is essential for binding to the receptor and which is not. If we want to make the virus more efficient at invading cancer cells, we can leave intact the part that interacts with the cancer cells and modify the rest so the virus can escape the attack of the immune system," Dr Bostina says.

Lead author and Otago PhD candidate Nadishka Jayawardena says he has "always been intrigued" by how naturally occurring micro-organisms can be used for human benefit.

"Being able to work on a virus that can kill cancers is very rewarding, especially knowing that one day our findings could potentially lead to tackling a major global health issue," he says.

Dr Bostina believes this study showcases the high quality of work being done at OMNI and hopes it will encourage the future funding of more challenging structural projects.

Publication details:
Structural basis for Anthrax Toxin Receptor 1 recognition by Seneca Valley Virus
Nadishka Jayawardena, Laura Burga, Richard Easingwood, Yoshimasa Takizawa, Matthias Wolf, and Mihnea Bostina.
Proceedings of the National Academy of Sciences
http://www.pnas.org/cgi/doi/10.1073/pnas.1810664115

http://bit.ly/2EXN1fT

An end to arachnophobia 'just a heartbeat away'

Treatment of fears like arachnophobia could be reliant on the beat of a heart.

Researchers have discovered that exposing people with phobias to their fear - for examples, spiders for those who have arachnophobia - at the exact time their heart beats, led to the phobia reducing in severity.

Hugo Critchley, Chair of Psychiatry at Brighton and Sussex Medical School (BSMS) and principle investigator, said: "Many of us have phobias of one kind or another - it could be spiders, or clowns or even types of food. Treatment usually involves exposing the person to their fear, but this can take a long time. Our work shows that how we

respond to our fears can depend on whether we see them at the time our heart beats, or between heartbeats. You could say we're within a heartbeat of helping people beat their phobias."

In phobias, disproportionately intense, disabling anxiety is induced by specific situations or triggers.

Treatment is often prolonged and involves a graded exposure to fear-evoking stimuli, but has made some progress in recent years through the use of computerised therapy.

This new research shows that phobias can be treated more effectively by linking computerised therapy to the patients' own heart rhythms.

Researchers at BSMS had previously revealed how bodily arousal signals that occur with each individual heartbeat can change the emotional impact of potential threats, for example, when experienced during a heartbeat they can appear greater. In this proof-of-concept clinical trial, a computerised exposure therapy for spider phobia was combined with online measurements of heartbeats.

For one group of patients, pictures of spiders were presented in-time with heartbeats (during the signalling of cardiac arousal), while for another patient group, pictures of spiders were presented in-between heartbeats. A third control group saw spiders randomly in the therapy sessions.

Although there was some improvement among all patients, as you would expect in exposure therapy, those individuals exposed to spiders in-time with their own heartbeats showed a greater reductions in self-reported fear of spiders, anxiety levels and their physiological responses to spiders.

These improvements were also shown to depend on differences in how well an individual patient can accurately feel their own heart beating in their chest, suggesting a further way of tailoring the treatment to benefit each patient.

http://bit.ly/2yMkhBe

Suicide more prevalent than homicide in US, but most Americans don't know it

In the United States, suicide is twice as common as homicide -- and more often involves firearms -- but public perception is just the opposite.

News reports, movies and TV shows may contribute to the perception of a high risk of firearm homicide, authors of a new study say, leaving a substantial gap between ideas and reality and potentially leading to further danger.

Now, first-of-its kind research, led by the University of Washington, Northeastern University and Harvard University, delves into public perceptions of gun violence and the leading causes of death in the U.S. The study, published Tuesday in the Annals of Internal Medicine, seeks to facilitate national public discussions about firearm ownership and storage.

"This research indicates that in the scope of violent death, the majority of U.S. adults don't know how people are dying," said Erin Morgan, lead author and doctoral student in the Department of Epidemiology at the UW School of Public Health.

"Knowing that the presence of a firearm increases the risk for suicide, and that firearm suicide is substantially more common than firearm homicide, may lead people to think twice about whether or not firearm ownership and their storage practices are really the safest options for them and their household."

To analyze national public perceptions, researchers used data from the 2015 National Firearms Survey, a web-based survey of nearly 4,000 U.S. adults. In that survey, individuals were asked to rank the relative causes of violent death in their state over the past year. The data were then compared to each state's official death count.

The results indicated that although suicide was more common than homicide in all 50 states, the majority of respondents did not identify it as such.

"The relative frequencies that respondents reported didn't match up with the state's data when we compared them to vital statistics," Morgan said. "The inconsistency between the true causes and what the public perceives to be frequent causes of death indicates a gap in knowledge and a place where additional education can be helpful."

Researchers say education about the actual risks is critical. If people believe homicide is the top risk, for example, they might purchase a gun to protect themselves. And without an understanding of the high risk of suicide, people may be less inclined to store firearms safely.

To Morgan and her colleagues, this education on firearm risks needs to extend to the media and entertainment industries.

"By having mass media and other communication mechanisms enable further discussions of suicide, we, as a society, can have a more informed conversation about suicide prevention," Morgan said.

Moving forward, the researchers are interested in learning more about how people form their perceptions of gun violence, in order to begin shifting those beliefs.

"We know that this is a mixture of mass and individual communication, but what really leads people to draw the conclusions that they do?" Morgan said. "If people think that the rate of homicide is really high because that's what is shown on the news and on fictional TV shows, then these are opportunities to start to portray a more realistic picture of what's happening."

Contributing authors of the study were Ali Rowhani-Rahbar, the Bartley Dobb Professor for the Study and Prevention of Violence and associate professor at the UW School of Public Health; Deborah Azrael, professor at the Harvard T.H. Chan School of Public Health, and Matthew Miller, professor at Northeastern University Bouvé College of Health Sciences. The research was funded by The Joyce Foundation and the Fund for a Safer Future.

http://bit.ly/2P6toqS

Bigger brains associated with greater cancer risk

The more brain cells you have, the higher your risk of brain cancer

It may simply be that having a big brain is itself the cause.

That's what doctor and PhD candidate Even Hovig Fyllingen at the Norwegian University of Science and Technology (NTNU) has determined with his research colleagues.

"Aggressive brain cancer is a rare type of cancer, but once you have it, the chance of survival is relatively low," he says.

Lifestyle matters less

For some types of cancer, lifestyle makes a big difference. People who smoke have a greater risk of lung cancer than non-smokers, for example. A person's lifestyle matters less for brain tumor development.

A large brain means more brain cells. And the more cells you have, the more cell divisions that can go wrong and create mutations that lead to cancer.

Big organs, bigger risk

"Several studies have shown that the size of different organs is an important factor in cancer development. For example, women with larger breasts have a greater risk of breast cancer. We wanted to check if this was also the case for brain tumors," says Fyllingen.

To tackle the question, he relied on material from the Nord-Trøndelag Health Study (HUNT). It comprises health data and blood samples that have been collected in multiple waves of data gathering from thousands of Norwegians in the Nord-Trøndelag county region.

The purpose of the study is to find out why some individuals become ill while others stay healthy, what affects our health and how our health affects our lives.

Fyllingen used the third version of the survey, called HUNT3, and compared it to St. Olavs Hospital's neurosurgery database. He

extracted data on everyone who had been operated on for high-grade gliomas (brain tumors) between 2007 and 2015 and compared their data with healthy controls from the HUNT study.

The researchers used MRI scans to measure the size of the brain. Then 3D models were made from them so that the intracranial brain volume could be measured in millilitres.

Mostly men who get brain tumors

The study also shows that more men than women develop brain tumours.

"Men have a larger brain than women because men's bodies are generally larger. It doesn't mean that men are smarter, but you need to have more brain cells to control a large body. This is also the case with animals. In bigger bodies, organs like the heart, lungs and brain are also bigger," says Fyllingen.

Yet it turns out that women with big brains have a greater risk of developing brain tumors compared to men with big brains.

"Seventy per cent more men than women develop brain tumors, but when we correct for head size, it's no longer beneficial to be female. Women with large brains are particularly susceptible. Why that is I have no idea," says Fyllingen.

http://bit.ly/2Jy73wp

Giant flightless birds were nocturnal and possibly blind

Nocturnal lifestyle is a trait shared by the elephant bird's closest living relative, the kiwi

If you encountered an elephant bird today, it would be hard to miss. Measuring in at over 10 feet tall, the extinct avian is the largest bird known to science. However, while you looked up in awe, it's likely that the big bird would not be looking back.

According to brain reconstruction research led by The University of Texas at Austin, the part of the elephant bird brain that processed vision was tiny, a trait that indicates they were nocturnal and possibly blind. The findings were published Oct. 31 in the journal Proceedings of the Royal Society B.

Giant nocturnal elephant birds are shown foraging in the ancient forests of Madagascar at night. **John Maisano for the University of Texas at Austin Jackson School of Geosciences.**

A nocturnal lifestyle is a trait shared by the elephant bird's closest living relative, the kiwi -- a practically blind, chicken-size denizen of New Zealand -- and a clue that is helping scientists learn more about the elephant bird's behavior and habitat, said Christopher Torres, a Ph.D. candidate who led the research.

"Studying brain shape is a really useful way of connecting ecology -- the relationship between the bird and the environment -- and anatomy," Torres said. "Discoveries like these give us tremendous insights into the lives of these bizarre and poorly understood birds."

Julia Clarke, a professor at the UT Jackson School of Geosciences and Torres' Ph.D. adviser, co-authored the study. Torres is a student in UT's Department of Integrative Biology in the College of Natural Sciences.

Elephant birds were large, flightless and lived in what is now Madagascar until a mixture of habitat loss and potential human meddling led to their demise between 500 and 1,000 years ago.

"Humans lived alongside, and even hunted, elephant birds for thousands of years," Torres said. "But we still know practically nothing about their lives. We don't even really know exactly when or why they went extinct."

Scientists had previously assumed that elephant birds were similar to other big, flightless birds, like emus and ostriches -- both of which are active during the day and have good eyesight. But Torres and

Clarke revealed that elephant birds had distinctly different lifestyles through reconstructions of their brains.

Bird skulls wrap tightly around their brains, with the turns and curves of the bone corresponding to brain structures. The researchers studied the skulls of two species of elephant birds. By using CT-imaging data of the two elephant bird skulls, the researchers were able to create digital brain reconstructions called endocasts. In addition to the elephant bird skulls, the researchers also created endocasts for close relatives of the elephant bird, both living and extinct.

In both elephant bird skulls, the optic lobe -- a bundle of brain nerves that controls eyesight -- was very small, with the structure almost absent in the larger species. The lobe had the most in common with that of a kiwi, which Torres said came as a "total shock" because of the kiwi's poor vision and nocturnal behavior.

"No one has ever suspected that elephant birds were nocturnal," Torres said. "The few studies that speculated on what their behavior was like explicitly assumed they were active during the day."

Andrew Iwaniuk, an associate professor at the University of Lethbridge and an expert on brain evolution in birds who was not involved with the research, said that he had a similar reaction to the findings.

"I was surprised that the visual system is so small in a bird this big," he said. "For a bird this large to evolve a nocturnal lifestyle is truly bizarre and speaks to an ecology unlike that of their closest relatives or any other bird species that we know of."

In addition to vision, the endocasts rendering of the olfactory bulb -- the part of the brain that processes the sense of smell -- helped shed light on the habitats where elephant birds lived. The larger of the two species of elephant bird had a large olfactory bulb, a trait associated with forest dwelling. In contrast, the smaller elephant bird species had a smaller olfactory bulb, possibly indicating that it lived in grasslands. The smaller species also appears to have somewhat keener vision, which means it may have been more active at dusk than during the pitch black of night.

"Details like these not only tell us about what the lives of elephant birds were like, but also what life in general was like on Madagascar in the distant past," Clarke said. "As recently as 500 years ago, very nearly blind, giant flightless birds were crashing around the forests of Madagascar in the dark. No one ever expected that."

This work was funded by a National Science Foundation grant and the Jackson School of Geosciences.

http://bit.ly/2AKdutv

Researchers identify three shades of blue

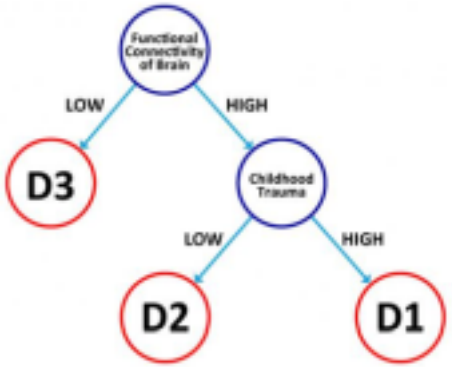
OIST scientists have used brain imaging to identify three sub-types of depression--including one that is unresponsive to commonly prescribed serotonin boosting drugs.

The study for the first time has identified three distinct sub-types of depression. D1: This sub-type is characterized by high functional connectivity of the brain and a history of childhood trauma. D2: This sub-type is characterized by high functional connectivity of the brain and an absence of childhood trauma. D3: This sub-type is characterized by both low functional connectivity of the brain and absence of childhood trauma. Neural Computational Unit, OIST.

According to the World Health Organization, nearly 300 million people worldwide suffer from depression and these rates are on the rise. Yet, doctors and scientists have a poor understanding of what causes this debilitating condition and for some who experience it, medicines don't help.

Scientists from the Neural Computational Unit at the Okinawa Institute of Science and Technology Graduate University (OIST), in collaboration with their colleagues at Nara Institute of Science and Technology and clinicians at Hiroshima University, have for the first time identified three sub-types of depression. They found that one

out of these sub-types seems to be untreatable by Selective Serotonin Reuptake Inhibitors (SSRIs), the most commonly prescribed medicines for the condition. The study was published in the journal *Scientific Reports*.



Serotonin is a neurotransmitter that influences our moods, interactions with other people, sleep patterns and memory. SSRIs are thought to take effect by boosting the levels of serotonin in the brain. However, these drugs do not have the same effect on everyone, and in some people, depression does not improve even after taking them. "It has always been speculated that different types of depression exist, and they influence the effectiveness of the drug. But there has been no consensus," says Prof. Kenji Doya.

For the study, the scientists collected clinical, biological, and life history data from 134 individuals - half of whom were newly diagnosed with depression and the other half who had no depression diagnosis- using questionnaires and blood tests. Participants were asked about their sleep patterns, whether or not they had stressful issues, or other mental health conditions.

Researchers also scanned participants' brains using magnetic resonance imaging (MRI) to map brain activity patterns in different regions. The technique they used allowed them to examine 78 regions covering the entire brain, to identify how its activities in different regions are correlated. "This is the first study to identify depression sub-types from life history and MRI data," says Prof. Doya.

With over 3000 measurable features, including whether or not participants had experienced trauma, the scientists were faced with the dilemma of finding a way to analyze such a large data set accurately. "The major challenge in this study was to develop a statistical tool that could extract relevant information for clustering similar subjects together," says Dr. Tomoki Tokuda, a statistician and the lead author of the study. He therefore designed a novel statistical method that would help detect multiple ways of data clustering and the features responsible for it. Using this method, the researchers identified a group of closely-placed data clusters, which consisted of measurable features essential for accessing mental health of an individual. Three out of the five data clusters were found to represent different sub-types of depression.

The three distinct sub-types of depression were characterized by two main factors: functional connectivity patterns synchronized between different regions of the brain and childhood trauma experience. They found that the brain's functional connectivity in regions that involved the angular gyrus -- a brain region associated with processing language and numbers, spatial cognition, attention, and other aspects of cognition -- played a large role in determining whether SSRIs were effective in treating depression.

Patients with increased functional connectivity between the brain's different regions who had also experienced childhood trauma had a sub-type of depression that is unresponsive to treatment by SSRIs drugs, the researchers found. On the other hand, the other two subtypes - where the participants' brains did not show increased connectivity among its different regions or where participants had not experienced childhood trauma - tended to respond positively to treatments using SSRIs drugs.

This study not only identifies sub-types of depression for the first time, but also identifies some underlying factors and points to the need to explore new treatment techniques. "It provides scientists studying neurobiological aspects of depression a promising direction in which to pursue their research," says Prof. Doya. In time, he and

his research team hope that these results will help psychiatrists and therapists improve diagnoses and treat their patients more effectively.

https://wb.md/2QqcimN

US Survey: 39% Say Alternative Therapies Can Cure Cancer

Nearly 4 in 10 Americans (39%) "somewhat" or "strongly" agree that cancer can be cured solely through "alternative" therapies

Nick Mulcahy

Nearly 4 in 10 Americans (39%) "somewhat" or "strongly" agree that cancer can be cured solely through "alternative" therapies, such as oxygen therapy, diet, and herbs, without standard cancer treatments, according to a national survey commissioned by the American Society of Clinical Oncology (ASCO).

The survey, which probed public opinion about a variety of cancer-related issues, was conducted online by the Harris Poll in July and August 2018. It involved 4887 US adults aged 18 years and older. Among the respondents were 1001 persons who currently have cancer or who have had cancer in the past.

ASCO gave top billing to the survey responses about alternative therapies. "Correcting widespread misinformation about cancer treatments" is one of a number of critical, urgent issues in oncology, said the organization's president, Monica Bertagnolli, MD, in a press statement.

"These findings are not only shocking but incredibly disturbing," said Skyler Johnson, MD, of the Yale Cancer Center at Yale University in New Haven, Connecticut, who was approached for comment.

However, Johnson added that an "actual [treatment] decision" — and its "life-limiting consequences" — are different from answering a survey, which has "virtually no negative consequences."

Still, the survey results are proof of the "rampant misinformation" about cancer treatments among the public, said Johnson.

Cancer patients are "often inundated" with recommendations about alternative medicine cures, he said, from well-meaning friends, family members, and even random acquaintances, "despite no evidence to support these claims.

"My wife experienced this first hand through her cancer diagnosis. My brother-in-law is experiencing it now during his cancer treatment," said Johnson.

Johnson emphasized that a strong belief in the curative powers of alternative medicine for cancer can be disastrous.

He and colleagues reported a study last year that restrospectively analyzed outcomes in patients with early-stage cancers of various types and found a 2.5-fold higher risk for death among those who rejected conventional medicine and received only alternative treatments, compared with those who received conventional cancer treatment. When they conducted an analysis of specific cancer types, the risk was even higher — a sixfold increased risk for death among breast cancer patients and a 4.5-fold increase among colorectal cancer patients who used only alternative therapies.

Alarming Findings

"If this survey accurately reflects beliefs of the American public, it is alarming that so many mistakenly believe that alternative medicine can cure cancer," said David Gorski, MD, PhD, of the Barbara Ann Karmanos Cancer Institute at Wayne State University in Detroit, Michigan, who is also managing editor of *Science-Based Medicine* .

The ASCO survey also found that younger people are the most likely to believe that alternative medicine alone can cure cancer. Nearly half of survey respondents aged 18 to 37 years and aged 38 to 53 years (47% and 44%, respectively) responded that they "somewhat" or "strongly" agree that cancer can be cured solely through alternative therapies, without standard cancer treatments. "It's particularly alarming that such views appear to be more prevalent among younger people," said Gorski.

"I also can't help but wonder how much of this is due to the rise of belief in conspiracy theories that seems to have occurred over the last several years. After all, the belief in natural cures 'they' don't want you to know about or that big pharma is hiding in order to preserve their profits is a long-standing conspiracy theory," he told *Medscape Medical News.*

Misinformation about alternative cancer treatments is not limited to the United States.

This week, Liz Ball, MD, an oncoplastic breast surgeon in Suffolk, United Kingdom, tweeted that an alternative cancer treatment flier was "pushed through her letter box" at home. The flier advertised a 1-day seminar (cost: £30, lunch not included).

Ball, who tweets under the name Liz O'Riordan and is the coauthor of the *Complete Guide to Breast Cancer* (Vermilion Publishing), posted the flyer online. The professionally executed promotion read: "Cancer: The Latest Breakthroughs/Are chemotherapy, radiotherapy and surgery really the answers to cancer? What natural, non-toxic therapies can work, and why have these been marginalised."

O'Riordan said she was "slightly tempted to go and stir up trouble from the audience."

More About the Survey

In the ASCO survey, participants were asked to agree or disagree with the statement, "Cancer can be cured solely through alternative therapies, without standard cancer treatments."

Previously, the participants had been told that "alternative therapies could include but are not limited to 'natural' cancer treatments such as enzyme therapy or oxygen therapy, diet, vitamins/minerals/herbs, et cetera."

They were also told that "standard cancer treatments could include but are not limited to surgery, radiation therapy, chemotherapy, immunotherapy, [and] hormone-based therapies."

The ASCO survey also revealed that 57% of Americans say that, faced with a cancer diagnosis, they would be most concerned about the financial impact on their families or about paying for treatment; 54% said they would be most concerned about dying or about cancer-related pain and suffering.

Responses in the survey also show that there is support for measures aimed at lowering the cost of prescription drugs. For example, 88% of those surveyed agreed that Medicare should directly negotiate prescription drug prices with manufacturers, and 77% agreed that US residents should be able to buy cancer drugs from pharmacies in other countries.

http://bit.ly/2yKEjfy

Study: Allowing Sunlight In Through Windows Can Kill Dust-Dwelling Bacteria

Microbial communities associated with indoor dust abound in the built environment.

The transmission of sunlight through windows is a key building design consideration, but the effects of light exposure on dust communities remain unclear. In a **new study** published in the journal ***Microbiome***, scientists found that in dark rooms 12% of bacteria on average were alive and able to reproduce; in comparison, only 6.8% of bacteria exposed to daylight and 6.1% of bacteria exposed to ultraviolet (UV) light were viable.

"Humans spend most of their time indoors, where exposure to dust particles that carry a variety of bacteria, including pathogens that can make us sick, is unavoidable," said study lead author Dr. Ashkaan Fahimipour, a researcher in the Biology and the Built Environment Center at the University of Oregon.

"Therefore, it is important to understand how features of the buildings we occupy influence dust ecosystems and how this could affect our health."

Dust kept in the dark contained organisms closely related to species associated with respiratory diseases, which were largely absent in dust exposed to daylight.

Dr. Fahimipour and colleagues found that a smaller proportion of human skin-derived bacteria and a larger proportion of outdoor air-derived bacteria lived in dust exposed to light that in than in dust not exposed to light.

This may suggest that daylight causes the microbiome of indoor dust to more strongly resemble bacterial communities found outdoors.

The researchers made eleven identical climate-controlled miniature rooms that mimicked real buildings and seeded them with dust collected in residential homes.

They applied one of three glazing treatments to the windows of the rooms, so that they transmitted visible, UV or no light.

After 90 days, they collected dust from each environment and analyzed the composition, abundance, and viability of the bacteria present.

"Our study supports a century-old folk wisdom, that daylight has the potential to kill microbes on dust particles, but we need more research to understand the underlying causes of shifts in the dust microbiome following light exposure," Dr. Fahimipour said.

"We hope that with further understanding, we could design access to daylight in buildings such as schools, offices, hospitals and homes in ways that reduce the risk of dust-borne infections."

Ashkaan K. Fahimipour et al. *2018. Daylight exposure modulates bacterial communities associated with household dust.* Microbiome *6: 175; doi: 10.1186/s40168-018-0559-4*

http://bit.ly/2AIV8Jk

Fossil Pigments Reveal Dinosaur Origin of Bird Egg Colors

The hues and patterns of modern bird eggs trace back to their dinosaurian ancestors

By Kate Wong on November 1, 2018

The eggshells of modern birds exhibit a spectacular array of rainbow hues—from butter yellow to blood red, palest aqua to darkest cyan. Some are spotted or speckled; others are blemish-free. How and when did the astonishing diversity of egg colors and patterns evolve? Among modern-day amniotes (the group that includes birds, reptiles and mammals), only birds produce colored eggs. The other egg layers make plain white ones. So the prevailing wisdom has been egg color is strictly a bird innovation—but new findings indicate that long before robin's egg blue, there was *Deinonychus*'s egg blue.

Pigments found in fossilized eggshells show modern birds inherited their colorful eggs from dinosaurs. **Credit: Jasmina Wiemann**

In a paper published in this week in *Nature* researchers report on pigments found in fossilized eggshells from several dinosaur species.

The work indicates the dazzling variety of colors and patterns in modern bird eggs traces back to a single evolutionary origin in nonavian dinosaurs. (Technically, birds are a subgroup of dinosaurs; hence the distinction between avian and nonavian.) The discovery adds to a growing body of evidence from fossil pigments that is revolutionizing dinosaur science.

The first hints egg color might have originated in nonavian dinosaurs came last year, when Jasmina Wiemann, a PhD student at Yale University, and her colleagues announced their discovery of the pigment responsible for blue-green egg color in fossilized eggshells of several oviraptorid dinosaurs from China. Oviraptorids were relatively small, bipedal dinosaurs with grasping hands, toothless beaks and feathers. The finding established that at least one group of nonavian dinosaurs had colored eggs, raising the question of whether

birds inherited egg color from their nonavian dinosaur ancestors or the coloration evolved independently in birds and nonavian dinosaurs.

In the new study Wiemann and her colleagues sampled the eggshells of 19 species of birds, crocodilians and nonavian dinosaurs and analyzed their chemical composition using a technique called Raman spectroscopy, which can identify pigments. The colors of modern bird eggs derive from just two pigments: biliverdin and protoporphyrin IX. The researchers detected both pigments in their fossil eggshell samples. Mapping the results onto a family tree, the team determined egg color arose just once—within the Eumaniraptora group of dinosaurs, which includes oviraptorids and some other nonavian dinosaurs as well as all modern birds. Sauropods (*Apatosaurus* and its ilk) and ornithischians (*Triceratops* and kin) do not appear to have laid pigmented eggs. And the few eumaniraptoran lineages that lost egg color did not regain it—presumably because the gene cascades that give rise to egg color are so complex, Wiemann notes.

The study results offer insights into the long-standing question of why egg color evolved in the first place. Scientists have previously proposed a number of hypotheses to explain the phenomenon, arguing pigments may have either helped camouflage eggs in certain environments, provided protection against damaging solar radiation or fortified the shell, among other benefits. The fossil eggshell pigments Wiemann and her colleagues detected come from dinosaurs known to have deposited their eggs in aboveground nests rather than burying them like their predecessors did. This association suggests a shift in nesting behavior was a key driver of the emergence of egg color, although other factors may have also contributed. For example, in the case of the Chinese oviraptorids—which are thought to have nested near rivers—blue-green egg color may well have helped them blend in with the nest materials and surrounding vegetation, concealing them from predators.

Outside experts find the team's claims for pigment preservation in the fossil eggs convincing. "This is good stuff," says Jakob Vinther of the University of Bristol in England, an authority on ancient pigments. He notes the team demonstrated Raman spectroscopy can reliably distinguish pigments from proteins, which can look quite similar.

The findings could have intriguing implications for understanding parental care in dinosaurs. In the 1990s paleontologists working in Mongolia recovered an exquisitely preserved fossil of an oviraptorid positioned atop a nest of eggs. Hailed as powerful evidence the brooding behavior of modern birds originated in nonavian dinosaurs, the fossil, presumed to be female, was nicknamed "Big Mama." But years later researchers examined a number of fossils of adult dinosaurs preserved with egg clutches (including oviraptorids), comparing the fossil specimens' egg volume and bone structure details with those of modern birds. Their conclusion: the brooding dinosaurs were probably male. The new egg color evidence "adds the missing piece of the puzzle," Wiemann says. In modern birds such as robins blue egg color is often associated with higher levels of paternal care. The thinking is that the eggs' color is a signal of quality in the mom and hence her young, and as such it prompts the dad to go the extra mile in providing for his family. The revelation oviraptorids and some other eumaniraptorans had blue eggs thus supports the claim paternal care in birds originated in nonavian dinosaurs. That is, Big Mama might be more appropriately named Big Papa.

"The discovery of a single origin of eggshell color in dinosaurs is a wonderful reminder that modern birds inherited many traits from their dinosaurian ancestors," says Mary Stoddard of Princeton University, who studies the evolution of bird eggs and was not

involved in the new work. She notes that in recent years the realization many nonavian dinosaurs possessed colorful feathers has transformed scientists' thinking about dinosaur biology and behavior. This new study, she adds, "is likely to inspire a whole new area of research on dinosaur nesting and incubation behavior."

http://bit.ly/2yPJ87w

Boy's Rare Brain Condition Means He Could Be Literally Scared to Death

A 5-year-old boy has a rare brain condition that could cause him to be literally scared to death, according to news reports.

By Rachael Rettner, Senior Writer | October 31, 2018 01:50pm ET

Reed Havlik, who lives in Iowa, has a condition called vanishing white matter disease, a disorder that's been reported in only about 200 people worldwide, according to South West News Service (SWNS). Vanishing white matter disease is a genetic condition that mainly affects the brain and spinal cord, and causes deterioration of nerve fibers known as "white matter," according to the U.S. National Library of Medicine's Genetics Home Reference (GHR).

Five-year-old Reed Havlik has a rare brain condition called vanishing white matter disease. People with the condition are particularly vulnerable to stresses, including fright, that can worsen symptoms or even lead to death. **SWNS**

People with the condition are particularly vulnerable to stresses, including infections, head trauma or even "extreme fright," GHR says. These stresses could worsen symptoms, and lead to coma or even death.

That means that Reed and his family need to be particularly vigilant around Halloween.

"We have got to be really careful what we expose him to because he could be frightened to death," Reed's mother, Erika Havlik, told SWNS. "The stress of it all can speed it [the disease] up. We do celebrate Halloween but only on a really small scale."

People with the condition have a genetic mutation that prevents the body from producing enough myelin, a fatty substance that insulates and protects nerves, according to the Children's Hospital of Pittsburgh. It's this lack of myelin that leads to deterioration of the nerves.

Symptoms can include muscle stiffness and problems with coordination. The disease is progressive, meaning that symptoms get worse over time, and there is currently no cure.

Reed was diagnosed in 2015, at age 2, and his family has been told that he could die from the disease in three to seven years, SWNS reported.

"We are trying to give him as many opportunities in life and try to soak up every second we have with him," Havlik said. "Our world has been altered completely. It's been life-changing. Everyone has been showering him with as much love as they can to ensure he's as happy as possible."

Reed's family is raising money for research into this disease through a GoFundMe campaign.

https://go.nature.com/2AL7WyK

A neurodegenerative-disease protein forms beneficial aggregates in healthy muscle

Protein aggregation is a characteristic of several neurodegenerative diseases. But disease-associated aggregates of the protein TDP-43 have now been shown to have a beneficial role in healthy muscle.

Lindsay A. Becker & Aaron D. Gitler

Most neurodegenerative disorders are characterized by the build-up of clumps of proteins in the brain[1]. A prevailing view in the field is

that these large protein assemblies are inherently abnormal and are toxic to cells. Writing in *Nature*, Vogler *et al.*[2] challenge this canon by reporting that muscle cells can contain physiological, reversible protein aggregates that have features similar to the aggregates seen in neurodegenerative disease, but that actually seem to be beneficial.

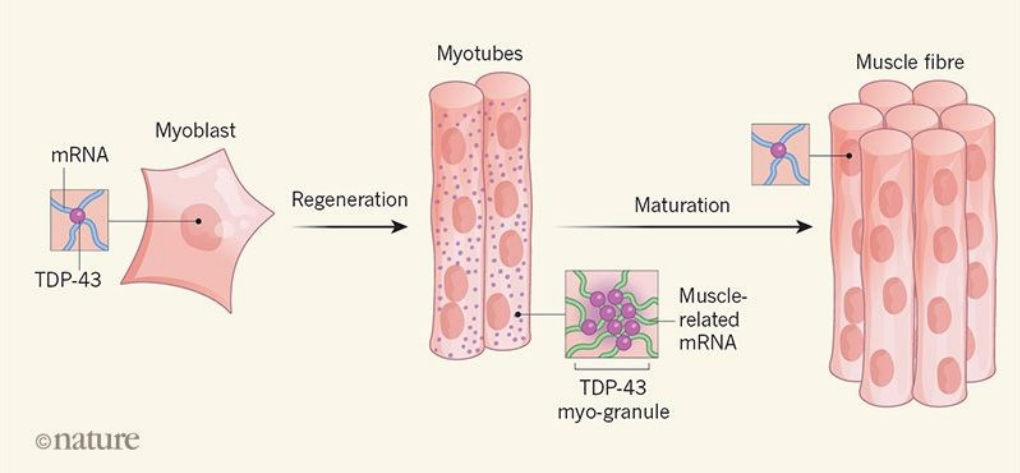


Figure 1 | ***A functional aggregate forms during muscle regeneration. In muscle precursor cells called myoblasts, the protein TDP-43, which binds messenger RNA, is located in the nucleus. Following muscle injury, myoblasts fuse into multi-nucleated fibres called myotubes that mature into muscle. Vogler et al.[2] show that TDP-43 transiently leaves the nucleus and assembles into large aggregate structures dubbed myo-granules, in which the protein binds to, and so might regulate, a distinct set of mRNA molecules involved in muscle formation. After recovery from injury, as the muscle matures, the myo-granules disassemble and TDP-43 returns to the nucleus.***

The protein TDP-43 forms aggregates in nerve cells in nearly all cases of the neurodegenerative disorder amyotrophic lateral sclerosis (ALS, also known as motor neuron disease)[3]. TDP-43 aggregation is also seen in other diseases, including frontotemporal dementia (FTD)[4] and inclusion body myopathy (IBM)[5], in which neurons and muscle cells, respectively, degenerate. FTD and IBM share genetic risk factors with ALS, indicating that the three have common disease mechanisms. In each disease, aggregates of TDP-43 are specifically found in the cytoplasm of dying cells. TDP-43 also has a normal job in the nucleus of healthy cells, where it acts as an RNA-binding protein[4].

Vogler *et al.* set out to investigate the behaviour of TDP-43 in healthy muscle. In doing so, they made a surprising observation. As expected, TDP-43 was located in the nucleus of muscle stem cells. But when the authors coaxed these cells to differentiate into young muscle fibres called myotubes, or if they used a chemical to injure a mouse's leg muscle to stimulate muscle regeneration, TDP-43 accumulated in the cytoplasm. There, it formed transient granular structures, which the researchers dubbed myo-granules, before moving back to the nucleus a few days later, as the myotubes became mature muscle fibres (Fig. 1). These data suggest that cytoplasmic TDP-43 myo-granules could have a role in muscle formation and regeneration.

Do myo-granules resemble the TDP-43 aggregates associated with neurodegenerative diseases? Disease aggregates are typically held together by strong bonds that are resistant to even heavy-duty detergents. Likewise, Vogler and colleagues found that TDP-43 myo-granules were resistant to such detergents. Another key feature of many neurodegenerative-disease proteins (although not all disease-associated TDP-43 aggregates) is that they can adopt a specific conformation, known as amyloid. Amyloids are long fibres made up of building blocks of the misfolded disease proteins arranged in a highly organized manner[6]. Using an array of analytical methods — including an antibody to specifically detect amyloid-like material, and high-resolution microscopy and X-ray diffraction techniques to enable examination of the myo-granule's structure — the authors demonstrated that TDP-43 myo-granules have amyloid-like properties.

Next, Vogler *et al.* investigated differences between TDP-43 in cytoplasmic myo-granules and in the nucleus, by examining the RNAs to which the protein binds in the two settings. They found that

the types of messenger RNA that bind to TDP-43 changed markedly as muscle precursors differentiated into muscles. The mRNAs found associated with aggregated TDP-43 included those that encode proteins associated with the sarcomere — a unit of muscle structure that causes muscle contraction. These data suggest that TDP-43 myo-granules might control the development of sarcomeres.

To confirm a role for TDP-43 in muscle formation, the authors generated mice whose muscle stem cells lacked one of two copies of the gene that encodes the protein. Lowering the level of TDP-43 in this way led to a decrease in the diameter of the muscle fibres generated in response to injury, indicating that TDP-43 is important for full muscle regeneration — probably because it somehow regulates the expression of muscle mRNAs. However, this experiment does not prove that myo-granule formation is necessary for TDP-43 function in muscle regeneration; reducing TDP-43 levels causes cellular dysfunction in many cell types, but Vogler *et al.* report myo-granules only in myotubes.

Regardless of the physiological function of TDP-43 myo-granules, the authors' data beg the question of whether these structures can eventually turn into disease aggregates. To investigate this possibility, the group turned to mice carrying a mutated form of the gene *VCP* that can cause ALS, FTD and IBM in humans[7]. The mutant mice, in which muscle, brain and bone tissue degenerates[5], had many more myotubes harbouring TDP-43 myo-granules than did wild-type mice. This suggests that *VCP* mutations might increase the risk of tissue degeneration by increasing the prevalence of myo-granules. In this scenario, perhaps small seeds of TDP-43 from myo-granules could be transported to the nerves that innervate muscle, where they might initiate a cascade of TDP-43 aggregation. Indeed, the earliest signs of neurodegeneration in ALS seem to originate at the nerve terminals adjacent to muscle, resulting in a 'dying-back' phenomenon that eventually reaches the main body of the neuron, which houses the nucleus[8].

The differences between TDP-43 disease aggregates and myo-granules are as interesting as the similarities. Unlike myo-granules, most TDP-43 disease aggregates seem to have an amorphous structure, although some do have amyloid-like characteristics[9]. Moreover, the disease aggregates seem to be irreversible, whereas myo-granules disassemble as muscle cells mature. Because of this, myo-granules could provide an opportunity to investigate how strongly bound aggregate structures are disassembled. Factors that promote the disassembly of myo-granules might also be effective at clearing disease-associated aggregates.

Vogler and colleagues' findings raise an intriguing question. Strenuous exercise and weight training stimulate repeated rounds of muscle growth and repair — could this activity increase the production of TDP-43 myo-granules, increasing the propensity of TDP-43 to aggregate and so leading to diseases such as ALS? Indeed, there is some evidence for increased prevalence of ALS in elite athletes[10,11]. However, much more evidence for the role of myo-granules and more human data will be needed before such a link can be assumed.

This paper sets the stage for future work characterizing the physiological function and regulation of TDP-43 myo-granules, and for investigating how these complexes might contribute to disease. There are other examples of amyloid-like protein complexes that form in healthy cells[12,13], but Vogler *et al.* describe the first that are made up of a protein that can also aggregate in disease. The race is on to search for more of these kinds of functional granule in other cell types. The idea that amyloid-like structures might have beneficial roles, rather than simply being associated with disease, represents a change in our understanding of these protein aggregates.

Myo-granules provide a unique opportunity to unravel the differences between a safe and a dangerous aggregate.

Read the paper: TDP-43 and RNA form amyloid-like myo-granules in regenerating muscle **doi: 10.1038/d41586-018-07141-2**

http://bit.ly/2DkGKtm

Seeds of Parkinson's disease may hide in the appendix

New study suggests the appendix harbors a supply of a brain-damaging protein involved in Parkinson's disease

By Kelly ServickOct. 31, 2018 , 2:00 PM

The appendix has a reputation of being useless at best. We tend to ignore this pinkie-size pouch dangling off our large intestine unless it gets inflamed and needs cutting out. But a new study suggests this enigmatic organ in the gut harbors a supply of a brain-damaging protein involved in Parkinson's disease—even in healthy people. The study is the largest yet to find that an appendectomy early in life can decrease a person's risk of Parkinson's or delay its onset.

"It plays into this whole booming field of whether Parkinson's possibly starts in the gut," says Per Borghammer, a neuroscientist at Aarhus University in Denmark who was not involved in the study. "And that would be a radical change in our understanding of the disease."

Look inside the brain of a person with Parkinson's and you'll find clumps of a misfolded form of a protein known as α-synuclein (αS). The protein's normal function isn't fully clear, but in this clumpy state, it may damage and kill neurons, including those near the base of the brain that help control movement. The results are the hallmark tremors and body rigidity of Parkinson's.

But gastrointestinal symptoms—especially constipation—are also common in Parkinson's patients, and can appear decades before other problems. Scientists have found that people are less likely to get Parkinson's if they've had a vagotomy, a treatment for stomach ulcers that severs the vagal nerve, which branches down from the brain into various tissues of the gut.

That finding feeds a still-controversial theory, proposed more than a decade ago by neuroscientist Heiko Braak, that the seeds of Parkinson's disease somehow climb up out of the gut and into the brain. "It's kind of like the telephone game," explains John Woulfe, a neuropathologist at the Ottawa Hospital Research Institute. Dysfunctional αS spreads up the fibers of the vagal nerve, the theory goes, by converting healthy forms of the protein to misfolded, clumpy ones.

In the new study, neuroscientist Viviane Labrie and her team at the Van Andel Institute in Grand Rapids, Michigan, decided to zero in on the appendix. Though it's not necessary for life, it may not be completely useless; the organ holds immune cells that may help coordinate the gut's response to pathogens, and bacteria that may help maintain a healthy balance of gut microbes. (Inflammation and microbiome disturbances are both proposed factors in Parkinson's risk.)

Four recently published studies looked for evidence that people who get appendectomies are less likely to get Parkinson's; three couldn't find it, but Labrie's team did. "This study accomplishes what those studies lacked," Woulfe says—a large group of people tracked over a sufficiently long time. It relies on a national registry that has logged medical records for 1.7 million Swedish citizens since 1964. There is roughly a 1% chance that a person will develop Parkinson's after age 65, but for the Swedes who had an appendectomy, the risk of developing the disease was about 20% lower than for those who kept their appendix, the researchers report today in *Science Translational Medicine*.

"The magnitude [of the effect] is remarkable," says Michael Zasloff, an immunologist at Georgetown University Medical Center in Washington, D.C., and CEO of a company called Enterin that is

testing a potential Parkinson's drug meant to prevent αS from building up in intestinal nerve cells.

When researchers broke the Swedish population into rural and urban dwellers, however, the benefit of appendectomy only held for the rural group. That's a clue, Labrie says, that an appendectomy might be most protective in Parkinson's cases that have some environmental trigger. (Pesticide exposure is a possible candidate.)

To confirm that protective effect, the team analyzed more detailed disease records from an international study of 800 people with Parkinson's. They found that for those who got an appendectomy 20 years or more before their diagnosis, the onset of Parkinson's was delayed, on average, by 3.6 years. "When we get rid of [the appendix], you are safe for a few years, but then it just starts somewhere else in the gut," Borghammer suggests. But if an appendectomy happened later in life, closer to the Parkinson's diagnosis, the disease's time of onset was not delayed much beyond the average. An appendectomy also didn't protect people with one of several inherited genetic mutations strongly linked to Parkinson's.

Labrie's team then analyzed appendix samples for different forms of αS. Of 48 samples from healthy people, all but two contained a clumped form of αS similar to that seen in the Parkinson's brain. That prevalence came as a shock. "It's present in all of us," Labrie says, but it only seems to cause trouble if it sneaks up to the brain.

And the appendix may be an important breeding ground for clump-prone αS. When the researchers exposed normal αS to the contents of healthy appendix tissue cells in a dish, the proteins were cleaved into a shorter form, which is more prone to aggregate, and possibly better able to spread to the brain.

As to why most people won't get Parkinson's despite having clumpy αS in their appendix, Labrie's team can only speculate. The team did find a distinctive feature of the appendix of a person with Parkinson's: It appeared to have about fourfold higher levels of a shortened, clump-prone form of αS than a healthy person's appendix—though it's not yet clear that this difference contributed to the development of disease. Maybe some people are inherently better able to manage clumped αS and keep it sequestered away from the brain, the researchers suggest. Or maybe some insult—an infection or a change in the population of gut bacteria—prompts the appendix to make more αS, possibly as a means of recruiting more immune cells and protecting the gut.

Given all the uncertainty, Labrie isn't suggesting anyone have their appendix taken out to avoid Parkinson's. "Preventive surgery is too far," she says. But she hopes future Parkinson's treatments might control how αS is cut and processed in the body, and thus how it accumulates. In the meantime, her team is now searching for other differences between the appendix of a healthy person and a person with Parkinson's to explain how and when its resident protein might go rogue.

Posted in: Health doi:10.1126/science.aav9158

http://bit.ly/2OpB0PN

Neanderthal children shivered and suffered in ancient Europe

Research provides powerful insight into some of the most intimate moments of life

By Ann Gibbons

Pity the poor Neanderthal mother: She had to nurse her children through colder winters and more illnesses than the mothers of most prehistoric modern humans in Europe, according to a new study of the teeth of two Neanderthal kids who lived 250,000 years ago in France. And both Neanderthal toddlers suffered from repeated lead exposure—the earliest known evidence of lead poisoning in members of the human family. The study offers a startlingly intimate view of the lives of ancient children.

The study is "mind blowing" because it gives such a detailed record of how harsh winters, the water supply, and nursing duration can influence growth in early childhood, says paleoanthropologist Leslea Hlusko of the University of California, Berkeley, who was not part of the team. The researchers "provide powerful insight into some of the most intimate moments of life—the relationship between the Neanderthal as a baby and its mama."

Researchers have long known that Neanderthals, with their barrel chests and robust limbs, were well-adapted for survival in the frigid temperatures of Europe, where their fossils date back more than 400,000 years. But it's been difficult to tie climate events to individual Neanderthals' lives or even to specific fossil sites.

Now, researchers have shown the direct effects of climate on the lives of two young children (who lived until they were teens or young adults) from Payre, an archaeological site in the Rhone Valley of southeast France, and a modern human child who lived at the same site 5400 years ago.

Biological anthropologist Tanya Smith of Griffith University in Brisbane, Australia, prepared thin sections of the teeth of two Neanderthal children and one modern human child. With a polarized light microscope, she painstakingly traced the daily growth lines that are recorded in the enamel, much like tree rings. Her international colleagues also measured oxygen isotopes, barium, and lead in the teeth.

By timing the surges of barium, a marker of milk consumption in the teeth, they found that both Neanderthals nursed for 2.5 years before they were weaned. That's just about the length of time that modern humans in hunter-gatherer societies nurse their babies, Smith says. It also suggests the weaning time of another Neanderthal, which Smith had previously traced to 15 months, was not the norm, she says.

The ratio of different isotopes of oxygen in the children's teeth suggests the Neanderthal children endured cooler winters and more extreme seasonal variation in climate than did the more recent modern human from the same site, a finding that fits other evidence of a more stable climate during the past 10,000 years. Both Neanderthals also had more stress lines—signals of disruption in enamel growth—during winter, suggesting they were sicker in that season. These disruptions were less frequent in the modern human child.

Both Neanderthals were also exposed to lead at least twice. This represents the oldest documented exposure to lead in hominin remains, the researchers report today in *Science Advances*. Two lead mines lie only 25 kilometers from the site, and the children may have ingested lead-rich food or water—or inhaled lead from smoky fires.

The evidence that Neanderthals nursed their young until they were 2.5 years through sickness and cold spells suggests Neanderthal moms took care of their young as intensively as modern mothers do. Now, researchers are eager to try these methods of studying growth in other types of humans. "These techniques help us build more nuanced pictures of what their lives were like season to season," says biological anthropologist Katie Hinde of Arizona State University in Tempe. "This gives us insight into the origins of health and disease and let us understand more about the environments that shape humans and our close relatives."

doi:10.1126/science.aav9157

http://bit.ly/2PCsim4

This ball of gas is racing around the black hole at our galaxy's heart

Superheated gas races almost as close to the black hole as possible at 30% the speed of light

By Daniel CleryOct. 31, 2018 , 5:00 AM

Earlier this year, astronomers were looking for signs that S2, the star with the closest known orbit to the supermassive black hole thought to be at the center of the Milky Way, might—as predicted by Albert Einstein—deviate from the orbital path proscribed by Newtonian gravity.

ESO/Gravity Consortium/L. Calçada

But while they were watching, they spied something else: three bright infrared flares unrelated to the star (visualization above). Those flares, the researchers reveal today, are the signs of superheated gas racing almost as close to the black hole as possible without getting sucked in—at 30% the speed of light.

Observing the action so close to the galactic center, known as Sagittarius A*, is extremely challenging because it is distant, small, and shrouded in gas and dust. The team used the world's largest optical instrument, the European Southern Observatory's Very Large Telescope in Chile, and combined the light of its four 8.2-meter mirrors to get the resolution of a 130-meter virtual telescope using a new instrument called GRAVITY.

Following up on the serendipitous discovery, the astronomers saw the three flares move in small 45-minute orbits, and the polarization of their light rotated full circle in the same period. The scientists calculated that this must be material circulating around the black hole, just outside the closest orbit in which objects can move without being sucked in. The finding, the team says, is another firm piece of evidence that Sagittarius A* is the galaxy's fathomless dark heart.

doi:10.1126/science.aav9025

http://bit.ly/2D0d6sc

Minimally invasive surgery associated with worse survival for women with cervical cancer compared to open hysterectomy

Two MD Anderson studies could impact surgical guidelines for early-stage disease

When comparing standard-of-care surgical options for women with early-stage cervical cancer, two studies led by researchers at The University of Texas MD Anderson Cancer Center discovered that minimally invasive radical hysterectomy is associated with higher recurrence rates and worse overall survival (OS), compared to abdominal radical hysterectomy.

The results of both studies are published today in the *New England Journal of Medicine*. The first, a randomized-controlled Phase III trial, was led by Pedro Ramirez, M.D., professor, Gynecologic Oncology and Reproductive Medicine. The second, an epidemiologic study, was led by J. Alejandro Rauh-Hain, M.D., assistant professor, Gynecologic Oncology and Reproductive Medicine and Health Services Research.

According to the authors, the findings already have changed care at MD Anderson and could impact the surgical management of all women with early-stage disease, which accounts for nearly half of the 13,240 cervical cancers expected to be diagnosed this year.

"Minimally invasive surgery was adopted as an alternative to open radical hysterectomy before high-quality evidence regarding its impact on survival was available," said Rauh-Hain. "Both Dr. Ramirez and I were surprised to find that in our respective studies, surgical approach negatively affected oncologic outcomes for women with early-stage cervical cancer."

In the gynecologic oncology community, minimally invasive surgery for cervical cancer gained acceptance more than a decade ago as an alternative to abdominal radical hysterectomy when laparoscopy and then robotic technology were introduced. However, impact on survival and other cancer-related outcomes had not been studied in randomized trials or large, well-designed observational studies.

"Until now, data focused primarily on surgical outcomes and the immediate period after, such as the recovery of the patient, length of stay, transfusion needs, and overall return to functional daily activities," said Ramirez. "Our research is the first to prospectively compare the two surgical approaches and evaluate oncologic outcomes, including disease-free and overall survival and recurrence rates."

The findings are critical, say the researchers, because cervical cancer is curable with surgery in its earliest stage but treatments are much less effective after disease recurrence.

Phase III clinical trial reports worse outcomes with minimally invasive hysterectomy

In their study, Ramirez and colleagues hypothesized that minimally-invasive radical hysterectomy was equivalent to the open approach in terms of disease-free survival (DFS). The international study was a multi-institutional collaboration with 33 centers worldwide. It opened in 2008 and was designed to randomize 740 women with early-stage (1A or 1B) cervical cancer to undergo either minimally invasive or open radical hysterectomy (1:1 ratio). Patients were equally stratified for risk factors, such as histologic subtypes, tumor size, stage, lymph node involvement, and adjuvant treatment.

In 2017, with 631 patients enrolled, the study was stopped because of a noted safety signal. Women receiving minimally invasive radical hysterectomy were found to have higher rates of recurrences, worse progression-free survival (PFS), and worse OS.

The researchers found:

- **Minimally invasive radical hysterectomy was associated with a three-fold increase in disease progression, compared to open radical hysterectomy.**
- **The rate of disease-free survival at 4.5 years was 86 percent with a minimally invasive surgery and 96.5 percent with open surgery.**
- **The three-year OS overall survival was 91.2 percent in the minimally invasive group compared to 97.1 percent in the open surgery arm.**

"Our study reinforces the need for more randomized clinical trials in the field of surgery," said Ramirez. "Too often, success of a new intervention in surgery is measured by retrospective data. We always need to test and measure our procedures to determine what is best for our patients."

The study also highlights the need for further research, said Ramirez. We should consider evaluation of the impact of minimally invasive surgery in other scenarios, like fertility preserving surgery in early-cervical cancer, where such an approach is still commonly used.

Retrospective study reinforces clinical trial findings

Rauh-Hain's retrospective, epidemiologic study also confirmed that minimally invasive radical hysterectomy was associated with worse OS than abdominal radical hysterectomy among patients with early-stage cervical cancer. The study, performed in collaboration with Harvard, Columbia University, and Northwestern University, includes analysis of data from two large cancer databases to compare survival rates between patients who underwent either of the two surgery types.

The team first analyzed the National Cancer Database (NCDB); this nationwide outcomes registry covers approximately 70 percent of newly diagnosed cancer cases in over 1,500 U.S. hospitals. The secondary analysis reviewed data from the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) database.

Analysis of the data revealed:

- **Over a 45-month median follow-up, the four-year mortality risks were 9.1 percent among women receiving minimally invasive radical hysterectomy compared to 5.3 percent for abdominal radical hysterectomy.**

- **Adoption of minimally invasive radical hysterectomy coincided with the beginning of a decline in four-year relative survival rates of 0.8 percent per year between 2006 and 2010 in this population.**

"Our research also found that compared with open surgery, minimally invasive surgery increased the risk of death among women who underwent radical hysterectomy for early-stage cervical cancer," said Rauh-Hain. "Given these two studies, we believe that we can no longer recommend minimally invasive radical hysterectomies for our patients with early-stage cervical cancer."

An important limitation of the retrospective study is the inability to explain why minimally invasive radical hysterectomy was associated with inferior survival. Additional studies are needed to understand the cause of the survival differences, explained Rauh-Hain.

Overall impact to the field

The findings have impacted care and management of women with early-stage cervical cancer at MD Anderson. These patients are no longer offered minimally invasive radical hysterectomy; only open radical hysterectomy is performed. Trial participants enrolled at MD Anderson and randomized to minimally invasive radical hysterectomy will be considered for closer surveillance at the time of follow up.

The research could impact national treatment guidelines for the management of the disease, say Ramirez and Rauh-Hain.

Both strongly encourage women who have undergone laparoscopic or robotic radical hysterectomy, either on the trial or as part of standard care, to have an informed conversation with their physician regarding the findings of this study, which should include their personal need for monitoring surveillance.

Ramirez and Rauh-Hain both note that their respective findings solely affect the care and management of patients with early-stage cervical cancer. However, the findings could impact fertility-sparing surgeries, such as radical trachelectomy, for women with early-stage cervical cancer, said Ramirez. As follow up, an international multi-institutional registry comparing minimally invasive to open radical trachelectomy is being led by MD Anderson.

Neither Ramirez nor Rauh-Hain have conflicts to declare for their respective studies.

Ramirez's study was supported, in part, through a departmental research fund in the Department of Gynecologic Oncology and Reproductive Medicine, MD Anderson, with the rest of the funding from Medtronic.

Rauh-Hain's study was supported by grants from the National Cancer Institute (P30CA016672, 4P30CA060553-22, and R25CA092203), National Institute of Child Health and Human Development (K12HD050121-12), and by the American Association of Obstetricians and Gynecologists Foundation, the Foundation for Women's Cancer, the Jean Donovan Estate, and the Phebe Novakovic Fund.

Additional authors on the prospective and retrospective studies can be found on the New England Journal of Medicine*'s web site.*

http://bit.ly/2JDro3l

Hot brew coffee has higher levels of antioxidants than cold brew

Comparing the properties of cold- and hot-brew coffee, researchers found similar acidity in both, but higher antioxidant levels in hot coffee

(PHILADELPHIA) -- In a new study, Jefferson (Philadelphia University + Thomas Jefferson University) researchers found chemical differences between hot and cold brew coffee that may have health impacts. In particular, the researchers found that hot-brewed coffee has higher levels of antioxidants, which are believed to be responsible for some of the health benefits of coffee.

The study, published Oct. 30 in *Scientific Reports,* also found that the pH levels of both hot and cold coffee were similar, ranging from 4.85 to 5.13 for all coffee samples tested. Coffee companies and lifestyle blogs have tended to tout cold brew coffee as being less acidic than hot coffee and thus less likely to cause heartburn or gastrointestinal problems.

The study was done by Niny Rao, PhD, associate professor of chemistry, and Megan Fuller, PhD, assistant professor of chemistry, both of them coffee drinkers who wondered whether the chemical make-up of cold brew differed from that of hot coffee.

While the popularity of cold brew coffee has soared in recent years--the U.S. market grew 580 percent from 2011 to 2016--they found almost no studies on cold brew, which is a no-heat, long-steeping method of preparation. At the same time, there is well-documented research that hot-brewed coffee has some measurable health benefits, including lower risk of some cancers, diabetes and depression.

While the overall pH levels were similar, Fuller and Rao found that the hot-brewed coffee method had more total titratable acids, which may be responsible for the hot cup's higher antioxidant levels.

"Coffee has a lot of antioxidants, if you drink it in moderation, research shows it can be pretty good for you," Fuller said. "We found the hot brew has more antioxidant capacity."

And considering hot and cold brews have comparable pH levels, Rao said, coffee drinkers should not consider cold brew a "silver bullet" for avoiding gastrointestinal distress.

Article reference: *Niny Z. Rao and Megan Fuller, "Acidity and Antioxidant Activity of Cold Brew Coffee," Scientific Reports, DOI: 10.1038/s41598-018-34392-w, 2018.*

http://bit.ly/2yQQpUp

Good news! Study says life span normal when Parkinson's does not affect thinking

When Parkinson's does not affect thinking skills early on, life span is not affected

MINNEAPOLIS - In the past, researchers believed that Parkinson's disease did not affect life expectancy. But recent studies showed a somewhat shorter life span. Now a new study suggests that when the disease does not affect thinking skills early on, life span is not affected. The study is published in the October 31, 2018, online issue of *Neurology*®, the medical journal of the American Academy of Neurology.

"This is good news for many people with Parkinson's and their families," said study author David Bäckström, MD, of Umeå University in Umeå, Sweden.

The study looked at people with Parkinson's disease and other types of parkinsonism, such as multiple system atrophy and progressive supranuclear palsy. People with those two disorders had the shortest life expectancy, with a mortality rate that was more than three times higher than for the general population.

The study involved 182 people who were newly diagnosed with parkinsonism and were followed for up to 13.5 years. Of the participants, 143 had Parkinson's disease, 18 had progressive supranuclear palsy and 13 had multiple system atrophy. At the start of the study and at least once a year, the participants were tested for Parkinson's symptoms and memory and thinking skills. During the study, 109 of the people died.

People with problems with memory and thinking skills, or mild cognitive impairment, at the beginning of the study were 2.4 times more likely to die during the study than people who did not have memory and thinking problems. Bäckström said that assuming that the average age at the start of the study was about 71 for people with Parkinson's disease, the expected survival for people with no mild cognitive impairment was 11.6 years, compared to 8.2 years for those with mild cognitive impairment.

A total of 54 percent of those with Parkinson's disease died during the study, compared to 89 percent of those with progressive supranuclear palsy and 92 percent of those with multiple system atrophy.

Bäckström said that assuming the average age at the start of the study was about 72 for people with all types of parkinsonism, the expected survival for people with Parkinson's disease was 9.6 years and 6.1

years for people with progressive supranuclear palsy and multiple system atrophy.

Other factors early in the disease that were associated with a shorter life span were having freezing of gait, where people are briefly unable to walk, and a loss of the sense of smell.

A limitation of the study was that autopsies were used to confirm the diagnoses in only five of the 109 people who died, so there may have been some people who were diagnosed incorrectly.

The study was supported by the Swedish Research Council, Erling Persson Foundation, Umeå University, Västerbotten County Council, King Gustaf V and Queen Victoria Freemason Foundation, Swedish Parkinson Foundation, Kempe Foundation, Swedish Parkinson's Disease Association, Torsten Söderberg Foundation, Swedish Brain Foundation, European Research Council and Knut and Alice Wallenberg Foundation.

http://bit.ly/2JEOTci

Cooling 'brains on fire' to treat Parkinson's

A promising new therapy to stop Parkinson's disease in its tracks has been developed at The University of Queensland.

UQ Faculty of Medicine researcher Associate Professor Trent Woodruff said the team found that a small molecule, MCC950, stopped the development of Parkinson's in several animal models.

"We have used this discovery to develop improved drug candidates and hope to carry out human clinical trials in 2020," Dr Woodruff said.

"Parkinson's disease is the second-most common neurodegenerative disease worldwide, with 10 million sufferers, whose control of body movements is affected.

"The disease is characterised by the loss of brain cells that produce dopamine, which is a chemical that co-ordinates motor control, and is accompanied by chronic inflammation in the brain.

"We found a key immune system target, called the NLRP3 inflammasome, lights up in Parkinson's patients, with signals found in the brain and even in the blood.

"MCC950, given orally once a day, blocked NLRP3 activation in the brain and prevented the loss of brain cells, resulting in markedly improved motor function."

There are no medications on the market that prevent brain cell loss in Parkinson's patients, with current therapies focusing on managing symptoms rather than halting the disease.

UQ Institute for Molecular Bioscience researcher Professor Matt Cooper said drug companies had traditionally tried to treat neurodegenerative disorders by blocking neurotoxic proteins that build up in the brain and cause disease.

"We have taken an alternative approach by focusing on immune cells in the brain called microglia that can clear these toxic proteins," he said.

"With diseases of ageing such as Parkinson's, our immune system can become over-activated, with microglia causing inflammation and damage to the brain.

"MCC950 effectively 'cooled the brains on fire', turning down microglial inflammatory activity, and allowing neurons to function normally."

The study is published in *Science Translational Medicine* (DOI: 10.1126/scitranslmed.aah4066), and was made possible by generous support from The Michael J. Fox Foundation for Parkinson's Research and Shake it Up Australia Foundation, which fund innovative research into therapies for Parkinson's disease.

"We are extremely grateful to our funders who have supported multiple research projects on this target at UQ, and to their donors who support medical research for those living with Parkinson's," Dr Woodruff said.

The study was undertaken at the School of Biomedical Sciences and involved UQCCR Group Leader in Clinical Neuroscience Dr Richard Gordon, an Advance Queensland Research Fellow, and PhD student Eduardo Albornoz.

"The findings provide exciting new insight into how the spread of toxic proteins occurs in Parkinson's disease and highlights the important role of the immune system in this process," Dr Gordon said. "With continued funding support, we are exploring new treatment strategies including repurposing drugs to target mechanisms by which the immune system and the inflammasome contribute to disease progression."

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New Study Finds Correlation between Showerhead Bacteria and Lung Infections

Bacteria thrive in showerheads and throughout household water distribution systems.

Nov 2, 2018 by Enrico de Lazaro

While most of these bacteria are innocuous, some are potential pathogens, including members of the **genus *Mycobacterium*** that can cause **nontuberculous mycobacterial (NTM) lung infections**. In a **new study** published in the journal ***mBio***, a researcher team led by University of Colorado, Boulder scientists found that showerheads often harbor abundant mycobacterial communities that vary in composition depending on geographic location, water chemistry, and water source. They also identified geographic regions within the United States where showerheads have particularly high abundances of potentially pathogenic lineages of mycobacteria, and these 'hot spots' generally overlapped those regions where NTM lung disease is most prevalent.

Mycobacteria are frequently abundant in showerheads, and many showerheads harbor mycobacterial lineages that include known pathogens.

"Bacteria grow and persist in biofilms coating the inside of showerheads and shower hoses despite the seemingly inhospitable conditions found in these habitats," said study lead author Dr. Matthew Gebert of the Cooperative Institute for Research in Environmental Sciences at the University of Colorado, Boulder and colleagues.

"These bacteria must tolerate rapid temperature fluctuations, long intervals of stagnation or desiccation followed by high-shear turbulent flow events, and the low nutrient and organic carbon concentrations typical of most drinking water."

"In many cases, showerhead-associated bacteria must also be able to tolerate residue from the chemical disinfectants — including chlorinated compounds — which are often added to municipal drinking water to limit bacterial contamination."

"Most of the bacteria that can become aerosolized and inhaled when the shower is in use are likely harmless. However, this is not always the case."

"Bacteria within the genus *Mycobacterium* are commonly detected in showerhead biofilms and throughout the water distribution system."

There are nearly 200 described species of NTM mycobacteria, which are defined as any members of the genus that are not *Mycobacterium tuberculosis* or *M. leprae* — which cause tuberculosis and leprosy, respectively.

Despite their importance, the diversity, distributions, and environmental predictors of showerhead-associated mycobacteria remain largely unresolved.

To address these knowledge gaps, Dr. Gebert and co-authors worked with citizen scientists to collect showerhead biofilm samples and associated water chemistry data from 656 households located in the United States and 13 countries in Europe.

They found that showerheads often harbor abundant mycobacterial communities that vary in composition depending on geographic location, water chemistry, and water source.

Households that received water treated with chlorine disinfectants had particularly high abundances of certain mycobacteria.

"By harnessing DNA sequencing technology, we were able to identify which bacterial species that lived in showerhead slime, and how abundant they were," the study authors said.

"Mycobacteria were far more abundant in showerheads receiving municipal tap water than in those receiving well water, as well as more abundant in U.S. households versus European."

"These patterns are probably driven in part by differences in the use of chlorine disinfectants. Mycobacteria tend to be somewhat resistant to the chlorine-based disinfectants used more heavily in the United States than in Europe — so in Europe, other bacterial species may be better able to thrive and outcompete the disease-causing strains."

"Showerhead materials seemed to matter, too, with more mycobacteria in metal showerheads than in plastic ones — plastic leaches some chemicals that support diverse bacterial communities, possibly preventing the mycobacteria from becoming too abundant."

When the researchers mapped out where potentially pathogenic mycobacteria thrived, the maps revealed 'hot spots' that roughly match regions where NTM lung disease is most prevalent — parts of Southern California, Florida, and New York, highlighting the potentially important role of these showerhead bacteria in disease transmission.

"Our results highlight the public health relevance of mycobacteria in showerhead biofilms and advance our understanding of NTM transmission dynamics," they said.

"This study demonstrates that mycobacterial distributions in showerhead biofilms are often predictable from household location and water chemistry."

"The results will help develop strategies to reduce exposures to these emerging pathogens."

Matthew J. Gebert et al. *Ecological Analyses of Mycobacteria in Showerhead Biofilms and Their Relevance to Human Health.* mBio, *published online October 30,2018; doi: 10.1128/mBio.01614-18*

http://bit.ly/2yPM9o2

Nasal gene spray inspired by llama antibodies could prevent all types of flu

Four llama antibodies and a harmless virus: This outlandish recipe could be the basis of a nasal spray designed to foil infection from all strains of influenza.

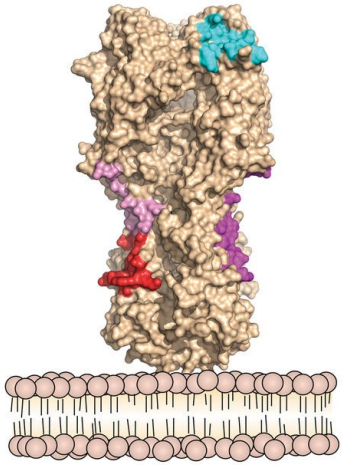
By Jon Cohen

The spray, containing a virus engineered to make a protein derived from the llama antibodies, has passed its first animal test, protecting mice from every known flu strain that infects humans, a research team reports.

Although the strategy must go through more testing before human trials can begin, researchers who have struggled to develop a "universal" vaccine against the highly mutable flu virus say it merits serious attention. The nasal spray could prove a boon to the elderly, who typically suffer most from flu and get only weak protection from existing vaccines. And unlike traditional influenza vaccines, which are tailormade each flu season to match the viruses in circulation, it could be stockpiled as protection against a flu pandemic. "This is a great story and shows the power of antibody engineering," says immunologist Antonio Lanzavecchia, a leading flu vaccine researcher at the Institute for Research in Biomedicine in Bellinzona, Switzerland.

Antibody engineer Joost Kolkman at Janssen Infectious Diseases in Beerse, Belgium, and his colleagues thought an unusual class of antibodies made by llamas and their camel cousins might serve as a weapon against flu. These antibodies are unusually small because they lack the "light" peptide chain that normally bulks up each arm of the Y-shaped proteins. Researchers can further pare down the remaining "heavy" chains to create so-called nanobodies, able to reach into crevices of viruses that their full-size counterparts can't touch.

To create nanobodies against the flu, the Janssen group injected llamas with a vaccine containing three different influenza viruses, as well as the viral surface protein, hemagglutinin, from two other flu strains. They then harvested four antibodies that each neutralized many flu strains. Ultimately, the team was able to engineer a gene that expressed a protein made up of nanobodies derived from all four antibodies. "It's very easy to link the domains together into one single molecule," Kolkman says. They spliced the gene into a benign adenovirus-associated virus (AAV) that's used in gene therapy experiments.



A flu-fighting antibody targets four sites (colored areas) on the virus's hemagglutinin surface protein. **Xueyong Zhu And Ian Wilson, Scripps Research Institute**

Test tube studies showed the four-in-one antibody prevented infection by 60 different influenza viruses from both the type A and B groups that infect people. "It's been quite hard to find an antibody that neutralizes both A and B," says Ian Wilson, a structural biologist at the Scripps Research Institute in San Diego, California, who helped work out how the nanobodies bound to the virus.

Mice given the synthetic antibody—delivered either by squirting the doctored virus into their noses of the mice or by infusing the protein directly into their circulation—had significantly higher survival rates than untreated rodents when injected with a variety of influenza strains. Wilson, who has published more than 50 papers on influenza antibodies, says he's never seen one with greater breadth and potency. Because AAVs can persist for months, the strategy could offer extended production. "Hopefully it would last the entire flu season in humans," Wilson says.

Immunologist James Crowe, an influenza antibody specialist and vaccine developer at Vanderbilt University in Nashville, cautions that human immune systems may see the llama-derived proteins as foreign and develop antibodies against them. He also notes that although AAV-based treatments are being tested for life-threatening diseases, giving the virus as a flu preventive would face more intense scrutiny from regulators. "The bar for putting AAV in a healthy individual is going to be very high," Crowe says.

doi:10.1126/science.aav9274

http://bit.ly/2D01YeS

Diabetes medications may reduce Alzheimer's disease severity

Networks identified for developing new therapies

NEW YORK, NY - People with Alzheimer's disease who were treated with diabetes drugs showed considerably fewer markers of the disease--including abnormal microvasculature and disregulated gene expressions--in their brains compared to Alzheimer's patients without treatment for diabetes, Mount Sinai researchers report.

Results of the study will be published in *PLOS One* online on November 1st at 2PM.

This is the first study to examine what happens in the pathways of both brain tissue and endothelial cells--the cells lining blood vessels--in the brains of Alzheimer's patients treated with diabetes medication. The results of the study will inform future Alzheimer's disease studies and potential new therapies targeting specific cells, since they suggest that targeting the brain's capillary system could have beneficial effects in Alzheimer's patients.

Many elderly people with diabetes have brain changes that are hallmarks of Alzheimer's. Despite this linkage, two previous Mount Sinai studies on brain tissue found that the brains of people with both Alzheimer's disease and diabetes had fewer Alzheimer's lesions than the brains from people with Alzheimer's disease without diabetes.

The results suggested that anti-diabetes medications had a protective effect on the brains of Alzheimer's disease patients.

To determine what happens at the molecular level, this Mount Sinai research team developed a method to separate brain capillaries from the brain tissue of 34 people with Alzheimer's and type 2 diabetes who had been treated with anti-diabetes drugs and compare them to tissue from 30 brains of people with Alzheimer's without diabetes and 19 brains of people without Alzheimer's or diabetes. (Because most people who have diabetes are treated with insulin or oral medications, the scientists were unable to compare their results to brain tissue from people with Alzheimer's disease and diabetes who were not treated with anti-diabetes drugs.)

Then, they examined the vessels and brain tissue separately to measure Alzheimer's Disease associated changes in molecular RNA markers for brain capillary cells and insulin signaling.

The levels of about half of these markers were reduced in the vessels and brain tissue in the group with Alzheimer's and diabetes. The great majority of the RNA changes seen in Alzheimer's disease were absent in those Alzheimer's patients who had been treated with anti-diabetes drugs.

"The results of this study are important because they give us new insights for the treatment of Alzheimer's disease," said the study's senior author, Vahram Haroutunian, PhD, Professor of Psychiatry and Neuroscience at the Icahn School of Medicine at Mount Sinai.

"Most modern Alzheimer's treatments target amyloid plaques and haven't succeeded in effectively treating the disease," said Dr. Haroutunian. "Insulin and diabetes medications such as metformin are FDA approved and safely administered to millions of people and appear to have a beneficial effect on people with Alzheimer's. This opens opportunities to conduct research trials on people using similar drugs or on drugs that have similar effects on the brains' biological pathways and cell types identified in this study."

Other Mount Sinai authors of the paper include Sam Gandy, MD, PhD, Associate Director of the Alzheimer's Disease Research Center at Mount Sinai; Michal Schnaider-Beeri, PhD, Professor of Psychiatry; Pavel Katsel, PhD, Associate Professor of Psychiatry; Miguel Gama-Sosa, PhD, Associate Professor of Psychiatry; and Sonia Khan, associate researcher.

The Mount Sinai research team plans to study these drugs and their molecular pathways in greater detail using a combination of postmortem human brain cells and mouse models.

This study was supported by grants from the U.S. Department of Veterans Affairs and the National Institutes of Health.

http://bit.ly/2SLVOok

Schadenfreude May Come in 3 Flavors, Some Meaner Than Others

If you've ever reveled in the misfortune of another, you've experienced what the Germans call "schadenfreude." But which kind did you experience?

By Stephanie Pappas, Live Science Contributor

A new paper argues that there are three subtypes of schadenfreude, some of which might seem more defensible morally than others. People can experience glee in others' pain out of a genuine desire for justice, researchers wrote in an upcoming issue of the journal New Ideas in Psychology. Or people can be motivated by us-versus-them dynamics or even by petty personal jealousies.

What ties all these subtypes together, said lead study author Shensheng Wang, a graduate student in psychology at Emory University in Atlanta, is a common thread of dehumanization.

"When we fail to perceive others as humans, when we dehumanize others, we cut off the link between us and the person who experiences a misfortune," Wang told Live Science.

Types of schadenfreude

Wang first became interested in the concept of schadenfreude a few years ago, when he was researching how children experience envy and competition. Schadenfreude had come up in earlier research by other scientists on envy, Wang said, but he found that researchers tended to define it in different ways. Some, for example, saw the emotion as justice-based, as people sometimes report feeling more

schadenfreude for high achievers than for average Joes and Janes. Perhaps, these researchers argued, people want to cut others down to size when they think those individuals deserve comeuppance.

But feelings of schadenfreude don't emerge only when someone seemingly deserves it. People also feel the emotion about things like sports, Wang said, gaining pleasure when a rival team hits a losing streak.

Other studies had hinted that people might experience schadenfreude alongside envy or that they might be most prone to schadenfreude when the victim of misfortune was "the other" — someone not like them.

Wang argued that all of these scholars are cuing in on different types of schadenfreude, each with its own motivation. The first motivation, social justice, links to people's desires for fairness and punishment of wrongdoers, Wang said. The second type of motivation, aggression, draws a line between "us" and "them" and solidifies the social identity of the person feeling the schadenfreude as a member of the in-group. The third motivation, rivalry, occurs when the person feeling schadenfreude is motivated by personal envy and spite.

Humanity's dark side

So far, there isn't a lot of research attempting to discern schadenfreude subtypes, Wang said, adding that he hopes the new paper will spur more studies.

There is evidence, however, that feelings of schadenfreude might start young — perhaps as early as 2 years of age. In one 2014 study, researchers set up experiments to elicit schadenfreude in 24-month-olds. In one condition, the scientists asked a mother to read a book to herself while her child and a preschool classmate played. After 2 minutes, the mom would "accidentally" spill water on the pages of her book. In the second condition, the mother would do the same thing but cuddle her child's friend on her lap as she read, making her own child jealous of the attention.

The researchers found that the jealous kids were more gleeful about the spilled water than the kids who hadn't been primed to experience jealousy. This was likely an early expression of schadenfreude, the researchers reported in the journal PLOS One.

People show individual differences in how they experience schadenfreude, as well, Wang said. The emotion is more common in people who are high in psychopathy (callous and unempathetic), Machiavellian traits (scheming), narcissism (self-obsessed) and sadism. But, Wang said, schadenfreude is pervasive among people in all settings, from political rivalries to sports.

"I think this emotion can shed light on some of the darker sides of our humanity," he said.

http://bit.ly/2D4toR2

How cancer-causing papillomaviruses evolved

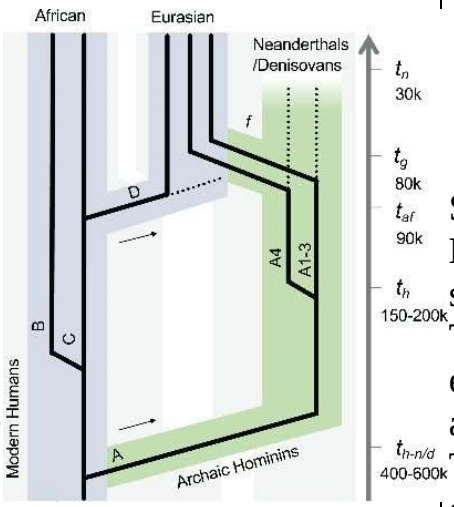
HPVs diverged from their most recent common ancestors approximately half a million years ago

Cancer-causing human papillomaviruses (HPVs) diverged from their most recent common ancestors approximately half a million years ago, roughly coinciding with the timing of the split between archaic Neanderthals and modern *Homo sapiens*, according to a study published November 1 in the open-access journal *PLOS Pathogens* by Zigui Chen of the Chinese University of Hong Kong, Robert Burk of the Albert Einstein College of Medicine, and colleagues.

Epidemiologic studies have demonstrated that persistent infection with HPVs is the main cause of cervix pre-cancer and cancer. But the origin and evolution of cancer-causing HPVs remain poorly understood. To better understand the molecular evolution of HPV16 and other types of HPVs that cause cancer, the researchers isolated viruses from primates, performed viral genomic analyses, and estimated the divergence times of cancer-causing HPV variants from their most recent common ancestors.

The findings suggest that the first stage of the evolution of cancer-causing papillomaviruses is niche adaptation of viruses to host ecosystems, followed by coevolution of viruses with their primate hosts for at least 40 million years.

Genomic analyses revealed an estimated ancient divergence of HPV16 variants from their most recent common ancestors approximately half a million years ago, roughly coinciding with the timing of the split between archaic Neanderthals and modern *Homo sapiens*.



Schematic illustration of HPV16 codivergence with archaic hominins. **Chen Z, *et al.* (2018)**

The findings revealed recent viral sexual transmission from Neanderthals to modern non-African humans through multiple interbreeding events in the past 80,000 years.

According to the authors, understanding the evolution of papillomaviruses should provide important biological insights and suggest mechanisms underlying HPV-induced cervical cancer.

"The evolution of oncogenic HPVs follows a methodical pathway of first adapting to a specific ecologic niche/anatomic regions of the human body (e.g., cervix), followed by co-divergence in archaic human ancestors and subsequent selection within specific human genetic backgrounds," notes Chen.

"Moreover, the evolution of HPVs can also provide novel insights about human evolution."

More information: *Chen Z, DeSalle R, Schiffman M, Herrero R, Wood CE, Ruiz JC, et al. (2018) Niche adaptation and viral transmission of human papillomaviruses from archaic hominins to modern humans. PLoS Pathog 14(11): e1007352. doi.org/10.1371/journal.ppat.1007352*

http://bit.ly/2OvJl4Q

Researchers at IRB Barcelona explain the origin of the periodicity of the genome

An explanation for a periodicity in the sequence of the genomes of all eukaryotes

Scientists at the Institute for Research in Biomedicine (IRB Barcelona) have found an explanation for a periodicity in the sequence of the genomes of all eukaryotes, from yeast to humans. The results published in the journal *Cell* offer an alternative explanation to the one based on natural selection, which has been accepted by the scientific community to date.

The researchers demonstrate that DNA damage and repair processes can play a role in the generation of sequence periodicity in the genomes of eukaryotic organisms. These processes are influenced by the orientation of the DNA structure when this molecule is packaged inside the cell nucleus, thus favouring a certain composition with a periodic nature in eukaryotic genomes.

"The answer we provide allows a better understanding of why our genome and that of other species have developed into what they are today," says Núria López-Bigas, head of the study and leader of the Biomedical Genomics lab at IRB Barcelona.

The "mysterious" periodicity of the genome

Since the sequence of the human genome and that of other organisms such as the mouse and fruit fly became known at the beginning of the 21st century, some researchers have noted a marked periodicity in the proportion of base pairs comprising adenine (A) and thymine (T). Indeed, the proportion of A/T pairs has been observed to be greater every 10 base pairs.

This periodicity has been associated with how DNA winds around nucleosomes (the simplest compaction form of DNA, in which it envelopes proteins called histones). The explanation given has been that natural selection would favour the appearance of A/T bases as

these bases would provide the DNA structure with a greater degree of flexibility, thus allowing it to wind around histones to form nucleosomes.

Tumour mutations provide the key

By studying the distribution of mutations in more than 3,000 human tumours, the team at IRB Barcelona observed that the mutations also accumulated every 10 DNA base pairs.

?"By examining mutation distribution along the genomes in regions in which we ruled out the presence of selection, we found a marked periodicity of 10 base pairs in the DNA that forms part of nucleosomes," explains Oriol Pich, PhD student and awardee of a fellowship from the Barcelona Institute of Science and Technology (BIST) and first author of the paper.

The periodicity of mutations occurs because the structure of the DNA packaged inside the nucleosome favours the appearance of regions that are prone to damage and to repair. Consequently, these regions are more susceptible to mutations.

Next, the researchers turned their attention to mutations that are passed from one generation to another, in both humans and plants. They found that these hereditary mutations also accumulated every 10 base pairs.

With this new discovery of how nucleosomes affect DNA mutations, the researchers deduced that it could also explain the development of the mysterious periodicity of the sequence of eukaryotic genomes.

Mutations over millions of years of evolution

The scientists at IRB Barcelona hypothesised that, as most mutations that we get are in cytosines (C) that convert into thymines (T), most of those regions most prone to mutating over millions of years have become A/T base pairs.

To test this notion, the researchers performed a mathematical simulation of genome evolution and demonstrated that the periodicity of the sequence of the human genome and that of other eukaryotes could have arisen from the periodic rate of mutations.

"We are really pleased to provide the scientific community with this alternative explanation regarding periodicity," say Oriol Pich and Núria López-Bigas, who highlight the importance of this kind of research. "It is basic knowledge derived from curiosity-driven research that allows us to achieve a better understanding of nature".

However, the results of the study are not only a breakthrough regarding current understanding of the human genome but they also explain how tumours acquire mutations. This knowledge is relevant for identifying mutations that are relevant for tumour development--another field of expertise of López-Bigas' group.

This study is an example of how basic research can bring about new scientific knowledge. The work has been funded by the European Research Council, through a Consolidator grant" awarded to Núria López-Bigas, by the Ministry of Science, through ERDFs, and by the Catalan Government.

Reference article:

Oriol Pich, Ferran Muiños, Radhakrishnan Sabarinathan, Iker Reyes-Salazar, Abel Gonzalez-Perez, Nuria Lopez-Bigas
Somatic and germline Mutation periodicity follow the orientation of the DNA minor groove around nucleosomes
Cell (2018) doi: 10.1016/j.cell.2018.10.004

http://bit.ly/2qrRv4t

Bug repellent made from coconut oil works better than DEET, government study says

New findings show that compounds found in coconut oil repel insects better than DEET. Veuer's Mercer Morrison has the story.

Joel Shannon

Compounds derived from coconut oil have been found to repel some insects better than DEET, a synthetic chemical considered the "gold standard" of repellents, according to a U.S. Department of Agriculture bulletin published Wednesday.

The release highlights a study by USDA researchers published on Sept. 19 in the journal Scientific Reports. The study found that fatty acids derived from coconut oil had long-lasting insect-repelling properties against flies, ticks, bed bugs and mosquitoes.

Lead researcher Junwei Zhu notes that compounds extracted from coconut oil – not the oil itself – were found as an effective repellent, according to a USDA release.

"Coconut oil itself is not a repellent," the release says.

The findings are significant in part because of safety concerns associated with DEET, a chemical used first used as an insect repellent by the military during World War II, the study says.

"DEET is an effective repellent, but it can sometimes come with some serious side effects like rashes, disorientation and even seizures, so our experts say you should avoid products with more than 30 percent DEET," Consumer Reports' Theresa Panetta said in a 2015 report.

But Panetta at that time had few alternatives to offer, saying many "natural and herbal repellents were not very effective at all" in testing.

Zhu's study says many natural repellents quickly lose their effect on insects. That wasn't the case for the coconut oil compounds, according to Zhu's research.

The USDA release says the coconut oil compounds out-preformed DEET at repelling stable flies, with an effective rate greater than 95 percent, compared with DEET's 50 percent.

The release says the coconut oil compounds repelled bed bugs and ticks for two weeks, as compared with DEET's three days of effectiveness.

However, the study notes that a much greater concentration of coconut oil acids are required to effectively repel mosquitoes as compared with DEET.

Study authors say they are hopeful the research could result in the development of coconut oil-based insect repellent products to fight diseases transmitted by mosquitoes. The study notes existing commercial applications of coconut oil: "coconut fatty acids are considered non-toxic, and are widely used in the food and cosmetic industries." The study also says the results could yield affordable agriculture products for cattle.

A leading manufacturer of DEET did not immediately respond to a USA TODAY request for comment on the study.

Coconut oil has made headlines as some researchers have spoken out against purported health benefits of the oil in weight loss. One Harvard professor went so far as to call the oil "pure poison."

http://bit.ly/2D4O0bx

Novel protective mask for medical personnel

Novel protective mask for medical personnel

by Andrea Six

Laughter is the best medicine, says medical research. But how are patients supposed to feel like smiling if the faces of the nursing staff and even their beloved ones are covered with masks? Researchers from Empa and EPFL are currently developing a novel face mask, which offers an unobstructed view of the wearer's facial expressions.

Anyone who has to go to the hospital for treatment will already not be in the best of spirits.

The situation is even more unsettling for small children or the elderly, who, overwhelmed with pain and medical procedures, just need to get well. After all, how is someone in a mask supposed to read a comforting story to a small child? And how is an enfeebled patient supposed to grasp what the masked individual plans on doing with the needle in his hand? It would be easier to deal with patients if the lips and facial expressions were visible through the mask. With this in mind, researchers from Empa in St. Gallen and EPFL's

EssentialTech program are currently developing the Hello Mask with an integrated transparent filter film.

"A conventional face mask is composed of several layers of relatively thick fibers," says Empa researcher Giuseppino Fortunato. And although the individual fibers of the white or green masks might well be see-through, their diameter and processing cause the incident light to scatter to such an extent that the mask turns opaque. The woven fibers of the Hello Mask, on the other hand, should leave a transparent surface that offers an unobstructed view of the lips, also enabling the wearer to communicate non-verbally with the patient via facial expressions.

Novel protective mask for medical personnel

Empa Researchers are working on transparent protective membranes made of finely spun fibers. This renders the facial expressions visible again. Credit: Swiss Federal Laboratories for Materials Science and Technology

For the see-through film to also filter out pathogens from the wearer's breath, however, it may only contain very tiny pores. This protects patients with a weakened immune system against infections, for instance. By the same token, the mask should also keep out germs: Nursing staff and the loved ones of people suffering from highly contagious diseases like Ebola covet a more humane contact with the patients, without jeopardizing their own health. The Hello Mask should bring more humanity to how highly contagious diseases are handled.

"Using a technique referred to as electrospinning, we can produce such fine membranes with a pore size of around 100 nanometers," explains Fortunato. The challenge in producing one of these masks, however, is to enable sufficient air to flow through the close-meshed material of the mask. The materials researchers are currently analyzing which kinds of polymer fibers can be used to produce a film with maximum respiratory activity.

https://wb.md/2qtUCZR

The Year's Most Important Study Adds to Uncertainty in Science

Use of evidence is what separates doctors from palm readers. Evidence helps prevent us from fooling ourselves. It tamps down our hubris.

John M. Mandrola, MD

Yet some expert clinicians have rightly criticized the overuse of evidence-based practice because it can lead to unthinking algorithmic medicine. That sort of practice is scary because evidence rarely provides easy answers, as in yes, do this, no, don't do that.

As medical science progresses, patients increasingly depend on clinicians to help translate evidence. To do that we must ask: Did the investigators ask the right question, did they recruit patients similar to everyday patients, did they choose fair comparators, and did the statistically significant results reach clinical relevance? These are tough enough to sort through.

Now, findings from an elegant study[1] from researchers led by Professor Brian Nosek at the University of Virginia in Charlottesville make the job of translating medical evidence even harder. His team has shown that the choices researchers make in analyzing a dataset can substantially affect the results.

For years, when I read a scientific paper, I've thought that *the* data yield *the* published result. What Nosek and his colleagues have found is that results can be highly contingent on the way the researchers analyze the data. And, get this: There is little agreement on the best way to analyze data.

The Study

Nosek's group recruited 29 teams comprising 61 researchers to use the same data set to answer one simple question: Are professional soccer referees more likely to give red cards for foul play to dark-skin–toned players than to light-skin–toned players? Red cards result

in instant ejection from the game, whereas a yellow card allows players to continue unless they incur another infraction.

This was a multiyear project that included building a data set of sports statistics largely from the 2012-2013 season for four European men's premiere leagues, then recruiting teams of researchers from varying fields and experience to do an initial analysis. In the first phase of the experiment, the teams submitted summaries of their approach to answering the question but worked independently.

In the next phase, Nosek's team brought the 29 groups together for a round-robin of peer evaluations in which each team provided feedback on other teams' analytic method. An aggregate of these evaluations was provided to each of the teams, which allowed the groups to learn from each other's approach.

In the next phase the teams, having learned from their peers, could change their approach to the analysis and possibly change their conclusions.

In the sixth phase of the study, investigators discussed and debated the final analyses. This prompted some teams to perform additional testing to assess whether results were driven by a few outliers—they were not. The discussion led to the discovery that variability of the results occurred not just because of analytic methods but also because of the choice of covariates.

The Results

The 29 teams chose 21 unique combinations of covariates and used many different analytic techniques, ranging from simple linear regression to complex multilevel regression and Bayesian approaches.

The point estimate of the odds ratio for effect size ranged from 0.89 (slightly negative) to 2.93 (moderately positive).

Twenty teams (69%) found a statistically significant effect and nine teams (31%) did not. Neither the level of expertise, peer ratings, nor the prior beliefs of investigators (assessed in surveys before investigators saw the data set) explained the variability of effect size.

Comments

This is big because everyone understands that analyzing different data or asking different questions yields varying results. These were the same data and the same question!

When you read a research study, the methods section usually has one or two sentences describing *the* (singular) analytic method. This paper shows that identical data sets can yield variable results—some statistically significant and others not.

What makes this previously undescribed area of heterogeneity so striking is that most of the analytic approaches used in Nosek's study were defensible and rated as reasonable by the other methodologists.

What These Findings Are Not

These analysis-contingent results are not the same as *P*-hacking or the garden of forking paths. *P*-hacking (aka cheating) occurs when researchers actively pursue significance and do numerous analyses of the data, then select and publish the method that produces the significant result. In this study, each research team set out their method before they had the data.

The garden of forking paths problem occurs when researchers refine their analysis plan after patterns in the data have been observed.[2] For instance, if an expected result does not show up as a main effect, the researchers can then look for interactions. Nosek and colleagues explained that because they asked only one basic question—were soccer referees more likely to give red cards to players with darker skin—this limited the problem of forking paths. What's more, the 29 teams had no incentive to find positive results.

Clinical Relevance

Don't be lulled into thinking this is merely an issue with social science questions. In an email, Brahmajee Nallamothu, MD, from the University of Michigan in Ann Arbor, pointed me to an excellent

clinical example: In 2010, *JAMA* published a paper using the UK General Practice Research Database showing that bisphosphonates aren't associated with cancer,[3] but 1 month later, the *BMJ* published a paper based on the same database showing that bisphosphonates are associated with cancer.[4]

What about the recent analysis of a UK database that reported a link between angiotensin-converting enzyme inhibitor use and lung cancer.[5] The point estimate of hazard just barely met significance at 1.14, with a 95% confidence interval of 1.01 to 1.29. Would another analytic method have produced nonsignificant results? What about 10 different analytic methods?

Also Pertinent to RCTs

The first question I asked Professor Nosek when we spoke on the phone was whether analysis-contingent results could apply to randomized controlled trials (RCTs). His "yes" answer alarmed me. Nosek said that whenever there is flexibility of choices, such as the choice of outcomes, which patients to include, and how to dichotomize variables you can expect variability.

Harlan Krumholz, MD, from Yale University in New Haven, Connecticut, also saw relevance to the RCT. By email, he wrote, "For any given question, different groups could address it very different ways—even with an RCT…. If you give them the question with freedom to design the experiment—they could conclude different things."

Nallamothu underscored the reality of variability in RCTS by noting the divergent results from the seemingly similar *MitraClip* trials, Mitra-FR[6] and COAPT.[7]

You may counter this argument by saying that RCTs and their analytic methods are pre-registered and this prevents researchers from switching methods after seeing the data. While more and more trials are pre-registered, Nosek pointed out that, in reality, lack of specificity in describing protocols can allow researchers flexibility in the final analysis.

In a paper from the *Proceedings of the National Academy of Sciences*,[8] he and his coauthors list no fewer than nine practical challenges to data analysis even with pre-registration. The short message from this long paper is captured in this quote: "Deviations from data collection and analysis plans are common in the most predictable investigations."

Another relevant and recent example of flexibility in RCTs concerns the problem of how changing trial endpoints can influence results.[9] This issue has provoked debate on the yet-to-be-completed ISCHEMIA trial of PCI vs medical therapy in patients with stable coronary heart disease.[10,11]

Multiple Analyses: A Path to Truth?

A wide-angle view of Nosek and colleagues' paper reveals a bit of good news, and perhaps a path toward scientific truth. In Figure 2, the authors show the 29 different odds ratios and confidence intervals in descending order. While roughly two thirds of the point estimates yielded significant positive effects and one third did not, the overall picture shows relatively consistent results. Most of the confidence intervals overlap, and, when they are taken together, one can see a trend toward a positive effect—so, yes, soccer referees likely do give more red cards to players with dark skin tones.

That got me thinking: Why don't investigators do multiple analyses more often? Nosek told me that statistical software makes it relatively easy to run different analyses on the data. Krumholz added that the discovery of data-contingent results points to the value of open science and data sharing, since this would allow many designs to come forward.

A team of Belgian and US authors termed such a process a *multiverse analysis*.[12] They wrote that the thinking behind doing multiple analyses of data "starts from the observation that data are not

passively recorded in an experiment or an observational study. Rather, data are to a certain extent actively constructed."

This group used a multiverse analysis to challenge a provocative analysis[13] suggesting that a woman's menstrual cycle influences religiosity and political attitude. When they analyzed the same data in other ways, with different, but defensible methods, they discovered that most *P* values did not indicate significant differences. To me, the best part of the multiverse approach to a scientific question is that it addresses a limitation of pre-registration. Namely, while pre-commitment to an experimental method is vital, doing so allows for only one—of many—analytic approaches. Perhaps medical science would be more reliable, more trusted, if scientists heeded the advice Nosek and colleagues offered in their concluding remarks: "We encourage scientists to come up with every different defensible analysis possible, run them all, and then compute the likelihood that the number of observed significant results would be seen if there was really no effect."

Conclusion

What this paper taught me, a user of medical science, is to be even more cautious in drawing conclusions from one or two papers. Would the result of the chosen analysis hold up to other reasonable ways to analyze the data?

The other clear lesson: Embracing the behaviors of open science, such as pre-registration, crowdsourcing, and doing multiple analyses, may lessen the number of "positive" newsworthy papers, but this may actually speed the rate of true medical progress.

Fewer scientific reversals would also likely boost the public's trust in science.

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http://bit.ly/2PKF166

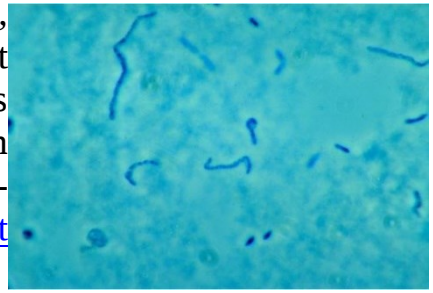
College Athlete Dies of Rare Bacterial Illness Called 'Forgotten Disease'

A college student-athlete in Kansas died suddenly from a rare bacterial infection after thinking her symptoms were due to tonsillitis, according to news reports.

By Rachael Rettner, Senior Writer

The 23-year-old, Samantha Scott, was a top coxswain on the rowing team at Kansas State University, according to a statement from the university. But about two weeks ago, she started to feel unwell.

Initially, it was thought that Scott had tonsillitis, or inflammation of the tonsils, according to local news outlet KDVR. Tonsillitis can cause symptoms such as sore throat, fever and pain when swallowing. But Scott had actually developed an illness called Lemierre syndrome, a condition that's so rare it was referred to as "all-but-forgotten disease" in a 2006 report of a similar case.



***An image of* Fusobacterium necrophorum*, a type of bacteria that is the most common cause of Lemierre syndrome, a rare infection that's been dubbed a "forgotten disease."* CDC/ Dr. Lillian V. Holdeman**

Lemierre syndrome is a bacterial infection that begins in the throat and causes symptoms such as sore throat and fever, followed by swelling of one of the jugular veins in the neck, according to National Institutes of Health's Genetic and Rare Diseases Information Center (GARD). Later, pus-filled tissue moves from the throat to various organs, including the lungs.

A number of different bacteria can cause Lemierre syndrome, but the most common is *Fusobacterium necrophorum*, a type of bacteria that can be found in the throat, even among healthy people.

Indeed, the condition often appears in healthy young people, but exactly why it develops is poorly understood. One theory is that certain viruses or other bacterial infections may allow the *F. necrophorum* bacteria to invade the mucous membrane in the throat, GARD says.

The condition can be treated with antibiotics, but quick action is needed, as a delay in diagnosis by four or more days leads to significantly worse outcomes, GARD says. Unfortunately, the diagnosis is often delayed because of the initially innocuous symptoms and lack of awareness of the disease, the 2006 case report said.

Despite being called a "forgotten disease," the syndrome appears to be becoming more common as doctors have tried to rein in their use of antibiotics, according to University of Alabama at Birmingham (UAB). About one in 70,000 young adults develops the condition each year, and about 6 percent die from the disease, UAB said.

Scott passed away on Saturday (Oct. 27).

Scott's family has started a GoFundMe campaign to cover the expenses from the medical bills and funeral costs. The family is also looking to start a scholarship fund on behalf of Scott for the Kansas State University rowing team, according to the GoFundMe page.

"Sam was known for her positive outlook on life and her contagious smile," her family wrote. "Those who knew her closely are able to talk in depth about her outgoing personality and ability to cheer anyone up."