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Study suggests diabetes medication improves heart structure

Reasons why this medication results in profound reductions in death and heart failure are largely unknown

A study led by St. Michael's Hospital researchers, and presented at a prestigious late-breaker session at the American Heart Association meeting in Chicago on Nov. 11, indicates that the diabetes medication empagliflozin has important effects that can improve cardiac structure in people with Type 2 diabetes who also have heart disease.

"Empagliflozin is used to reduce glucose in diabetes patients, but it also has profound cardiovascular benefits," said Dr. Subodh Verma, cardiac surgeon-scientist and director of the CardioLink platform at the Keenan Research Centre for Biomedical Science of St. Michael's. "The reasons why this medication results in profound reductions in death and heart failure are largely unknown," added Dr. Verma, who led the EMPA-HEART CardioLink-6 trial. "And whether it can directly and favourably remodel the heart has been an important unanswered question."

EMPA-HEART is the first randomized, double-blind, parallel group study to investigate the effect of empagliflozin on the structure and function of the left ventricle in individuals with Type 2 diabetes and a history of cardiovascular disease, using MRI testing over a six-month period.

Increased thickness of the heart's left ventricle is associated with heart disease and heart failure. The study found that when the subjects were given empagliflozin, it caused a significant regression in left ventricular mass index. The left ventricular mass index was assessed using cardiac MRI, the gold standard method for evaluating heart function.

The EMPA-HEART team included many physicians and scientists from St. Michael's, including Dr. Kim Connelly, Dr. Andrew Yan, Dr. David Mazer, Dr. David Fitchett, Dr. Peter Juni, director of the Applied Health Research Centre (AHRC), and Adrian Quan, research manager the CardioLink platform. It is the sixth CardioLink clinical trial. The late-breaker sessions are used for presentations deemed too important to wait for the next AHA meeting.

"The results are truly impressive, since they were observed on top of excellent standard of care and seen within a very short period of time," said Dr. Connelly, one of the co-principal investigators of the EMPA-HEART study. Dr. Mazer added that the data "provide important clues as to how this medication is working, and how it may prevent heart failure in people with Type 2 diabetes."

Boehringer Ingelheim, a pharmaceutical company that manufactures empagliflozin, provided an unrestricted grant to conduct the EMPA-HEART study and the empagliflozin compound used in the study.

http://bit.ly/2OFV1C4

Can scientists change mucus to make it easier to clear, limiting harm to lungs?

UNC School of Medicine and Duke University researchers show why coughing can't force mucus free from airways to help people battle cystic fibrosis and chronic bronchitis, and how new treatments could alter mucus to make coughing more therapeutic

CHAPEL HILL, NC - For healthy people, mucus is our friend. It traps potential pathogens so our airways can dispatch nasty bugs before they cause harm to our lungs. But for people with conditions such as cystic fibrosis (CF) and chronic obstructive pulmonary disorder (COPD), mucus can get too thick and sticky; coughing alone can't clear it. Infections develop, leading to severe chronic disease and early death. Now, for the first time, scientists at the UNC School of Medicine and Duke University demonstrated why coughing often cannot tear mucus apart and away from the airway lining. And they

showed how to make mucus thinner and less sticky so coughing can become a therapeutic aid.

The discovery, published in the Proceedings of the National Academy of Sciences, helps explain how CF harms lungs over time and underscores the importance of therapies that alter mucus enough to give immediate relief to people with CF. Combining a host of scientific disciplines from cell biology to materials science, the researchers established the most realistic experimental system to date for testing the mechanical properties of mucus in airway diseases, including COPD and asthma, that affect millions of people in the United States.

"The tools developed in this study will help us test strategies to improve mucus clearance in several important diseases where clearance fails," said lead author Brian Button, PhD, associate professor of biochemistry and biophysics and member of the UNC Cystic Fibrosis Research and Treatment Center at UNC-Chapel Hill. Senior author Michael Rubinstein, professor in the Department of Mechanical Engineering and Materials Science at Duke University, said, "We measured the adhesive forces that bind mucus to the airway lining and the cohesive forces that hold mucus together, and identified several agents that show promise in reducing the strength of mucus's adhesive and cohesive interactions."

In healthy people, mucus is 98 percent water. It lines airways to trap particles, including bacteria and other microbes, before they reach the lungs. Less than 1 percent of ordinary mucus consists of long, sticky, chain-like proteins called mucins, which give mucus its gel-like properties. CF, chronic bronchitis, and other "muco-obstructive" diseases feature mucus dramatically more viscous and elastic than normal, almost gelatin-like because it is loaded with mucins. In CF mucus, for example, the amount of mucins jumps to 10 percent and the amount of water decreases to 79 percent. While CF mucus is still mostly water, even small changes in mucin content can have dramatic effects on mucus viscoelasticity.

Typically, the cough reflex produces high-velocity airflows that tear mucus apart and tear it from the airway lining and at the same time. But scientists have never fully understood why coughing fails to clear mucus in muco-obstructive diseases such as CF. Guided by the theoretical work of Rubinstein, a longtime researcher at UNC-Chapel Hill before joining Duke in 2018, the researchers at UNC developed a sophisticated system for testing the mechanical forces required to dislodge and fracture normal and CF-type mucus.

The scientists first took airway-lining cells from the lungs of transplant patients and cultured them in laboratory dishes. These cells produced their own mucus layer. Button said, "They look like miniature versions of a real airway lining."

Because mucus is a very "soft" gel, the researchers developed a technique to embed small meshes, which firmly bind to the mucus. This mesh is then connected via silk thread to a motor with a force sensor to quantify the force required to pull and tear the mucus. This allowed them to test the adhesive and cohesive forces of mucus. And they could compare these forces in normal mucus and CF mucus.

"We found that the adhesive and cohesive strengths of mucus increase dramatically when the ratio of mucins to water is higher than normal," Button said. "In CF mucus, those strengths exceeded the forces produced by coughing. That means coughing would have a substantially reduced ability to clear mucus."

The UNC and Duke researchers also used this experimental set up to test the efficacy of two popular types of CF treatments on the properties of CF mucus. One treatment - inhaled saline and hypertonic saline (saltier than water in the body) - increases the water content in mucus to make it thinner. The other types of treatments - so-called "mucolytic" therapies - make mucus less viscous and elastic by chopping up or separating mucin molecules to reduce their

ability to stiffen mucus. The team found that both types of therapy work well at reducing the adhesive and cohesive strengths of CF mucus.

"For patients, one of these types of therapy should help," Button said. "But their effects are additive, so it would probably be better to combine both. And our research suggests that this approach could allow coughing to become beneficial to these patients, just as it is for the rest of us when we battle less serious ailments, such as viruses."

The researchers now plan to use their experimental system to study the properties of mucus and the effects of therapies in other airway diseases.

Other authors include co-senior author Richard Boucher, MD, the James C. Moesser Distinguished Professor of Medicine and director of the UNC Marsico Lung Institute; Bob Dennis, PhD, professor of biomedical engineering at UNC-Chapel Hill; UNC graduate student Henry Goodell; former UNC postdoctoral fellow Yu-Cheng Chen, PhD; former UNC research specialists Eyad Atieh, Robert Williams, and Elijah Lackey; former UNC postdoctoral fellow Siddharth Shenoy, PhD; UNC research specialist and lab manager Nathan Shenkute; and former UNC postdoctoral fellow Li Heng Cai, now an assistant professor at the University of Virginia.

The National Institutes of Health, the Cystic Fibrosis Foundation, and the National Science Foundation funded this research.

http://bit.ly/2qLhzYu

How mitochondria deploy a powerful punch against life-threatening bacteria

The constant battle for dominance between disease-causing bacteria and our immune systems has led to the evolution of some crafty warfare tactics on both sides.

One particularly nasty bacteria: methicillin-resistant Staphylococcus aureus, or MRSA.

Common in schools and health-care settings, MRSA has been known to cause occasionally life-threatening infections. This has recently led Michigan Medicine researchers to investigate how immune system cells deliver their deadly payloads to destroy invading organisms such as MRSA.

Their work is published in the journal Cell Host & Microbe.

When alerted of an invasion, immune cells called macrophages surround and engulf bacteria, quarantining them inside a compartment called a phagosome. The cell then destroys them with weapons called reactive oxygen species (ROS).

"One example of a reactive oxygen species is bleach," says Mary O'Riordan, Ph.D., a professor of microbiology and immunology at the University of Michigan and the study's principal investigator. "Just like you don't want bleach on your skin, bacteria don't want reactive oxygen to damage their outside surface."

Immune cells usually deploy ROS inside their phagosomes using a well-known mechanism, which involves dumping oxidants into the compartment to kill the bacteria.

But many bacteria -- including salmonella and MRSA -- have found ways to avoid this form of attack.

Mitochondria: a power player

O'Riordan and her colleagues, research investigator Basel Abuaita, Ph.D., and Tracey Schultz, sought to discover what backup system immune cells employed to fight these bacteria.

In doing so, they found an unexpected player: mitochondria.

"We discovered that macrophages sense invading MRSA and turn on the machinery to increase mitochondrial development of ROS," Abuaita says.

ROS is a natural byproduct of mitochondria's normal job in cells, the production of energy.

And the team found that when placed under stress, such as invasion by a foreign agent, chemical signals from the endoplasmic reticulum -- an organelle in the cell that acts as sort of a post office, packaging and sending substances around the cell -- notifies mitochondria to ramp up production of ROS.

Still, a question remained: how do mitochondria deliver their ROS to the phagosome?

"ROS are also damaging to our own cells, so we hypothesized that there must be some delivery mechanism," O'Riordan says. "Mitochondria have not traditionally been known to package and deliver substances to different parts of the cell."

Targeted delivery methods

Their studies revealed that the ROS were delivered in tiny mitochondrial vesicles, recently discovered as a way that mitochondria could talk to other parts of the cell. To find these payloads, Abuaita used florescent tags and live high-resolution imaging techniques to watch the process unfold in real time.

He infected a cell with MRSA under a microscope and inserted a dye that would glow in the presence of ROS. Mitochondria in the infected cell began to glow, as did the macrophage when the bacteria touched its outside membrane.

Once the macrophage ate the MRSA, he witnessed a glowing hot spot as the ROS was delivered to the phagosome. Why, though, would a cell have two different methods for deploying ROS?

"The immune system is full of redundancies," O'Riordan says. "It has to, by definition; every bacteria, virus, or parasite that we know is a pathogen is one because it has evolved ways to avoid the immune system.

"The immune system also has a real diversity of purpose and mechanism," she adds. "Being open to different ways of asking questions about the immune system and understanding the biology of these pathogens helped us to find the right experimental system to use."

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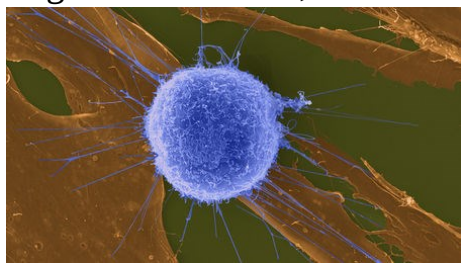
In a paradox, obesity is a 'net positive' for cutting-edge anticancer drugs

Obesity weakens the immune system and favors tumor growth by boosting the very same molecules those drugs target

By Jocelyn Kaiser

Second only to smoking, obesity is a top risk factor for cancer. But cancer doctors have noticed something surprising: overweight patients sometimes respond better than other patients to powerful drugs that harness the immune system to fight tumors. Now, researchers tracing the complex effects of obesity on cancer are glimpsing a possible explanation: Obesity weakens the immune system and favors tumor growth by boosting the very same molecules those drugs target.



Obesity can have surprising effects on T cells, such as this one on lung cancer cells. **Dennis Kunkel Microscopy/Science Source**

"For the most part, everybody assumes obesity is always bad. But [with these drugs], there was a net positive," says cancer immunologist William Murphy of the University of California (UC), Davis, who, with UC Davis oncologist Arta Monjazeb, led the work reported today in *Nature Medicine*. Murphy thinks the finding could point to ways to make the drugs more effective in all cancer patients. Called checkpoint inhibitors, the drugs work by blocking the activation of PD-1, a protein on the surface of immune sentinels called T cells. The body naturally triggers PD-1 to dampen immune responses, but tumors can also stimulate PD-1 to protect themselves. Lifting this molecular "brake" allows the T cells to attack the cancer cells. PD-1 inhibitors have caused untreatable tumors to vanish for years in people with melanoma, lung cancer, and some other cancer types.

But only a minority of patients respond to the drugs, and a study early this year in *The Lancet Oncology* showed that the responders disproportionately include people who are overweight. In 330 advanced melanoma patients given a PD-1 inhibitor, researchers at MD Anderson Cancer Center in Houston, Texas, found that those who were male and overweight lived much longer on average: nearly

27 months compared with 14 months for patients with a normal body mass index (BMI).

Now, Murphy's team has firmed up this clinical observation in the lab and identified a possible basis. After confirming that tumors grow faster in obese mice, his team studied the T cells of obese mice, monkeys, and people. They found that the cells were what immunologists call "exhausted." They were slow to proliferate and had stopped making secreted proteins that stimulate other immune system helpers. They also displayed more PD-1 than average, meaning cancer cells could more easily suppress them and grow unhindered.

Leptin, a hormone made by fat cells, is one factor in the PD-1 excess, Murphy's group found. Overweight animals and people produce high levels of the hormone, which normally signals the brain that the animal has had enough to eat. But leptin also affects the immune system, and the UC Davis team suspects it triggers a signaling pathway that increases PD-1 on T cells.

The PD-1 excess also has a paradoxical benefit: In obese mice, it makes T cells unusually responsive to PD-1 inhibitors, Murphy's team reports today in *Nature Medicine*. Once the drugs released this brake, the T cells sprang back into action. Nourished by glucose and other nutrients abundant in an overweight animal's tissues, they worked better at curbing tumors than in normal weight animals.

The finding suggests an "unexpected" benefit of obesity for cancer patients, says Harvard University immunologist Lydia Lynch. Her group reports in *Nature Immunology* today on a different way obesity impairs the immune system's ability to attack tumors: by hampering a type of immune cell called natural killer cells that seek out and destroy abnormal cells.

Murphy plans to explore whether giving normal weight mice with cancer a high-fat diet or leptin in order to mimic some effects of obesity could boost their response to PD-1 inhibitors. But such treatments for cancer patients could also have harmful effects, cautions tumor immunologist Suzanne Ostrand-Rosenberg of The University of Utah in Salt Lake City, who also studies how obesity spurs tumor growth. "It's a balance here, a very careful balance," Ostrand-Rosenberg says.

Whereas the UC Davis team's findings suggest obese patients may respond better to PD-1 drugs, normal weight patients can also benefit and it's too early to make treatment decisions based on BMI, says MD Anderson melanoma researcher Jennifer McQuade, lead author on *The Lancet Oncology* study. "Ultimately, we need an integrative analysis to understand the contributions of BMI, sex, age, and how these interact with each other," McQuade says.

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Kawasaki disease: One disease, multiple triggers

Recent clustering of Kawasaki disease in San Diego points to environmental causes

Researchers at University of California San Diego School of Medicine, Scripps Institution of Oceanography, and international collaborators have evidence that Kawasaki Disease (KD) does not have a single cause. By studying weather patterns and geographical distributions of patients in San Diego, the research team determined that this inflammatory disease likely has multiple environmental triggers influenced by a combination of temperature, precipitation and wind patterns. Results will be published in the November 12 online edition of Scientific Reports.

"We are seeing firsthand evidence of these weather patterns in San Diego, where eight children have recently been diagnosed with Kawasaki Disease. Recent low pressure systems in San Diego have been associated with two distinct clusters of the disease," said Jane C. Burns, MD, pediatrician at Rady Children's Hospital-San Diego and director of the Kawasaki Disease Research Center at UC San Diego School of Medicine. "Our research is pointing towards an

association between the large-scale environment, what's going on with our climate on a large scale, and the occurrence of these clusters."

Kawasaki disease is the most common acquired heart disease in children. Untreated, roughly one-quarter of children with KD develop coronary artery aneurysms -- balloon-like bulges of heart vessels -- that may ultimately result in heart attacks, congestive heart failure or sudden death.

Burns and her team examined 1,164 cases of KD treated at Rady Children's Hospital over 15 years. Noticeable clusters of KD cases were often associated with distinct atmospheric patterns that are suspected to transport or concentrate agents that result in KD. Days preceding and during the KD clusters exhibited higher than average atmospheric pressure and warmer conditions in Southern California, along with a high pressure feature south of the Aleutian Islands.

"For the first time, we have evidence that there is more than one trigger for Kawasaki Disease. Up until now, scientists have been looking for one 'thing' that triggers KD," said Burns. "Now we see that there are distinct clusters of the disease with different patterns suggesting varying causes."

Gene expression analysis further revealed distinct groups of KD patients based on their gene expression pattern, and that the different groups were associated with certain clinical characteristics.

"Our data suggest that one or more environmental triggers exist, and that episodic exposures are influenced at least in part by regional weather conditions. We propose that characterization of the environmental factors that trigger KD in genetically susceptible children should focus on aerosols inhaled by patients who share common disease characteristics," said Burns who has studied KD for more than 35 years.

Although KD is estimated to affect fewer than 6,000 children in the U.S. each year, the incidence is rising in San Diego County. While the average incidence per 100,000 children less than 5 years of age residing in San Diego County was approximately 10 for the decade of the 1990s, the estimate from 2006 to 2015 was 25.5. This increase may be attributed to the efforts of the KD team at Rady Children's Hospital to teach local physicians how to diagnose KD. Or it may be due to increasing exposure to the environmental triggers of the disease.

Prevalence rates of KD are increasing among children in Asia. Japan has the highest incidence rate, with more than 16,000 new cases per year. One in every 60 boys and one in every 75 girls in Japan will develop KD during childhood.

Incidence rates in the U.S. are approximately 19 to 25 cases per 100,000 children under age 5 -- but are higher in children of Asian descent. Predictive models estimate that by 2030, 1 in every 1,600 American adults will have been affected by the disease.

Co-authors include: Martin Rypdal from Arctic University of Norway; Veronika Rypdal from University Hospital of North Norway; Jessie Creamean from University of Colorado; and Jennifer A. Burney, Daniel Cayan, Emelia Bainto, Shannon Skochko, Adriana H. Tremoulet, Chisato Shimizu and Jihoon Kim from UC San Diego.

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New strategy discovered toward possible prevention of cancers tied to mono

Possible path forward in preventing the development of cancers tied to two viruses

Researchers from the University of Minnesota, the Howard Hughes Medical Institute, and the University of Toronto have discovered a possible path forward in preventing the development of cancers tied to two viruses, including the virus that causes infectious mononucleosis--more commonly known as mono or the "kissing disease"--that infects millions of people around the globe each year.

Published in *Nature Microbiology*, the research focuses on how the Epstein-Barr virus (EBV) and Kaposi's sarcoma herpesvirus (KSHV) shield themselves from destruction inside the human body.

"People infected with EBV or KSHV will have the virus for life," said Adam Cheng, a Medical Scientist Training Program (MSTP) student at the University of Minnesota Medical School and lead author on the study. "In most cases, the virus will remain dormant. However, sometimes these viruses can reactivate and lead to abnormal, cancerous cell growth. But now, in the wake of our research, data suggests it may be possible to suppress the virus indefinitely."

Under ideal conditions, a human DNA enzyme called APOBEC3B is capable of mutating and killing EBV and KSHV as it invades and replicates inside the body. However, researchers discovered that both viruses are able to produce defense proteins--BORF2 and ORF61, respectively--that bind directly to the APOBEC3B enzyme. In doing so, APOBEC3B is unable to mutate and kill the viral DNA and is directed away from sites of virus replication.

"Our work suggests that by blocking the virus's defense proteins, it may be possible to treat mono and prevent the development of cancers caused by EBV and KSHV," said senior author Reuben Harris, Ph.D. "The viral defense proteins are excellent targets for drug development."

Researchers used CRISPR/Cas9-mediated genome engineering to delete the EBV's defense protein. Through that process, the human APOBEC3B enzyme was able to mutate the virus, rendering it harmless and unable to replicate in cells.

"We are already working hard to extend these results from cells to mice and other complex organisms," said Harris. "The preliminary data are very promising and we hope to make great strides in future studies."

"This is a great example of how an unbiased basic science experiment can lead to novel therapeutic opportunities. We could not have anticipated such an unusual role of BORF2 in disabling APOBEC3B and protecting EBV genomes," said Lori Frappier, Ph.D., senior author on the study and professor at the University of Toronto.

Cheng and Harris are affiliated with the following University of Minnesota colleges and units: College of Biological Sciences's Department of Biochemistry, Molecular Biology and Biophysics; the Masonic Cancer Center; the Institute for Molecular Virology in the School of Dentistry; and the Center for Genome Engineering. Harris is also an investigator with the Howard Hughes Medical Institute.

Funding for this research was provided by the Howard Hughes Medical Institute, the National Cancer Institute and the Canadian Institutes for Health Research.

http://bit.ly/2DqNHrS

Scientists use patients' own cells and materials to engineer fully personalized tissue implants of any kind

New technology makes it possible to engineer any kind of tissue implant from one small fatty tissue biopsy

In a new study, Tel Aviv University researchers reveal how they invented the first fully personalized tissue implant, engineered from a patient's own materials and cells. The new technology makes it possible to engineer any kind of tissue implant from one small fatty tissue biopsy.

"We were able to create a personalized hydrogel from the materials of the biopsy, to differentiate fatty tissue cells into different cell types and to engineer cardiac, spinal cord, cortical and other tissue implants to treat different diseases," says Prof. Tal Dvir of TAU's Department of Biotechnology, Department of Materials Science and Engineering, Center for Nanoscience and Nanotechnology and the Sagol Center for Regenerative Biotechnology, who led the research for the study.

"Since both the cells and the material used derive from the patient, the implant does not provoke an immune response, ensuring proper regeneration of the defected organ," Prof. Dvir says.

The research was conducted by Prof. Dvir's postdoctoral researcher Reuven Edri and doctoral students Nadav Noor and Idan Gal, in collaboration with Prof. Dan Peer and Prof. Irit Gat Viks of TAU's

Department of Cell Research and Immunology and Prof. Lior Heller of Assaf HaRofeh Medical Center in Israel. It was recently published in *Advanced Materials*.

Currently, in tissue engineering for regenerative medicine, cells are isolated from the patient and cultured in biomaterials to assemble into a functional tissue. These biomaterials are always either synthetic or natural, derived from plants or animals. After transplantation, they may induce an immune response that leads to rejection of the implanted tissue. Patients receiving engineered tissues or any other implants are treated with immuno-suppressors, which themselves endanger the health of the patient.

"With our technology, we can engineer any tissue type, and after transplantation we can efficiently regenerate any diseased or injured organ—a heart after a heart attack, a brain after trauma or with Parkinson's disease, a spinal cord after injury," says Prof. Dvir. "In addition, we can engineer adipogenic (fatty tissue) implants for reconstructive surgeries or cosmetics. These implants will not be rejected by the body."

The researchers extracted a small biopsy of fatty tissue from patients, then separated its cellular and a-cellular materials. While the cells were reprogrammed to become induced pluripotent stem cells—able to make cells from all three basic body layers, so they can potentially produce any cell or tissue the body needs to repair itself—the extracellular material was processed to become a personalized hydrogel. After combining the resulting stem cells and the hydrogel, the scientists successfully engineered the personalized tissue samples and tested the patients' immune responses to them.

The researchers are currently engaged in regenerating an injured spinal cord and an infarcted heart with spinal cord and cardiac implants. They have also begun to investigate the potential of human dopaminergic implants to treat Parkinson's disease in animal models. The researchers plan to regenerate other organs, including intestines and eyes, using the patients' own materials and cells. "We believe that the technology of engineering fully personalized tissue implants of any type will allow us to regenerate any organ with a minimal risk of immune response," Prof. Dvir concludes.

More information: *Reuven Edri et al, Personalized Hydrogels for Engineering Diverse Fully Autologous Tissue Implants, Advanced Materials (2018). DOI: 10.1002/adma.201803895*

http://bit.ly/2BdevKU

Diabetic foot ulcers heal quickly with nitric oxide technology

Diabetic foot ulcers can take up to 150 days to heal. A biomedical engineering team wants to reduce it to 21 days.

They're planning to drop the healing time by amplifying what the body already does naturally: build layers of new tissue pumped up by nitric oxide. In patients with diabetes, impaired nitric oxide production lessens the healing power of skin cells and the Centers for Disease Control reports that 15 percent of Americans living with type II diabetes struggle with hard-to-heal foot ulcers. However, simply pumping up nitric oxide is not necessarily better. The long-term plan of Michigan Technological University researchers is to create nitric oxide-laden bandages that adjust the chemical release depending on the cell conditions.

To do that, they first have to figure what's going on with nitric oxide in skin cells. Assessing nitric oxide under diabetic and normal conditions in human dermal fibroblast cells is the focus of the team's latest paper, published this week in Medical Sciences.

Diabetes stats from the World Health Organization, International Diabetes Federation, "Diabetic foot ulcers and their recurrence" in *New England Journal of Medicine*, and "Advanced biological therapies for diabetic foot ulcers" in *Archives of Dermatology* reveal the challenge researchers in this field face:

1.5 million deaths globally in 2012
425 million people worldwide live with diabetes
15 percent or more live with diabetic foot ulcers
2.5 times more likely to die
90-150 days to heal
$176 billion spent in U.S. every year on diabetes

Cell-mediated Symphony of Complexity

Megan Frost is the interim chair of the Department of Kinesiology and Integrative Physiology as well as an associate professor of biomedical engineering and an affiliated associate professor of materials science and engineering. She runs a polymeric biomaterials lab at Michigan Tech where she works on nitric oxide-releasing technology.

"Nitric oxide is a powerful healing chemical, but it's not meant to be heavy-handed," Frost says. "We're looking at the profiles of healthy and diabetic cells to find a more nuanced way to recover wound function."

As a wound heals, three types of skin cells step in. Macrophages are the first responders--and the most widely studied cells--that arrive within 24 hours of damage. Next, fibroblasts arrive, which are like the body's engineers. They help lay down the extracellular matrix that makes it possible for the next cells, keratinocytes, to come in and do the heavy-lifting and rebuilding.

"Wound healing is a complex, cell-mediated symphony of events, progressing through a series of predictable and overlapping stages," Frost and her team write in their Medical Sciences paper. When any part of that orchestra is out of tune, the whole process falls flat. Fibroblasts, which are not as well studied as macrophages in the healing process, are a key instrument and past studies have shown their delayed response in patients with diabetes may be a major factor in slow healing time.

Nitric Oxide vs. Nitrite

That's where nitric oxide steps in, a kind of chemical metronome to get the process back into the right rhythm. But the body's dermal orchestra is not so simple--just as playing a metronome louder and louder isn't necessarily going to make a musician's timing improve, flooding a wound with nitric oxide isn't a cure all.

"The old approach is to add nitric oxide and sit back to see if it works," Frost says. "What we're finding is that it's not enough to apply and leave; we have to keep tabs on how much nitric oxide is actually needed."

A big problem that Frost and her team address is how nitric oxide is measured in the first place. Current practice substitutes measuring nitrite for nitric oxide--a misleading switch, Frost says, because nitrite is a byproduct with no time signature. While stable nitrite is easier to measure, by itself it cannot relay the real-time healing status like nitric oxide levels can.

So, Frost's lab built a nitric oxide-measuring device for their study by hand. That creates a challenge since it means taking measurements is much harder, which limits the dataset size, but Frost has an agreement with Zysense, LLC to streamline the building process and produce commercial nitric oxide measurement devices that would improve their research.

Next Steps

Collaboration is a key part of the engineering design process. To build a nitric oxide bandage with personalized healing power, the team plans to work next with the UP Portage Health System to gather cell samples from local patients. By expanding their cell samples--and applying the tech to real-world patients--the team will continue to broaden their database while deepening their knowledge of nitric oxide mechanisms.

In a few years, they plan to have a working bandage prototype, one that leaves off the clunky nitrite proxies and nitric oxide dumps. Instead, patients dealing with diabetic foot ulcers will see a light at

the end of the tunnel much sooner than half a year or more--the nitric oxide-releasing bandage could help heal one of healthcare's toughest diseases in less than a month.

http://bit.ly/2DINxNy

Weightlifting is good for your heart and it doesn't take much

You don't have to invest a lot of time lifting weights to lower your risk for cardiovascular disease.

AMES, Iowa - Lifting weights for less than an hour a week may reduce your risk for a heart attack or stroke by 40 to 70 percent, according to a new Iowa State University study. Spending more than an hour in the weight room did not yield any additional benefit, the researchers found.

"People may think they need to spend a lot of time lifting weights, but just two sets of bench presses that take less than 5 minutes could be effective," said DC (Duck-chul) Lee, associate professor of kinesiology.

The results - some of the first to look at resistance exercise and cardiovascular disease - show benefits of strength training are independent of running, walking or other aerobic activity. In other words, you do not have to meet the recommended guidelines for aerobic physical activity to lower your risk; weight training alone is enough. The study is published in Medicine and Science in Sports and Exercise.

Lee and his colleagues analyzed data of nearly 13,000 adults in the Aerobics Center Longitudinal Study. They measured three health outcomes: cardiovascular events such as heart attack and stroke that did not result in death, all cardiovascular events including death and any type of death. Lee says resistance exercise reduced the risk for all three.

"The results are encouraging, but will people make weightlifting part of their lifestyle? Will they do it and stick with it? That's the million-dollar question," Lee said.

Barriers to resistance training

The researchers recognize that unlike aerobic activity, resistance exercise is not as easy to incorporate into our daily routine. Lee says people can move more by walking or biking to the office or taking the steps, but there are few natural activities associated with lifting. And while people may have a treadmill or stationary bike at home, they likely do not have access to a variety of weight machines.

For these reasons, Lee says a gym membership may be beneficial. Not only does it offer more options for resistance exercise, but in a previous study Lee found people with a gym membership exercised more. While this latest study looked specifically at use of free weights and weight machines, Lee says people will still benefit from other resistance exercises or any muscle-strengthening activities.

"Lifting any weight that increases resistance on your muscles is the key," Lee said. "My muscle doesn't know the difference if I'm digging in the yard, carrying heavy shopping bags or lifting a dumbbell."

Other benefits of strength training

Much of the research on strength training has focused on bone health, physical function and quality of life in older adults. When it comes to reducing the risk for cardiovascular disease, most people think of running or other cardio activity. Lee says weight lifting is just as good for your heart, and there are other benefits.

Using the same dataset, Lee and his colleagues looked at the relationship between resistance exercise and diabetes as well as hypercholesterolemia, or high cholesterol. The two studies, published in Mayo Clinic Proceedings, found resistance exercise lowered the risk for both.

Less than an hour of weekly resistance exercise (compared with no resistance exercise) was associated with a 29 percent lower risk of developing metabolic syndrome, which increases risk of heart disease, stroke and diabetes. The risk of hypercholesterolemia was 32 percent lower. The results for both studies also were independent of aerobic exercise.

"Muscle is the power plant to burn calories. Building muscle helps move your joints and bones, but also there are metabolic benefits. I don't think this is well appreciated," Lee said. "If you build muscle, even if you're not aerobically active, you burn more energy because you have more muscle. This also helps prevent obesity and provide long-term benefits on various health outcomes."

http://bit.ly/2BdYswm

So, you think you're good at remembering faces, but terrible with names?

New research has revealed we are actually better at remembering names than faces

With the Christmas party season fast approaching, there will be plenty of opportunity to re-live the familiar, and excruciatingly-awkward, social situation of not being able to remember an acquaintance's name.

This cringe-worthy experience leads many of us to believe we are terrible at remembering names.

However, new research has revealed this intuition is misleading; we are actually better at remembering names than faces.

The authors of the study, from the University of York, suggest that when we castigate ourselves for forgetting someone's name we are placing unfair demands on our brains.

Remembering a person's face in this situation relies on recognition, but remembering their name is a matter of recall, and it is already well-established that human beings are much better at the former than the latter.

The researchers also point out that we only become aware that we have forgotten a name when we have already recognised the face.

We rarely have to confront the problem of knowing a name, but not a face - remaining blissfully unaware of the countless faces we should recognise, but walk straight past on the street.

For the study, the researchers designed a "fair test", pitting names against faces on a level playing field.

They set up an experiment to place equal demands on the ability of participants to remember faces and names by testing both in a game of recognition.

The results showed participants scored consistently higher at remembering names than faces - recognising as little as 64% of faces and up to 83% of names in the tests.

Dr Rob Jenkins, from the Department of Psychology at the University of York, said: "Our study suggests that, while many people may be bad at remembering names, they are likely to be even worse at remembering faces. This will surprise many people as it contradicts our intuitive understanding.

"Our life experiences with names and faces have misled us about how our minds work, but if we eliminate the double standards we are placing on memory, we start to see a different picture."

For the study, participants were given an allotted period of time to memorise unknown faces and names and then tested on which ones they thought they had seen before.

The researchers then repeated the test, but this time they complicated the experiment by showing participants different images of the same faces and the names in different typefaces. This was to make the test as realistic as possible, as real faces appear slightly differently, due to factors such as lighting and hairstyle, each time you see them.

On average, participants recognised 73% of faces when shown the same photo and 64% when shown a different photo. On the other

hand, they recognised 85% of names presented in the same format and 83% in different fonts and sizes.

When the researchers presented faces and names of famous people, participants achieved a much more balanced score - recognising a more or less the same number of faces as they did names.

The results show that we are particularly bad at recognising unknown faces, but even with faces and names we have encountered before, we still don't perform better at recognising faces than names at any point. Dr Jenkins added: "Knowing someone's face, but not remembering their name is an everyday phenomenon.

Our knee-jerk reaction to it is to say that names must be harder to memorise than faces, but researchers have never been able to come up with a convincing explanation as to why that might be. This study suggests a resolution to that problem by showing that it is actually a red herring in the first place."

I recognise your name, but I can't remember your face: an advantage for names in recognition memory is published in the Quarterly Journal of Experimental Psychology.

The research was funded by the European Research Council and the Economic and Social Research Council, UK.

http://bit.ly/2FtAhOo

Ears Grown From Apples? The Promise of Plants for Engineering Human Tissue

Inspiration for game-changing science can seemingly come from anywhere.

By Shelly Fan

Inspiration for game-changing science can seemingly come from anywhere. A moldy bacterial plate gave us the first antibiotic, penicillin. Zapping yeast with a platinum electrode led to a powerful chemotherapy drug, cisplatin.

For Dr. Andrew Pelling at the University of Ottawa, his radical idea came from a sci-fi cult classic called *The Little Shop of Horrors*. Specifically, he was intrigued by the movie's main antagonist, a man-eating plant called Aubrey 2.

What you have here is a plant-like creature with mammalian features, said Pelling at the Exponential Medicine conference in San Diego last week. "So we started wondering: can we grow this in the lab?"

Pelling's end goal, of course, isn't to bring a sci-fi monster to life. Rather, he wanted to see whether grocery-store-bought plants can supply the necessary structure for engineering replacement human tissues.

The Rise of Mechanobiology

Growing a human ear out of apples may seem irrational, but Pelling's key insight is that an apple's fibrous interior is strikingly similar to the microenvironments usually used in labs to bio-engineer human tissue.

To fabricate a replacement ear, for example, scientists normally carve or 3D print hollow support structures out of expensive bio-compatible materials. They then seed human stem cells into the structure, and painstaking supply a cocktail of growth factors and nutrients to urge the cells to grow. Eventually, after weeks and months of incubation, the cells spread and differentiate into skin-like cells on the scaffold. The result is a bio-engineered replacement ear.

The problem? The extremely high bar to entry: stem cells, growth factors, and materials for the scaffold are all difficult and expensive to procure.

But are those key components *really* necessary?

"We often think about biology through the lenses of the genome or biochemistry," said Pelling. But cells and tissue are living components—they stretch, compress, and shear, producing mechanical forces that act upon each other.

In a series of experiments, Pelling and others found that these mechanical forces aren't just a side product of biology; rather, they

seem to crucially regulate the underlying molecular machinery of the cell.

An early study found that every stage of the growth of embryos—a "fundamental process in biology"—can be regulated and controlled by mechanical information. In other words, physical forces can drive cells to divide and migrate through tissues as our genetic code guides the formation of an *entire* body.

In the lab, stretching and mechanically stimulating the cells seems to fundamentally change their behaviors, too. In one assay, Pelling's team peppered cancerous cells onto a sheet of skin cells grown on the bottom of a Petri dish. The cancer cells huddled together into little balls, forming a distinct barrier between the microtumor and the skin cells.

But when the team put the entire cellular system into a device that minutely stretches it—mimicking the body's breathing and movement—the tumor cells became aggressive, tunneling into the layer of skin cells.

"There's no gene modification…or biochemistry going on here. This is a purely mechanical influence," said Pelling. "There's a fundamental link between these things."

Even cooler: active movement isn't necessary for mechanical forces to transform the way cells behave. The shape of their microenvironment is enough to direct their actions.

For example, when Pelling put two cell types into a physical structure with grooves, the cells self-segregated within hours, with one type growing in the troughs and the other on the higher ledges. By simply sensing the shape of that grooved surface they "learned" to separate and spatially pattern over long ranges.

The takeaway: using shape alone, it's possible to stimulate cells to form complex three-dimensional patterns.

Here's where the apple comes in.

Apple of My…Ear?

Under the microscope, the microenvironment of an apple is on the same length scale as engineered surfaces for fabricating replacement tissues. That discovery got the team to wonder: is it possible to exploit that surface pattern of plants to grow human organs?

To test it out, they took an apple and washed away all its plant cells, DNA, and other biomolecules. This left them with a fibrous scaffold—the stuff that usually gets stuck in your teeth. When the team stuck human and animal cells inside, the cells began to grow and spread.

Encouraged, the team then hand-carved an apple into the shape of a human ear and repeated the process above. Within weeks the cells infiltrated, turning the chunk of apple into a fleshy human ear.

Of course, having the right shape isn't enough. The replacement tissue also has to survive inside the body.

The team next implanted an apple-based scaffold directly under the skin of a mouse. In just eight weeks, not only had the mouse's healthy cells invaded the matrix, the rodent's body also produced new collagen and blood vessels that helped keep the scaffold living and healthy.

That ticks three important aspects for an engineered tissue: it's safe, it's biocompatible, and it comes from a sustainable, ethical source.

"This thing is becoming a living part of the body and it used to be an apple, and we did this by going to the grocery store," said Pelling.

Moving Into the Clinical Space

Pelling is especially excited by his finding because of its simplicity: it doesn't require stem cells or exotic growth factors to work. The elegant approach exploits the physical structure of the plant.

The team is now broadening its work to three main areas of tissue engineering: soft tissue cartilage, bone, and spinal cord and nerve repair. The key is to match the specific microstructure of a plant to that of the tissue, Pelling explained.

“It’s really exciting to see these kinds of wild ideas translate this way,” he said.

And why restrict ourselves to the body parts nature gave us? If the shape of a scaffold is the sole determinant of engineering a tissue or organ, why not design our own?

Pelling took the idea and ran with it, commissioning a design company to sketch out the scaffold for three different types of ears: an average human ear, a pointy Spock-shaped one, and a wavy one designed to suppress or enhance different frequencies to—in theory—augment hearing.

“The point I want to emphasize is…the strength of blue-sky thinking is actually coupling it to the rigor of the scientific method,” Pelling concluded. Ultimately this is how we’ll create more dinventions and solve problems.

http://bit.ly/2zeQO39

Super-Earth discovered around the second nearest stellar system

The exoplanet orbits the red dwarf Barnard, the closest star to the Sun after the Alpha Centauri system

Just six light-years away, Barnard's star moves in Earth's night sky faster than any other star. This red dwarf, smaller and older than our Sun, is among the least active red dwarfs known, so it represents an ideal target to search for exoplanets. Now, an international team led by researchers from the Spanish National Research Council (CSIC) has found a cold Super-Earth orbiting around the Barnard´s star, the second closest star system to Earth. It is the first time that astronomers have discovered this type of exoplanet using the radial velocity method. The results of the study are published in the journal Nature.

"After a very careful analysis, we are over 99% confident that the planet is there, since this is the model that best fits our observations", assures the leader of the study, Ignasi Ribas, CSIC researcher at the Space Sciences Institute (ICE) and the Institute of Space Studies of Catalonia (IEEC). "However, we must remain cautious and collect more data to nail the case in the future, because natural variations of the stellar brightness resulting from starspots can produce similar effects to the ones detected".

A Subtle Stellar Wobble

The subtle wobble of the star has caught the attention of astronomers for some time. Since 1997 several instruments have collected a large number of measurements on that oscillation movement. A 2015 analysis suggested that the wobble could be caused by a planet with an orbital period of about 230 days. But more measurements were required.

Attempting to confirm the hypothesis, astronomers have regularly observed the Barnard´s star with high precision spectrometers such as CARMENES, at Calar Alto Observatory. The technique consists on using the Doppler effect on the starlight to measure how the speed of an object in our line of sight changes over time.

"With the radial velocity method, precision spectrometers are used to measure the Doppler effect. When an object moves away from us, the light we observe becomes slightly less energetic and redder. On the contrary, when the star approaches us, the light becomes more energetic and bluish", says Ribas.

"When we re-analyzed all the combined measurements, a clear signal arose at a period of 233 days. This signal implies that the Barnard´s star approaches and moves away from us at about 1.2 meters per second - approximately the walking speed of a person - and it is best explained by a planet orbiting it", says Ribas .

The planet candidate, called Barnard's star b (or GJ 699 b), is a super-Earth with a minimum of 3.2 Earth masses. It orbits its red star every 233 days near the snow-line, a distance where water freezes. Lacking atmosphere, its temperature is likely to be about -170ºC, which

makes it unlikely that the planet can sustain liquid water on the surface.

"Exoplanets so small and so far away from their parent star have not been discovered before using the Doppler technique", says Ribas. This means that astronomers are getting better at finding and exploring a relatively new kind of planets outside our Solar System.

"We all have worked very hard on this result", says Guillem Anglada-Escudé from Queen Mary University of London and co-leader of the study. "This is the result of a large collaboration organised in the context of the Red Dots project, which is why it has contributions from teams all over the world including semi-professional astronomers coordinated by the AAVSO".

Cristina Rodríguez-López, researcher at the Institute of Astrophysics of Andalusia (IAA-CSIC) and co-author of the paper, comments on the significance of this finding. "This discovery means a boost to continue on searching for exoplanets around our closest stellar neighbours, in the hope that eventually we will come upon one that has the right conditions to host life".

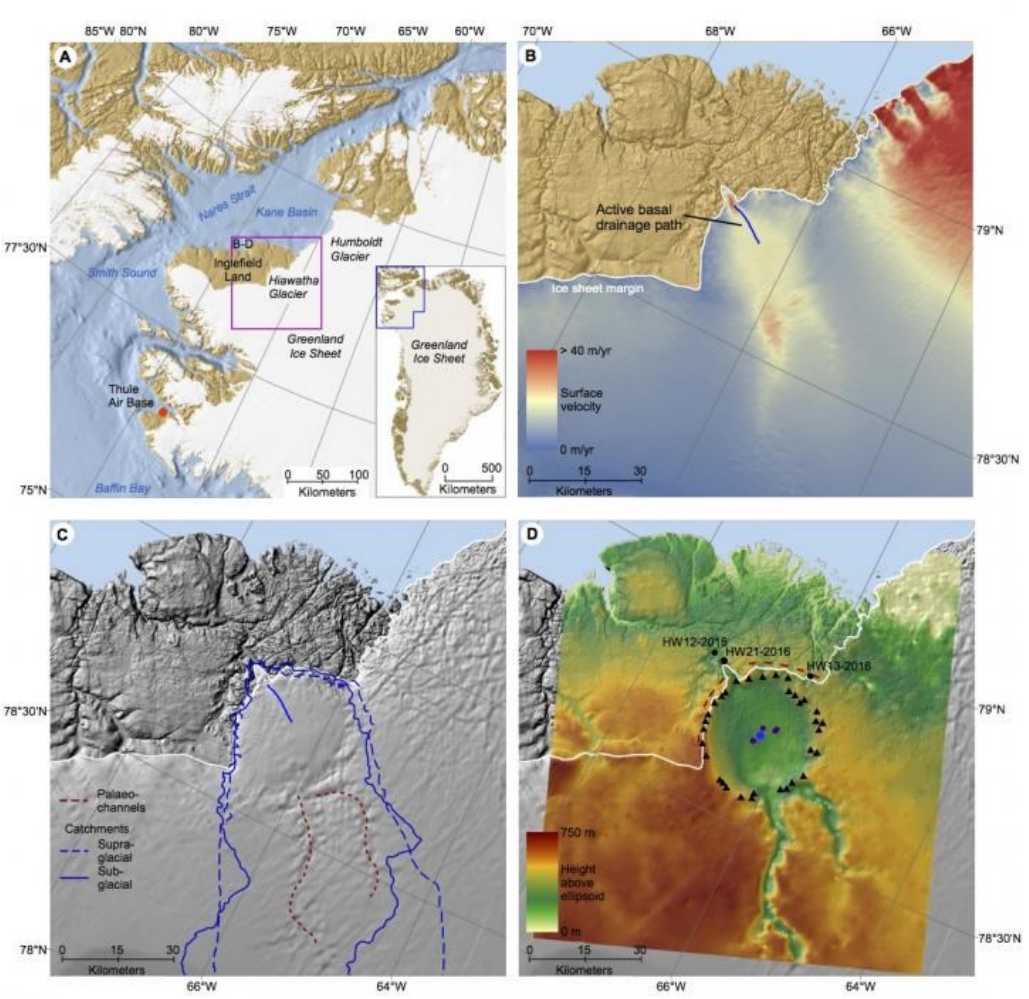
http://bit.ly/2Q3xTCd

Huge crater discovered in Greenland from impact that rocked Northern Hemisphere

Kilometer-wide iron asteroid slammed into Greenland perhaps as recently as 12,000 years ago

LAWRENCE -- A survey of ice in Greenland has uncovered evidence suggesting a kilometer-wide iron asteroid slammed into that island, perhaps as recently as 12,000 years ago during the end of the Pleistocene. The resulting 19-mile-wide impact crater has remained hidden under a half-mile-thick ice sheet until now. It recently was exposed by an ultra-wideband chirp radar system developed at the Center for the Remote Sensing of Ice Sheets (CReSIS) headquartered at the University of Kansas.

The impact crater beneath the Hiawatha Glacier in remote northwest Greenland is detailed in a new paper in Science Advances published today.



Inset map shows location relative to whole of Greenland. Magenta box identifies location of panels B-D. (B) 5-m ArcticDEM mosaic over eastern Inglefield Land. Colors are ice surface velocity. Blue line illustrates an active basal drainage path inferred from radargrams. (C) Hillshade surface relief based on the ArcticDEM mosaic which illustrates characteristics such as

surface undulations. Dashed red lines are the outlines of the two subglacial paleo-channels. Blue lines are catchment outlines, i.e., solid blue line is subglacial and hatched is supraglacial. (D) Bed topography based on airborne radar sounding from 1997-2014 NASA data and 2016 AWI data. Black triangles represent elevated rim picks from the radargrams and the dark purple circles represent peaks in the central uplift. Hatched red lines are field measurements of the strike of ice-marginal bedrock structures. Black circles show location of the three glaciofluvial sediment. **University of Kansas**

It was identified with data collected between 1997 and 2014 by KU for NASA's Program for Arctic Regional Climate Assessment and Operation IceBridge, and supplemented with more data collected in May 2016 using the Multichannel Coherent Radar Depth Sounder (MCoRDS) developed at KU.

"We've collected lots of radar-sounding data over the last couple of decades, and glaciologists put these radar-sounding datasets together to produce maps of what Greenland is like underneath the ice," said co-author John Paden, courtesy associate professor of electrical engineering & computer science at KU and associate scientist at CReSIS. "Danish researchers were looking at the map and saw this big, craterlike depression under the ice sheet and looked at satellite imagery and -- because the crater is on edge of the ice sheet -- you can see a circular pattern there as well. The two combined made a really strong case for this being an impact-crater site. Based on this discovery, a detailed radar survey was conducted in May 2016 using a new state-of-the-art radar designed and built by KU for the Alfred Wegener Institute in Germany."

Paden, who helped develop the MCoRDS radar signal processing software, participated in low-altitude flights in a grid pattern over the impact crater to detail its dimensions.

"You can see the rounded structure at the edge of the ice sheet, especially when flying high enough," he said. "For the most part the crater isn't visible out the airplane window. It's funny that until now nobody thought, 'Hey, what's that semicircular feature there?' From the airplane it is subtle and hard to see unless you already know it's there. Using satellite imagery taken at a low sun angle that accentuates hills and valleys in the ice sheet's terrain -- you can really see the circle of the whole crater in these images."

To confirm the satellite and radar findings, the research team performed subsequent ground-based studies of glaciofluvial sediment from the largest river draining the crater. The work showed the presence of "shocked quartz and other impact-related grains" that include glass. The research team believes these rocks and glassy grains are likely produced from impact melting of grains in the meta-sedimentary bedrock.

Work remains to determine with more precision the timing of the asteroid impact on Greenland. The authors write evidence "suggests that the Hiawatha impact crater formed during the Pleistocene, as this age is most consistent with inferences from presently available data." However, even this broad range in time remains "uncertain." Southwest of the crater, the team has found a region rich in possible debris ejected from the impact, which could help to narrow the date range.

"There would have been debris projected into the atmosphere that would affect the climate and the potential for melting a lot of ice, so there could have been a sudden freshwater influx into the Nares Strait between Canada and Greenland that would have affected the ocean flow in that whole region," Paden said. "The evidence indicates that the impact probably happened after the Greenland Ice Sheet formed, but the research team is still working on the precise dating."

Other KU personnel involved in the research that revealed the impact crater include Rick Hale, Spahr Professor and chair of the Department of Aerospace Engineering and associate director of CReSIS; Carl Leuschen, associate professor of electrical engineering & computer science and director of CReSIS, and Fernando

Rodriguez-Morales, courtesy assistant professor of electrical engineering & computer science. The KU researchers collaborated closely with colleagues from the University of Copenhagen and the Alfred Wegener Institute in Germany.

Paden said during the three years between the crater discovery and publication of the team's findings, it was gratifying and exciting to be part of the exclusive group of scientists that knew of the massive impact.

"It was really cool -- it was the kind of thing where I went home and told my kids about it," Paden said. "I said, 'Look at this! It's underneath the ice.' It's one of those fun moments. They were impressed. A lot of times, my research isn't that interesting to them, but this impact crater was something they could connect to."

Geomorphological and glaciological setting of Hiawatha Glacier, northwest Greenland. (A) Regional view of northwest Greenland.

http://bit.ly/2RZzrKS

Human evolution is still happening – possibly faster than ever

The rate of human DNA's evolution shows that human evolution hasn't stopped

Laurence D. Hurst *

Modern medicine's ability to keep us alive makes it tempting to think human evolution may have stopped. Better healthcare disrupts a key driving force of evolution by keeping some people alive longer, making them more likely to pass on their genes. But if we look at the rate of our DNA's evolution, we can see that human evolution hasn't stopped – it may even be happening faster than before.

Evolution is a gradual change to the DNA of a species over many generations. It can occur by natural selection, when certain traits created by genetic mutations help an organism survive or reproduce. Such mutations are thus more likely to be passed on to the next generation, so they increase in frequency in a population. Gradually, these mutations and their associated traits become more common among the whole group.

By looking at global studies of our DNA, we can see evidence that natural selection has recently made changes and continues to do so. Though modern healthcare frees us from many causes of death, in countries without access to good healthcare, populations are continuing to evolve. Survivors of infectious disease outbreaks drive natural selection by giving their genetic resistance to offspring. Our DNA shows evidence for recent selection for resistance of killer diseases like Lassa fever and malaria. Selection in response to malaria is still ongoing in regions where the disease remains common.

Humans are also adapting to their environment. Mutations allowing humans to live at high altitudes have become more common in populations in Tibet, Ethiopia, and the Andes. The spread of genetic mutations in Tibet is possibly the fastest evolutionary change in humans, occurring over the last 3,000 years. This rapid surge in frequency of a mutated gene that increases blood oxygen content gives locals a survival advantage in higher altitudes, resulting in more surviving children.

Diet is another source for adaptations. Evidence from Inuit DNA shows a recent adaptation that allows them to thrive on their fat-rich diet of Arctic mammals. Studies also show that natural selection favouring a mutation allowing adults to produce lactase – the enzyme that breaks down milk sugars – is why some groups of people can digest milk after weaning. Over 80% of north-west Europeans can, but in parts of East Asia, where milk is much less commonly drunk, an inability to digest lactose is the norm. Like high altitude adaptation, selection to digest milk has evolved more than once in humans and may be the strongest kind of recent selection.

We may well be adapting to unhealthy diets too. One study of family genetic changes in the US during the 20th century found selection for

reduced blood pressure and cholesterol levels, both of which can be lethally raised by modern diets.

Yet, despite these changes, natural selection only affects about 8% of our genome. According to the neutral evolution theory, mutations in the rest of the genome may freely change frequency in populations by chance. If natural selection is weakened, mutations it would normally purge aren't removed as efficiently, which could increase their frequency and so increase the rate of evolution.

But neutral evolution can't explain why some genes are evolving much faster than others. We measure the speed of gene evolution by comparing human DNA with that of other species, which also allows us to determine which genes are fast-evolving in humans alone. One fast-evolving gene is human accelerated region 1 (HAR1), which is needed during brain development. A random section of human DNA is on average more than 98% identical to the chimp comparator, but HAR1 is so fast evolving that it's only around 85% similar.

Though scientists can see these changes are happening – and how quickly – we still don't fully understand why fast evolution happens to some genes but not others. Originally thought to be the result of natural selection exclusively, we now know this isn't always true.

Recently attention has focused on the process of biased gene conversion, which occurs when our DNA is passed on via our sperm and eggs. Making these sex cells involves breaking DNA molecules, recombining them, then repairing the break. However, molecular repairs tend to happen in a biased manner.

DNA molecules are made with four different chemical bases known as C, G, A and T. The repair process prefers to make fixes using C and G bases rather than A or T. While unclear why this bias exists, it tends to cause G and C to become more common.

Increases in G and C at DNA's regular repair sites causes ultrafast evolution of parts of our genome, a process easily mistaken for natural selection, since both cause rapid DNA change at highly localised sites. About a fifth of our fastest evolving genes, including HAR1, have been affected by this process. If the GC changes are harmful, natural selection would normally oppose them. But with selection weakened, this process could largely go unchecked and could even help speed up our DNA's evolution.

The human mutation rate itself may also be changing. The main source of mutations in human DNA is the cell division process that creates sperm cells. The older males get, the more mutations occur in their sperm. So if their contribution to the gene pool changes – for example, if men delay having children – the mutation rate will change too. This sets the rate of neutral evolution.

Realising evolution doesn't only happen by natural selection makes it clear the process isn't likely to ever stop. Freeing our genomes from the pressures of natural selection only opens them up to other evolutionary processes – making it even harder to predict what future humans will be like. However, it's quite possible that with modern medicine's protections, there will be more genetic problems in store for future generations.

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Disclosure statement

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https://wb.md/2OPoPfq

Brain Inflammation Seen for First Time in Fibromyalgia

Researchers have reported for the first time that they have found inflammation in the brains of patients with fibromyalgia.

Marcia Frellick

Daniel S. Albrecht, PhD, a postdoctoral fellow with the Department of Radiology at Massachusetts General Hospital, and Harvard Medical School, Boston, and colleagues, joined with a research team led by Anton Forsberg, PhD, of the Department of Clinical Neuroscience at the Karolinska Institute in Stockholm, Sweden, to broaden generalizability and boost statistical power of the study.

The researchers write that although there has been mounting evidence that brain inflammation plays some role in fibromyalgia, this research is the first to show direct evidence of brain glial activation in the poorly understood and difficult-to-treat chronic condition.

The findings were published online September 14 in *Brain, Behavior, and Immunity*.

In a news release, study coauthor Marco Loggia, PhD, from the Martinos Center for Biomedical Imaging, Massachusetts General Hospital, explains, "The activation of glial cells we observed in our studies releases inflammatory mediators that are thought to sensitize pain pathways and contribute to symptoms such as fatigue."

The evidence may open the door to new treatments and give comfort to those who have been told their symptoms are psychological.

"We don't have good treatment options for fibromyalgia, so identifying a potential treatment target could lead to the development of innovative, more effective therapies. And finding objective neurochemical changes in the brains of patients with fibromyalgia should help reduce the persistent stigma that many patients face, often being told their symptoms are imaginary and there's nothing really wrong with them."

A group of 31 patients who met the American College of Rheumatology definition for fibromyalgia diagnosis (29 women, average age 50.7 ± 11 years old) and 27 healthy controls (25 women, average age 49.4 ± 11 years old) received a hybrid magnetic resonance/positron-emission tomography (MR/PET) brain scan. The study excluded patients with fibromyalgia if they had any pain conditions other than fibromyalgia.

Using the imaging results, researchers found higher levels of the glial marker TSPO, a translocator protein, in several regions of the brain in patients with fibromyalgia relative to healthy controls. They also found that the degree of glial activation was related to the degree of fatigue the patients reported.

"Overall, our data support glial modulation as a potential therapeutic strategy," the authors write.

Fibromyalgia affects about 4 million US adults, according to the Centers for Disease Control and Prevention.

The study was supported by the International Association for the Study of Pain, Martinos Center Pilot Grant for Postdoctoral Fellows, and Harvard Catalyst Advance Imaging Pilot. The Swedish part of the study received funding from Stockholm County Council, Swedish Research Council, Swedish Rheumatism Association, and Fibromyalgiförbundet. The study was also funded by the European Union Seventh Framework Programme and a donation from the Lundblad family. The authors have disclosed no relevant financial relationships.

Brain Behav Immun. Published online September 14, 2018. Full text

http://bit.ly/2DrpmCa

The first rains in centuries in the Atacama Desert devastate its microbial life

These recent rains are attributed to changing climate over the Pacific Ocean

The Atacama Desert, the driest and oldest desert on Earth, located in northern Chile, hides a hyper-arid core in which no rain has been recorded during the past 500 years. But this situation has changed in the last three years: for the first time, rainfall has been documented in the hyper-arid core of the Atacama and, contrary to what was expected, the water supply has caused a great devastation among local life. This is the main conclusion of an international study, published today in *Scientific Reports* and entitled "Unprecedented rains decimate surface microbial communities in the hyperarid core of the Atacama Desert", and directed by researchers from the Center for Astrobiology (CAB), a mixed center of the Spain's Higher Council for Scientific Research (CSIC) and the National Institute of Aerospace Technology (INTA). These recent rains are attributed to changing climate over the Pacific Ocean.

"Our group has discovered that, contrary to what could be expected intuitively, the never-before-seen rainfall has not triggered a flowering of life in Atacama, but instead the rains have caused enormous devastation in the microbial species that inhabited the region before the heavy precipitations", explains Dr. Alberto G. Fairén.

"Our work shows that high rainfall has caused the massive extinction of most indigenous microbial species. The extinction range reaches 85%, as a result of the osmotic stress that has caused the sudden abundance of water: the autochthonous microorganisms, which were perfectly adapted to thrive under conditions of extreme dryness and had strategies optimized for the extraction of the scarce humidity of their environment, have been unable to adapt to the new conditions of sudden flooding and have died from excess water", adds Fairén.

From Atacama to Mars

This study represents a great advance to understand the microbiology of extremely arid environments. It also presents a new paradigm to decode the evolutionary path of a hypothetical early microbiota of Mars, since Mars is a hyper-arid planet that experienced catastrophic floods in ancient times.

"Mars had a first period, the Noachian (between 4.5 and 3.5 billion years ago), in which there was a lot of water on its surface," says Fairén. "We know this from the enormous amount of hydrogeological evidence still present in the Martian surface, in the form of ubiquitous hydrated minerals, traces of dried rivers and lakes, deltas, and perhaps a hemispheric ocean in the northern plains," explains Fairén.

Mars eventually lost its atmosphere and its hydrosphere, and became the dry and arid world we know today. "But at times during the Hesperian period (from 3.5 to 3 billion years ago), large volumes of water carved its surface in the form of outflow channels, the largest channels in the Solar System. If there were still microbial communities withstanding the process of extreme drying, they would have been subjected to processes of osmotic stress similar to those we have studied in Atacama", Fairén details.

"Therefore, our Atacama study suggests that the recurrence of liquid water on Mars could have contributed to the disappearance of Martian life, if it ever existed, instead of representing an opportunity for resilient microbiota to bloom again", adds Fairén.

In addition, this new study notes that large deposits of nitrates at the Atacama Desert offer evidence of long periods of extreme dryness in the past. The nitrates were concentrated at valley bottoms and former lakes by sporadic rains about 13 million years ago, and can be food for microbes. The Atacama nitrates may represent a convincing analog to the nitrate deposits recently discovered on Mars by the rover Curiosity (and reported in a 2015 study entitled "Evidence for indigenous martian nitrogen in solid samples from the Curiosity rover investigations at Gale crater", in the Proceedings of the National Academy of Sciences). Earlier this year, Fairén and colleagues discovered that short-term wetter environments in early Mars, occurring sporadically in a generally hyperdry early planet, explains the observed martian mineralogy.

This study, entitled "Surface clay formation during short-term warmer and wetter conditions on a largely cold ancient Mars", was published in February in Nature Astronomy. "These long periods of dryness, followed by short-term wetter conditions, may also be in the origin of the nitrate deposits on Mars", concludes Fairén.

Fairén's work was funded by the European Research Council.

http://bit.ly/2r0rSrX

Drug combination makes cancer disappear in mice with neuroblastoma

'Significant' findings suggest potential for effective, non-toxic treatment for this aggressive childhood cancer

Dublin, Ireland: Researchers investigating new treatments for neuroblastoma - one of the most common childhood cancers - have found that a combination of two drugs made tumours disappear in mice, making it more effective than any other drugs tested in these animals.

Professor Murray Norris, deputy director of the Children's Cancer Institute Australia for Medical Research, Sydney, Australia, told the 30th EORTC-NCI-AACR [1] Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland, today (Thursday) that the findings were unusual and highly significant. But he warned that it would be some time before the drug combination would be tested in children and, if successful, made available more widely to treat children with this disease, even though both drugs are currently undergoing clinical trial in a range of adult cancers.

Neuroblastoma is one of the most common childhood cancers and is the leading single cause of cancer deaths in children under five. It is frequently found in the adrenal glands on top of the kidneys. Despite using intensive treatment regimens, children with the most aggressive forms of neuroblastoma have less than 50% survival rates.

Prof Norris said: "To study neuroblastoma in the laboratory, we use a genetically modified neuroblastoma mouse model that closely recapitulates clinical features of the disease, and these mice spontaneously develop neuroblastomas within weeks after birth. We have found that when we combined CBL0137 and panobinostat to treat mice bearing neuroblastomas, the tumours disappeared and never came back during the entire experiment, whereas the tumours continued to grow in mice that received either no treatment or only single drug treatment.

"This is a highly significant finding as this drug combination is the most effective therapy that we have observed in this neuroblastoma mouse model. It is unusual to see this effect, especially in these mice where neuroblastoma develops within seven weeks of birth and is aggressive in nature. In fact, the CBL0137/panobinostat combination is more effective than any other current clinical chemotherapy combinations that our laboratory has tested in these mice."

CBL0137, which belongs to a new class of drugs called curaxins, attacks the structure of cancer cells but is a safe drug that does not damage DNA in normal cells. Prof Norris and his colleagues used RNA sequencing technology that can detect drug-induced changes in tumours, to see how the combination of CBL0137 and panobinostat stopped neuroblastoma growing.

"Our results suggest that these drugs work through two different mechanisms that offer a two-pronged attack. One of these mechanisms appears to be a direct attack on the cancer cells themselves, killing them by inhibiting DNA repair; then a second mechanism is involved in inducing a robust immune response. This is very exciting and will hopefully facilitate the clinical development of effective and non-toxic therapies for childhood cancer," he said.

"Unlike conventional chemotherapy drugs that interact with DNA, CBL0137 is non-DNA damaging and therefore is comparatively less toxic. Developing CBL0137 combination therapies has the potential to reduce acute and long-term side effects and increase the quality of life of children with cancer while extending the survival rates of these children. Another important implication is that the CBL0137/panobinostat combination can activate an immune response which may significantly boost the efficacy of immunotherapy drugs that are otherwise ineffective for neuroblastoma."

The researchers are continuing their laboratory work to investigate further how the combination of these two drugs activates the immune response, and to test CBL0137/panobinostat with other immunotherapy drugs in mice. A phase I clinical trial of CBL0137 in children with neuroblastoma and other difficult-to-treat childhood cancers is planned to start in 2019, following the completion of a

phase I clinical trial of the drug in adults with solid cancers and previously treated blood cancers. The trial of CBL0137 alone in children will need to be completed successfully before a trial testing the combination of the two drugs can be planned, which means it will be a few years before it is known whether the treatment can be used more widely.

Further lab research by Prof Norris and his colleagues also showed that CBL0137 and panobinostat slowed the growth of aggressive childhood leukaemias in mice and significantly extended survival.

In addition to approving CBL0137 for phase I clinical trials in adults, the FDA has already approved panobinostat for multiple myeloma and it is being tested in clinical trials for a range of other cancers.

Co-chair of the EORTC-NCI-AACR Symposium, Dr James L. Gulley, who is Director of the Medical Oncology Service at the NIH / NCI Center for Cancer Research in the USA, and who is an expert in cancer immunotherapy but was not involved in this research, commented: "Although these are results from work conducted in mice, they are very interesting and suggest the exciting possibility that this drug combination might work more effectively than single agents in children with this rare but aggressive tumour. These are patients who desperately need better treatments. We await the results of the clinical trials with interest."

[1] EORTC [European Organisation for Research and Treatment of Cancer, NCI [National Cancer Institute], AACR [American Association for Cancer Research].

https://wb.md/2Q3kdXP

New Drug Option Fails for Rare Polio-Like Virus in Kids

Fluoxetine failed to improve outcomes in children with EV D68–associated acute flaccid myelitis, and in some cases was associated with worsening

Damian McNamara

Despite initial hope, the antidepressant fluoxetine (multiple brands) failed to improve outcomes in children with enterovirus (EV) D68–associated acute flaccid myelitis (AFM), and in some cases was associated with a worsening of the rare disorder. AFM can cause permanent paralysis in children.

Encouraged by preclinical research suggesting the drug may have some benefit in AFM, investigators found that the medication was well tolerated but that there was no signal of efficacy.

"The lack of an efficacy signal for the treatments for acute flaccid myelitis evaluated in this study emphasizes the need for development and prospective evaluation of more effective treatment and prevention strategies for this potentially devastating condition," study investigator Kevin Messacar, MD, Children's Hospital Colorado in Aurora said in a statement.

The study was published online November 9 in *Neurology*.

In 2014, 2016, and 2018, clusters of AFM were reported in the United States in association with a widespread outbreak of EV-D68 respiratory disease.

"We quite early knew we didn't have any effective treatment. Steroids didn't really work, plasma exchange didn't work, and some people tried antivirals, and they didn't really work," study coauthor Jay Desai, MD, an attending physician in the Division of Neurology at the Keck School of Medicine of the University of Southern California and a child neurologist at Children's Hospital Los Angeles, told *Medscape Medical News*.

Further complicating matters is the fact that the cause of AFM has not been absolutely established. "We suspect it is enterovirus D68," Desai said. However, he added, presence of enterovirus D68 has not been confirmed in the spinal fluid of those affected. The researchers also note that there could be more than one cause of AFM.

A selective serotonin reuptake inhibitor, fluoxetine is the only available medication approved by the US Food and Drug

Administration that has in vitro antiviral activity against circulating 2014 EV-D68 strains.

"Given the long-term, potentially permanent paralysis associated with AFM, the lack of effective alternative therapies and the possibility of antiviral activity against EV-D68, fluoxetine was proposed as a possible therapeutic agent for AFM," the investigators write. The attitude among the clinician-investigators, said Desai, was, "we should try fluoxetine because we have to try something."

To determine the safety, tolerability, and efficacy of fluoxetine for proven or presumptive EV-D68-associated AFM, the investigators conducted a retrospective observational cohort study of 56 children with AFM in 2015-2016 from 12 centers across the United States. The children ranged in age from 2.5 years to 9 years (median age, 3.8 years).

Study participants met clinical criteria for acute-onset limb weakness or cranial nerve dysfunction. Participants also had MRI evidence of lesions in the gray matter of the spinal cord or motor nuclei of the brainstem. Sign and symptom onset occurred between January 1, 2015, and November 1, 2016. The researchers identified an enterovirus in 24 of 56 patients (43%), most commonly EV-D68 (n = 20, 36%), in respiratory or stool specimens.

At initial examination, the patients' summative limb strength scores (SLSSs) were similar, but the 28 patients who underwent treatment with more than one dose of fluoxetine were more likely to have EV-D68.

In the total cohort, 30% presented with asthma or another underlying medical condition. Almost all, 91%, had a prodromal illness; 71% had fever, and 73% had respiratory symptoms.

Neurologic weakness followed onset of the prodromal condition by a median of 8.5 days. Fever, meningeal signs, and limb pain often accompanied the weakness.

A median of two limbs were involved; 84% of participants had upper extremity weakness, 55% developed lower limb weakness, and 36% had cranial nerve dysfunction.

Patients received all therapies, including fluoxetine, at the discretion of clinical care providers. A total 82% received intravenous immunoglobulin, 59% received corticosteroids, and 14% underwent plasmapheresis.

Clinicians preferentially administered fluoxetine to EV-D68-positive patients. Those who were more severely affected also received fluoxetine because, said Desai, "people were more desperate when kids were getting really ill."

The investigators compared 28 AFM patients who had been treated with more than one dose of fluoxetine to 26 patients who had not receive it. Two children who only received a single dose of the drug were considered part of the untreated group.

The study's primary outcome was change in SLSS in all four limbs between initial presentation and latest follow-up. Possible scores range from 20 (normal strength) to 0 (complete quadriparesis).

The researchers found similar muscle strength at baseline between the group that received fluoxetine and the untreated group, with mean SLSS scores of 12.9 vs 14.3 (P = .31).

A Worsening Effect?

However, the fluoxetine cohort experienced more severe paralysis at nadir (time of maximum muscle weakness: mean SLSS, 9.3 vs 12.8; P = .02) and at the latest follow-up (mean SLSS, 12.5 vs 16.4; P = .005).

In adjusted analyses, the mean change in SLSS at latest follow-up compared with initial examination was 0.2 lower (95% confidence interval [CI], −1.8 to +1.4) in fluoxetine-treated patients compared to 2.5 higher (95% CI, 0.7 - 4.4) in untreated patients (P = .02).

The researchers controlled for age, sex, additional therapies, and strength at baseline examination using propensity-weighted adjustments.

"We did an analysis to control for confounders. The scores were lower, ultimately, for kids treated with fluoxetine. Did this treatment actually make it worse? think it's a possibility," said Desai.

The fluoxetine group experienced a longer length of stay (median, 14 vs 7 days; *P* = .007). Treated patients also were more likely to require care in the intensive care unit (ICU), rehabilitation services, and ventilator and supplemental feeding support compared to untreated patients.

Fluoxetine was well tolerated, with no serious adverse events reported. However, for two participants, the drug was discontinued after a single dose -- one because of perceived anxiety, and another because of weakness not severe enough to warrant further treatment. One participant in the fluoxetine group died. There were no deaths among the untreated patients.

The study had several potential limitations, said Desai. Fluoxetine treatment was initiated a median of 5 days after the onset of neurologic symptoms. However, at this point, most patients had reached their nadir of muscle weakness.

Because the study used retrospective data and had a nonrandomized, open-label design, the evidence is of class level IV. "Despite significant limitations, this study has important implications to inform future therapeutic trials in AFM," the researchers note.

Desai noted that at this point there does not appear to be any other candidate agents for AFM on the horizon.

Leading clinicians and scientists are collaborating on accelerating research and clinical advances in AFM. The Acute Flaccid Myelitis Working Group, based at Johns Hopkins Medicine in Baltimore, for example, holds conference calls several times a week with thought leaders to address diagnosis, etiology, and care for affected children in the ICU setting and after hospital discharge.

Consensus articles to help guide clinicians caring for these patients are forthcoming, said Desai, who is a member of this working group. "If there is going to be another wave of AFM, then we need to be better prepared," he said.

Lost in Translation

Commenting on the findings for *Medscape Medical News*, Emmanuelle Tiongson, MD, a pediatric neurologist at Children's Hospital Los Angeles, who was not affiliated with the study, said fluoxetine was promising, "especially early on" in the research.

"It had a direct antiviral effect on the enterovirus D68, but as is common with a lot of studies that start in the lab, once you take them to people, it doesn't always translate. A lot of agents fail when they get to human studies, because humans are very different from a petri dish or a mouse in the laboratory," she said.

Tiongson also noted that the doses of fluoxetine used in the study were higher than typical antidepressant doses, and because of the potential for side effects, "it would be difficult to justify it, in children especially, unless it was totally proven."

The study was funded by several grants from the National Institutes of Health. Dr Desai has received research support from the Epilepsy Foundation of Greater Los Angeles and funding from Novartis, Neurelis, and UCB. Dr Tiongson has disclosed no relevant financial relationships.

Neurology. Published online November 9, 2018. Abstract

http://bit.ly/2zeZNl0

Surgery & combination therapy optimizes results in aggressive prostate cancer management

Surgery followed by appropriate use of radiation and hormone therapy minimizes the risk of death for men with Gleason Score 9 or 10 prostate cancer; surgery alone not as effective

Boston, MA -- Men presenting with aggressive prostate cancer - Gleason Score of 9 or 10 - comprise most of those who will die from prostate

cancer worldwide, and despite surgical removal of the prostate (radical prostatectomy), their cancer will recur more than 80 percent of the time.

In a new multinational study of 639 men with a Gleason Score of 9 or 10, researchers at Brigham and Women's Hospital investigated how treatment with surgery plus the appropriate use of post-operative, low-dose radiation and hormone therapy, before cancer recurrence, fared as an option for these men. They found that death from prostate cancer within five years following this option or the standard option of high dose radiation and hormone therapy was less than 10 percent likely as compared to 22 percent with surgery alone. Results published today in JAMA Oncology suggest post-operative radiation and hormone therapy, before cancer recurrence, as a new prostate cancer treatment option for men with a Gleason Score of 9 or 10.

"In many cases when cancer recurs, radiation and hormone therapy are recommended, but our findings indicate that the best survival outcomes can be achieved by implementing these therapies directly after surgery and not waiting for the cancer to recur," said Anthony Victor D'Amico, MD, PhD, chief, Genitourinary Radiation Oncology at the Brigham. "While more than 75 percent of men in this study had risk factors for recurrence following surgery for which radiation and hormone therapy could have been recommended, only one-third received those treatments."

A prior study showed that the risk of death is much higher when surgery alone is performed, compared to the risk following the standard treatment option of high dose radiation and hormone therapy. D'Amico points out that the lack of use of radiation and hormone therapy following surgery for men with Gleason Score 9 or 10 prostate cancer is largely due to concern about overtreatment. "However, overtreatment in this population with aggressive and advanced prostate cancer is very unlikely given that prostate cancer will recur in at least 80 percent of these men within five years of surgery and require radiation or hormone therapy at that time," D'Amico said.

Researchers note additional study is needed to determine whether treating these men with post-operative low-dose radiation and hormone therapy before cancer recurrence can produce the low prostate cancer death observed in the study. Given that no randomized trials are available to answer this question specifically for men with Gleason Score 9 or 10 prostate cancer, this is the only evidence to date supporting this new treatment option.

The authors declare no conflicts of interest or relevant funding sources.

http://bit.ly/2FusGiI

Why we shouldn't like coffee, but we do

Weirdly, people with a higher sensitivity to bitter caffeine taste drink more coffee

Bitterness is natural warning system to protect us from harmful substances

People with heightened ability to detect coffee's bitterness learn to associate good things with it

Our genetics affect coffee consumption

CHICAGO --- Why do we like the bitter taste of coffee? Bitterness evolved as a natural warning system to protect the body from harmful substances. By evolutionary logic, we should want to spit it out.

But, it turns out, the more sensitive people are to the bitter taste of caffeine, the more coffee they drink, reports a new study from Northwestern Medicine and QIMR Berghofer Medical Research Institute in Australia. The sensitivity is caused by a genetic variant.

"You'd expect that people who are particularly sensitive to the bitter taste of caffeine would drink less coffee," said Marilyn Cornelis, assistant professor of preventive medicine at Northwestern University Feinberg School of Medicine. "The opposite results of our study suggest coffee consumers acquire a taste or an ability to detect

caffeine due to the learned positive reinforcement (i.e. stimulation) elicited by caffeine."

In other words, people who have a heightened ability to taste coffee's bitterness -- and particularly the distinct bitter flavor of caffeine -- learn to associate "good things with it," Cornelis said.

Thus, a bigger tab at Starbucks.

The study will be published Nov. 15 in Scientific Reports.

In this study population, people who were more sensitive to caffeine and were drinking a lot of coffee consumed low amounts of tea. But that could just be because they were too busy drinking coffee, Cornelis noted.

The study also found people sensitive to the bitter flavors of quinine and of PROP, a synthetic taste related to the compounds in cruciferous vegetables, avoided coffee. For alcohol, a higher sensitivity to the bitterness of PROP resulted in lower alcohol consumption, particularly of red wine.

"The findings suggest our perception of bitter tastes, informed by our genetics, contributes to the preference for coffee, tea and alcohol," Cornelis said.

For the study, scientists applied Mendelian randomization, a technique commonly used in disease epidemiology, to test the causal relationship between bitter taste and beverage consumption in more than 400,000 men and women in the United Kingdom. The genetic variants linked to caffeine, quinine and PROP perception were previously identified through genome-wide analysis of solution taste-ratings collected from Australian twins. These genetic variants were then tested for associations with self-reported consumption of coffee, tea and alcohol in the current study.

"Taste has been studied for a long time, but we don't know the full mechanics of it," Cornelis said. "Taste is one of the senses. We want to understand it from a biological standpoint."

The paper is titled "Understanding the role of bitter taste perception in coffee, tea and alcohol consumption through Mendelian randomization."

http://bit.ly/2RYFxew

Why 536 was 'the worst year to be alive'

"It was the beginning of one of the worst periods to be alive, if not the worst year"

By Ann GibbonsNov. 15, 2018 , 2:00 PM

Ask medieval historian Michael McCormick what year was the worst to be alive, and he's got an answer: "536." Not 1349, when the Black Death wiped out half of Europe. Not 1918, when the flu killed 50 million to 100 million people, mostly young adults. But 536. In Europe, "It was the beginning of one of the worst periods to be alive, if not the worst year," says McCormick, a historian and archaeologist who chairs the Harvard University Initiative for the Science of the Human Past.

A mysterious fog plunged Europe, the Middle East, and parts of Asia into darkness, day and night—for 18 months. "For the sun gave forth its light without brightness, like the moon, during the whole year," wrote Byzantine historian Procopius. Temperatures in the summer of 536 fell 1.5°C to 2.5°C, initiating the coldest decade in the past 2300 years. Snow fell that summer in China; crops failed; people starved. The Irish chronicles record "a failure of bread from the years 536–539." Then, in 541, bubonic plague struck the Roman port of Pelusium, in Egypt. What came to be called the Plague of Justinian spread rapidly, wiping out one-third to one-half of the population of the eastern Roman Empire and hastening its collapse, McCormick says.

Historians have long known that the middle of the sixth century was a dark hour in what used to be called the Dark Ages, but the source of the mysterious clouds has long been a puzzle. Now, an ultraprecise analysis of ice from a Swiss glacier by a team led by McCormick and

glaciologist Paul Mayewski at the Climate Change Institute of The University of Maine (UM) in Orono has fingered a culprit. At a workshop at Harvard this week, the team reported that a cataclysmic volcanic eruption in Iceland spewed ash across the Northern Hemisphere early in 536. Two other massive eruptions followed, in 540 and 547. The repeated blows, followed by plague, plunged Europe into economic stagnation that lasted until 640, when another signal in the ice—a spike in airborne lead—marks a resurgence of silver mining, as the team reports in *Antiquity* this week.

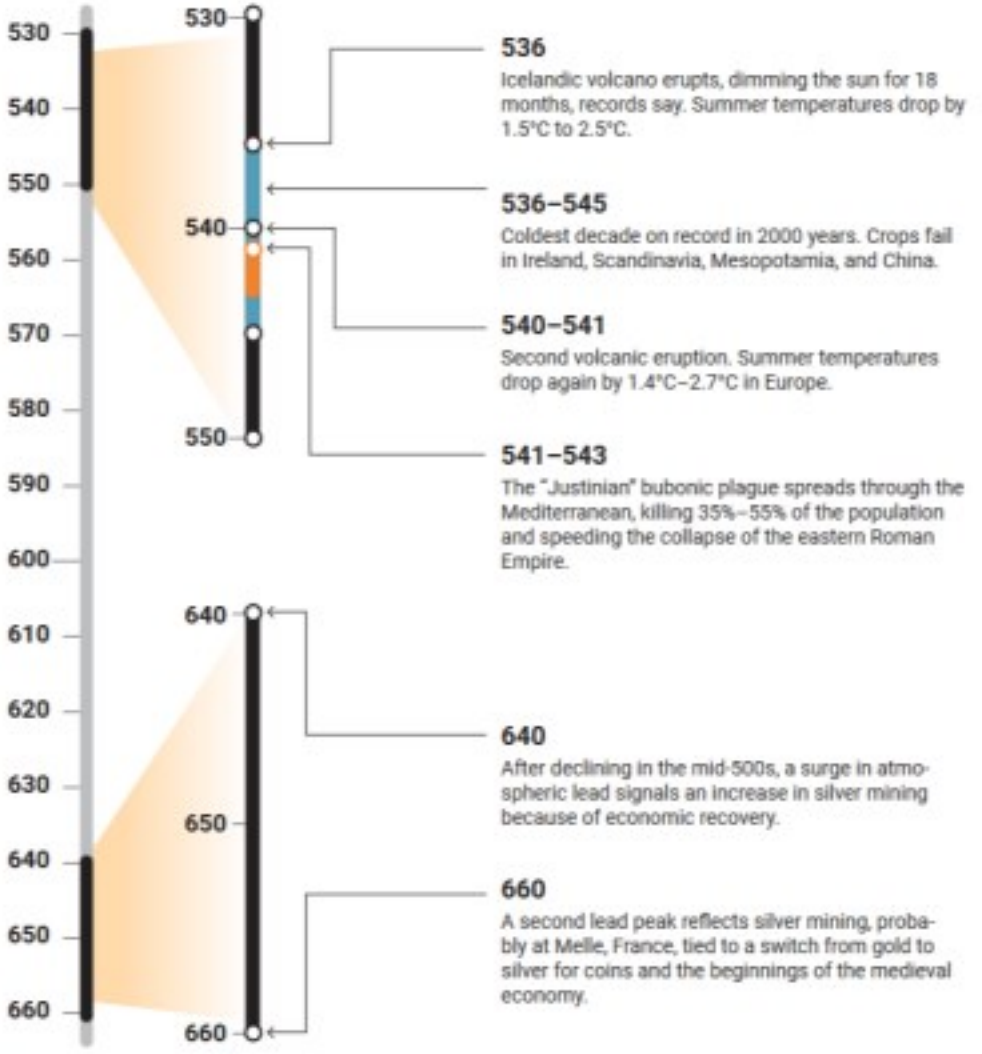
To Kyle Harper, provost and a medieval and Roman historian at The University of Oklahoma in Norman, the detailed log of natural disasters and human pollution frozen into the ice "give us a new kind of record for understanding the concatenation of human and natural causes that led to the fall of the Roman Empire—and the earliest stirrings of this new medieval economy."

Ever since tree ring studies in the 1990s suggested the summers around the year 540 were unusually cold, researchers have hunted for the cause. Three years ago polar ice cores from Greenland and Antarctica yielded a clue. When a volcano erupts, it spews sulfur, bismuth, and other substances high into the atmosphere, where they form an aerosol veil that reflects the sun's light back into space, cooling the planet. By matching the ice record of these chemical traces with tree ring records of climate, a team led by Michael Sigl, now of the University of Bern, found that nearly every unusually cold summer over the past 2500 years was preceded by a volcanic eruption. A massive eruption—perhaps in North America, the team suggested—stood out in late 535 or early 536; another followed in 540. Sigl's team concluded that the double blow explained the prolonged dark and cold.

Mayewski and his interdisciplinary team decided to look for the same eruptions in an ice core drilled in 2013 in the Colle Gnifetti Glacier in the Swiss Alps. The 72-meter-long core entombs more than 2000 years of fallout from volcanoes, Saharan dust storms, and human activities smack in the center of Europe. The team deciphered this record using a new ultra–high-resolution method, in which a laser

Darkest hours and then a dawn

A high-resolution ice core record combined with historical texts chronicles the impact of natural disasters on European society.



(GRAPHIC) A. CUADRA/SCIENCE; (DATA) C. P. LOVELUCK *ET AL.*, *ANTIQUITY* 2018; M. SIGL *ET AL.*, *NATURE* 2015; M. MCCORMICK

carves 120-micron slivers of ice, representing just a few days or weeks of snowfall, along the length of the core. Each of the samples—some 50,000 from each meter of the core—is analyzed for about a dozen elements. The approach enabled the team to pinpoint storms, volcanic eruptions, and lead pollution down to the month or even less, going back 2000 years, says UM volcanologist Andrei Kurbatov.

In ice from the spring of 536, UM graduate student Laura Hartman found two microscopic particles of volcanic glass. By bombarding the shards with x-rays to determine their chemical fingerprint, she and Kurbatov found that they closely matched glass particles found earlier in lakes and peat bogs in Europe and in a Greenland ice core. Those particles in turn resembled volcanic rocks from Iceland. The chemical similarities convince geoscientist David Lowe of The University of Waikato in Hamilton, New Zealand, who says the particles in the Swiss ice core likely came from the same Icelandic volcano. But Sigl says more evidence is needed to convince him that the eruption was in Iceland rather than North America.

Either way, the winds and weather systems in 536 must have been just right to guide the eruption plume southeast across Europe and, later, into Asia, casting a chilly pall as the volcanic fog "rolled through," Kurbatov says. The next step is to try to find more particles from this volcano in lakes in Europe and Iceland, in order to confirm its location in Iceland and tease out why it was so devastating.

A century later, after several more eruptions, the ice record signals better news: the lead spike in 640. Silver was smelted from lead ore, so the lead is a sign that the precious metal was in demand in an economy rebounding from the blow a century before, says archaeologist Christopher Loveluck of the University of Nottingham in the United Kingdom. A second lead peak, in 660, marks a major infusion of silver into the emergent medieval economy. It suggests gold had become scarce as trade increased, forcing a shift to silver as the monetary standard, Loveluck and his colleagues write in *Antiquity*. "It shows the rise of the merchant class for the first time," he says.

Still later, the ice is a window into another dark period. Lead vanished from the air during the Black Death from 1349 to 1353, revealing an economy that had again ground to a halt. "We've entered a new era with this ability to integrate ultra–high-resolution environmental records with similarly high resolution historical records," Loveluck says. "It's a real game changer."

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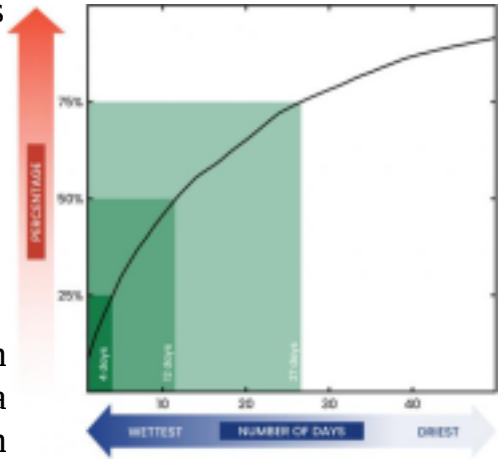
Half of the world's annual precipitation falls in just 12 days, new study finds

Climate change likely to make global precipitation more uneven

Currently, half of the world's measured precipitation that falls in a year falls in just 12 days, according to a new analysis of data collected at weather stations across the globe.

By century's end, climate models project that this lopsided distribution of rain and snow is likely to become even more skewed, with half of annual precipitation falling in 11 days. These results are published in Geophysical Research Letters, a journal of the American Geophysical Union.



An analysis of rainfall measured at weather stations across the globe between 1999 and 2014 found that the median time it took for half of a year's precipitation to fall was just 12 days. A quarter of annual precipitation fell in just six days, and three-quarters fell in 27 days. **©UCAR. Image: Simmi Sinha.**

Previous studies have shown that we can expect both an increase in extreme weather events and a smaller increase in average annual precipitation in the future as the climate warms, but researchers are still exploring the relationship between those two trends.

"This study shows how those two pieces fit together," said Angeline Pendergrass, a scientist at the National Center for Atmospheric Research (NCAR) and the lead author of the new study. "What we found is that the expected increases happen when it's already the wettest -- the rainiest days get rainier."

The findings, which suggest that flooding and the damage associated with it could also increase, have implications for water managers, urban planners, and emergency responders. The research results are also a concern for agriculture, which is more productive when rainfall is spread more evenly over the growing season.

The research was supported by the U.S. Department of Energy and the National Science Foundation, which is NCAR's sponsor.

What it means to be extreme

Scientists who study extreme precipitation -- and how such events may change in the future -- have used a variety of metrics to define what qualifies as "extreme." Pendergrass noticed that in some cases the definitions were so broad that extreme precipitation events actually included the bulk of all precipitation.

In those instances, "extreme precipitation" and "average precipitation" became essentially the same thing, making it difficult for scientists to understand from existing studies how the two would change independently as the climate warms.

Other research teams have also been grappling with this problem. For example, a recent paper tried to quantify the unevenness of precipitation by adapting the Gini coefficient, a statistical tool often used to quantify income inequality, to instead look at the distribution of rainfall.

Pendergrass wanted to find something even simpler and more intuitive that could be easily understood by both the public and other scientists. In the end, she chose to quantify the number of days it would take for half of a year's precipitation to fall. The results surprised her.

"I would have guessed the number would be larger -- perhaps a month," she said. "But when we looked at the median, or midpoint, from all the available observation stations, the number was just 12 days."

For the analysis, Pendergrass worked with Reto Knutti, of the Institute for Atmospheric and Climate Science in Zurich, Switzerland. They used data from 185 ground stations for the 16 years from 1999 through 2014, a period when measurements could be validated against data from the Tropical Rainfall Measuring Mission (TRMM) satellite. While the stations were dispersed globally, the majority were in North America, Eurasia, and Australia.

To look forward, the scientists used simulations from 36 of the world's leading climate models that had data for daily precipitation. Then they pinpointed what the climate model projections for the last 16 years of this century would translate to for the individual observation stations.

They found that total annual precipitation at the observation stations increased slightly in the model runs, but the additional precipitation did not fall evenly. Instead, half of the extra rain and snow fell over just six days.

This contributed to total precipitation also falling more unevenly than it does today, with half of a year's total precipitation falling in just 11 days by 2100, compared to 12 in the current climate.

"While climate models generally project just a small increase in rain in general, we find this increase comes as a handful of events with much more rain and, therefore, could result in more negative impacts,

including flooding," Pendergrass said. "We need to take this into account when we think about how to prepare for the future."

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http://bit.ly/2DtL34F

Exercise is medicine, and doctors are starting to prescribe it

There is a movement afoot (pun intended) to get more people exercising by involving their family doctors.

Scott Lear *

In the United Kingdom, the government recently released *Moving Medicine* — an online resource to help doctors talk to their patients about the importance of exercise in relation to conditions as diverse as cancer and dementia. This is a welcome initiative given that physical inactivity is the fourth leading cause of death in the world, according to the World Health Organization.

The benefits of exercise have been proven over and over again: Exercise reduces risk of depression, type 2 diabetes, heart disease, stroke and many cancers, and prevents early death.

If it was a pill, exercise would be a trillion-dollar money-maker prescribed to everyone.

Exercise as a therapy is mentioned in almost all prevention and treatment guidelines, which are written by doctors themselves. Still, most patients never hear their doctor talk about it. And fewer than one in four Canadians meet current guidelines for physical activity, which recommend that people participate in moderate (such as brisk walking) and vigorous (such as jogging, swimming or running) activity for at least 150 minutes per week.

Part of the reason is that most doctors in practice today received little, if any, training on the role of exercise in managing disease. Years ago I taught a 30-minute lecture on the topic at a Canadian medical school and this was all the students got over their four-year program. This is about to change.

Free gym prescriptions

In recent years, Canadian medical schools — such as the Cumming School of Medicine at the University of Calgary — have revised their curricula to incorporate aspects of exercise in the prevention and treatment of disease. This is one part of growing initiatives like *Exercise is Medicine* that advocate for the role of exercise and encourage doctors to prescribe it.

Similarly, the *Prescription to Get Active* program in Alberta allows doctors to prescribe free 30-day gym memberships to patients.

A grassroots program called *Walk with a Doc* has local doctors walking with their patients. The program was begun by Dr. David Sabgir, a cardiologist in Columbus, Ohio, who was frustrated with his inability to affect behaviour change in the clinical setting and invited his patients to go for a walk with him in a local park one Saturday morning. More than 100 people showed up, and there are now 400 chapters worldwide.

There have also been calls for exercise to be considered a vital sign, much like blood pressure and heart rate. Health insurance provider Kaiser Permanente requires doctors in the United States to record how much physical activity a patient does.

Patients who receive exercise prescriptions and counselling from their doctors are more likely to be active, so these initiatives are a good start. More needs to be done, however, when only one-third of doctors talk to their patients about exercise.

Reactionary health-care system

Not surprisingly, doctors who exercise themselves are more likely to counsel their patients about physical activity. Therefore, targeting doctors to be more active may provide a substantial population effect.

At the same time, doctors say they need more and better training with respect to the benefits of exercise and how to counsel patients.

The need for this change in approaching health and disease comes from two key realizations. One is that there are a growing number of people with preventable chronic illness, and our health-care system is not adequately prepared to deal with all these patients.

Our system is reactionary; it is designed to wait until someone has a disease instead of preventing it. But chronic illnesses are not like diseases of old. They cannot be cured, although many can be prevented. Exercise is increasingly recognized as important to this change.

Exercise for cancer care

Second, we have greater knowledge about the benefits of exercise in treating disease in addition to preventing it. Exercise is used for cardiac rehabilitation, after a heart attack.

Exercise works as well as drugs that lower cholesterol and blood pressure in preventing early death. And diabetics who exercise require less medication to manage their blood sugar.

Even in treating cancer, exercise can reduce the side-effects of treatment, such as anxiety, depression and fatigue. This has prompted the Clinical Oncology Society of Australia to release a position statement recommending exercise as part of regular cancer care. It is believed to be the first of its kind in the world, but hopefully not the last.

Doctors would benefit from additional incentives such as specific billing codes that allow for prescribing of exercise as well as more continuing medical education sessions on how to do so.

Educating current and future doctors that exercise is as good, if not better, than many medications will be essential to prevent the increasing burden of chronic illnesses.

Scott Lear writes the weekly blog Feel healthy with Dr. Scott Lear.
**Professor of Health Sciences, Simon Fraser University*

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http://bit.ly/2FqS0Gl

Sucking your baby's pacifier to clean it may prevent allergies

Protective effect apparent during first year of life

SEATTLE - If the thought of sucking your baby's pacifier to clean it and then popping it in your baby's mouth grosses you out, think again. New research being presented at the American College of Allergy, Asthma and Immunology (ACAAI) Annual Scientific Meeting suggests a link between parental sucking on a pacifier and a lower allergic response among young children.

"We interviewed 128 mothers of infants multiple times over a period of 18 months and asked how they cleaned their child's pacifier," says allergist Eliane Abou-Jaoude, MD, ACAAI member and lead author on the study conducted by Henry Ford Health System in Detroit. "We found the children of mothers who sucked on the pacifier had lower IgE levels." IgE is a type of antibody related to allergic responses in the body. Although there are exceptions, higher IgE levels indicate a higher risk of having allergies and allergic asthma."

Of the 128 mothers completing multiple interviews, 58 percent reported current pacifier use by their child. Of those who had a child using a pacifier, 41 percent reported cleaning by sterilization, 72 percent reported hand washing the pacifier, and 12 percent reported parental pacifier sucking.

"We found that parental pacifier sucking was linked to suppressed IgE levels beginning around 10 months, and continued through 18

months," says allergist Edward Zoratti, MD, ACAAI member and co-author of the study. "Further research is needed, but we believe the effect may be due to the transfer of health-promoting microbes from the parent's mouth. It is unclear whether the lower IgE production seen among these children continues into later years."

"We know that exposure to certain microorganisms early in life stimulates development of the immune system and may protect against allergic diseases later," says Dr. Abou-Jaoude. "Parental pacifier sucking may be an example of a way parents may transfer healthy microorganisms to their young children. Our study indicates an association between parents who suck on their child's pacifier and children with lower IgE levels but does not necessarily mean that pacifier sucking causes lower IgE."

Abstract Titles: Association Between Pacifier Cleaning Methods and Child Total IgE
Author: Eliane Abou-Jaoude, MD

https://nyti.ms/2PE7Vpt

Rapid Cure Approved for Sleeping Sickness, a Horrific Illness

Parasites transmitted by tsetse flies travel to the brain, causing paranoia, fury and death. Until now, killing them required hospitalization and harsh drugs.

By Donald G. McNeil Jr.

The first treatment for sleeping sickness that relies on pills alone was approved on Friday by Europe's drug regulatory agency, paving the way for use in Africa, the last bastion of the horrific disease.

With treatment radically simplified, sleeping sickness could become a candidate for elimination, experts said, because there are usually fewer than 2,000 cases in the world each year.

The disease, also called human African trypanosomiasis, is transmitted by tsetse flies. The protozoan parasites, injected as the flies suck blood, burrow into the brain. Before they kill, drive their victims mad in ways that resemble the last stages of rabies.

The personalities of the infected change. They have terrifying hallucinations and fly into rages; they have been known to beat their children and even attack family members with machetes.

They may become ravenous and scream with pain if water touches their skin. Only in the end, do they lapse into a long coma and die.

The new drug, fexinidazole, cures all stages of the disease within 10 days.

Previously, everyone with the parasites found in a blood test also had to undergo a spinal tap to see if the parasites had reached their brains. If so, patients had to suffer through a complex and sometimes dangerous intravenous regimen requiring hospitalization.

An oral treatment that can safely be taken at home "is a completely new paradigm — it could let us bring treatment down to the village level," said Dr. Bernard Pecoul, founder and executive director of the Drugs for Neglected Diseases Initiative, which was started in 2005 by the medical charity Doctors Without Borders to find new cures for tropical diseases.

Previous treatments for sleeping sickness ranged from inconvenient to nightmarish.

The current intravenous drug, eflornithine, must be given over many days with intravenous fluids that weigh about 125 pounds, a big burden in the supply chain for rural hospitals, Dr. Pecoul said.

Melarsoprol, the intravenous treatment used until a decade ago, contains an arsenic derivative. It corroded veins, triggered convulsions and killed 5 percent of the patients who got it.

"An all-oral treatment has been a dream of mine for decades," said Dr. Victor Kande, an adviser to the health ministry of the Democratic Republic of Congo who oversaw clinical trials of the drug. "This is a huge leap in how we can tackle this disease."

Getting fexinidazole tested and approved is one of the neglected disease initiative's biggest triumphs.

The drug was created in the 1980s by Hoechst, a German drug company, but later abandoned.

In 2009, seeking new anti-parasitic medicines, the initiative asked Sanofi, which held the patent, to reformulate it for sleeping sickness. Ultimately, the drive for approval cost $63 million and involved clinical trials including 750 patients in Congo and the Central African Republic. Two million villagers were screened.

The costs were paid by seven European countries, the Bill and Melinda Gates Foundation, Doctors Without Borders and other donors.

About 65 million people live in regions in west and central Africa where the most common strain of sleeping sickness, Trypanosoma brucei gambiense, circulates. A less common form circulates in southern Africa, and the harsh, older treatments are still needed to cure it.

http://bit.ly/2QZlIDP

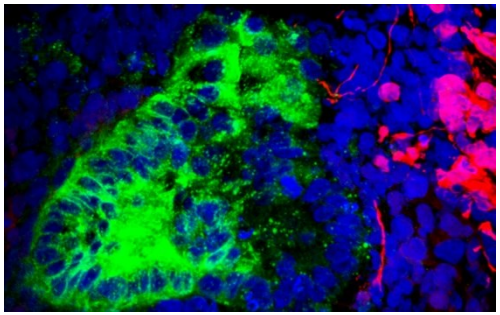
Lab-Grown Mini Kidneys 'Go Rogue,' Sprout Brain and Muscle Cells

Miniature lab-grown kidneys have been hiding something from the scientists who grew them.

By Mindy Weisberger, Senior Writer

Instead of developing into different varieties of kidney cells, some of the cells took a different path and became brain and muscle cells.

These simple mini kidneys — also known as kidney organoids — are grown from stem cells that are encouraged to develop into clusters of specific kidney cells. But it turns out that the "recipes" that encourage the development of specialized kidney cells were also cranking out cells from other organs, according to a new study.



Scientists have identified brain and muscle cells lurking in kidney organoids. The image shows brain neurons in red and kidney cells in green. **Humphreys Lab**

The scientists set out to grow kidney organoids in the lab and then analyze them to see what was happening inside of them, on a cellular level. To do that, the researchers looked at data collected from thousands of the organoids' genes, representing more than 83,000 cells in 65 mini kidneys. They expected to see a diverse variety of kidney cells, comparable to what one would see in a normal, fully grown human kidney. But they discovered that 10 percent to 20 percent of the organoids' cells were not kidney cells at all, but brain and muscle cells.

Growing a mini kidney takes about four weeks, said study co-author Benjamin Humphreys, chief of the Division of Nephrology at Washington University School of Medicine in St. Louis. To grow them, stem cells are bathed in a chemical cocktail that nurtures their growth into a range of kidney cells.

"You don't end up with one kidney cell type — you end up with many that approximate the different structures that you find in a real kidney," Humphreys told Live Science.

To identify the cellular makeup of their four-week-old mini kidneys, the study authors used a technique known as single-cell RNA sequencing, which examines activity in individual cells rather than in cell populations. This provides a more detailed view of individual cell identity and function — and in this case, it revealed that some of the mini kidneys' cells were in fact brain and muscle cells.

"We call these 'off-target' cells," Humphreys said. The appearance of these cells can spell trouble for researchers who use kidney organoids to model diseases, "because when off-target cells appear in an organoid, it means that it doesn't faithfully model a human kidney," he said.

Rogue brain cells in the mini kidneys emerged early in the organoids' development, the researchers found. After analyzing the cell receptors in growing organoids, the scientists discovered that they could inhibit the signaling pathways of rogue cells, cutting down on the number of brain cells by about 90 percent. This technique could easily be applied to any type of organoid research, to restrict the growth of off-target cells, the study authors reported.

Genetic data from the mini kidneys delivered another surprise: the kidney cells in the organoids were immature, presenting another potential drawback in using organoids to model diseases, Humphreys said. (The researchers had expected the cells to be mature in four weeks.) What's more, incubating the organoids for longer didn't produce more mature kidney cells; rather, it encouraged the growth of more rogue cells, according to the study.

Future research strategies could focus on fine-tuning the signals that a developing kidney organoid sends to its cells as they differentiate, "to make cells behave more like mature adult kidney cells," Humphreys said.

The findings were published online today (Nov. 15) in the journal Cell Stem Cell.

http://bit.ly/2Fwhqec

EMA Curtails Use of Fluoroquinolone, Quinolone Antibiotics

EMA recommends suspending or restricting use due to risk for "disabling and potentially permanent" adverse effects

Megan Brooks

A committee for the European Medicines Agency (EMA) has recommended suspending entirely or restricting the use of fluoroquinolone and quinolone antibiotics because of the risk for "disabling and potentially permanent" adverse effects, the agency announced today.

The EMA Committee for Human Medicinal Products (CHMP) endorsed recommendations put forth in October by the agency's Pharmacovigilance Risk Assessment Committee (PRAC). The committee concluded that marketing authorization for medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid should be suspended.

The CHMP also confirmed that the use of the remaining fluoroquinolone antibiotics should be restricted.

PRAC began its review in 2017.

Updated prescribing information for healthcare professionals and information for patients will describe the disabling and potentially permanent adverse effects and will advise patients to stop treatment with a fluoroquinolone antibiotic at the first sign of an adverse effect involving muscles, tendons or joints, and the nervous system, the EMA said.

The new restrictions on the use of fluoroquinolone antibiotics advise against their use for the following:

- ***To treat infections that might get better without treatment or are not severe (such as throat infections);***
- ***To treat nonbacterial infections, eg, nonbacterial (chronic) prostatitis;***
- ***For preventing traveler's diarrhea or recurring lower urinary tract infections (urinary infections that do not extend beyond the bladder);***
- ***To treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.***

"Importantly, fluoroquinolones should generally be avoided in patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic," the EMA said.

Fluoroquinolones "should be used with special caution in the elderly, patients with kidney disease and those who have had an organ transplantation because these patients are at a higher risk of tendon

injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided," the EMA advised.

On the basis of available evidence, the EMA concluded that fluoroquinolones are associated with prolonged (up to months or years), serious, disabling, and potentially irreversible drug reactions affecting more than one and sometimes multiple systems, organ classes, and senses.

The adverse effects include tendonitis, tendon rupture, arthralgia, pain in the extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste, and smell.

Tendon damage (especially to the Achilles tendon but also other tendons) can occur within 48 hours of starting a fluoroquinolone, but the damage may be delayed several months after stopping treatment, the EMA said.

Patients who are older, have renal impairment, or have undergone solid organ transplant and those being treated with a corticosteroid are at higher risk for tendon damage. Concomitant treatment with a fluoroquinolone and a corticosteroid should be avoided.

The agency said patients should stop fluoroquinolone treatment at the first sign of tendon pain or inflammation and notify their provider of symptoms of neuropathy, such as pain, burning, tingling, numbness, or weakness, to help prevent the development of a potentially irreversible condition.

The EMA said the benefits and risks of fluoroquinolones will be monitored continuously, and a drug utilization study will evaluate the effectiveness of these new measures in reducing inappropriate use of fluoroquinolones.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all European Union countries.

Ripple Effect?

In 2016, the US Food and Drug Administration (FDA) enhanced warnings about the link between fluoroquinolones and disabling and potentially permanent side effects involving tendons, muscles, joints, nerves, and the central nervous system, as reported by *Medscape Medical News*.

Earlier this year, the FDA ordered label changes for fluoroquinolones so as to strengthen warnings about the antibiotics' risks for mental health adverse effects and serious blood glucose disturbances.

"The FDA warning was very clear and has already had an effect of lowering the use of these medications, which I would hope would be sufficient and the FDA would not now have a secondary reaction to the move by the [EMA]," Donald Ford, MD, a family physician from the Cleveland Clinic in Ohio, noted in an interview with *Medscape Medical News*.

"My hope is that these medications will remain available, because there are some times when nothing else will work, and you simply have to take something that has known side effects, mitigate them as much as you can, warn patients, be transparent, but it's better than dying from an infection that you can't treat otherwise," Ford said.

For clinicians in Europe, "I have to imagine there would be some recourse on being able to appeal or get special permission to use these medications in cases where you have run out of options," Ford added.

Amesh Adalja, MD, member of the public health committee for the Infectious Diseases Society of America, said he's "not surprised to see regulatory agencies starting to take action, given there has been increasing concern over the side effects of this class of drugs.

"However, it's important to remember that any medication and every antibiotic has a side effect profile, and there is always a risk-benefit calculation. I don't think the fluoroquinolones should be completely gone from the market because they do have really important uses,

and that should not be forgotten in this type of debate," Adalja told *Medscape Medical News*.

"It's also important to remember that the fluoroquinolones have activity against some bioterrorism agents, like plague, for example, and anthrax," said Adalja, who is with the Johns Hopkins Center for Health Security in Baltimore, Maryland.

More information about the announcement is available on the EMA website.

http://bit.ly/2r1OFnf

Scientists explain how wombats drop cubed poop

Wombats, the only known species capable of organically producing cubes, could inspire future soft tissue manufacturing and transportation methods

WASHINGTON, D.C. -- Wombats, the chubby and beloved, short-legged marsupials native to Australia, are central to a biological mystery in the animal kingdom: How do they produce cube-shaped poop? Patricia Yang, a postdoctoral fellow in mechanical engineering at the Georgia Institute of Technology, set out to investigate.

Cubical feces in the wombat's intestine. **Photo by P. Yang and D. Hu/Georgia Tech**

Yang studies the hydrodynamics of fluids, including blood, processed food and urine, in the bodies of animals. She was curious how the differences in wombats' digestive processes and soft tissue structures might explain their oddly shaped scat.

During the American Physical Society's Division of Fluid Dynamics 71st Annual Meeting, which will take place Nov. 18-20 at the Georgia World Congress Center in Atlanta, Georgia, Yang and her co-authors, Scott Carver, David Hu and undergraduate student Miles Chan, will explain their findings from dissecting the alimentary systems, or digestive tracts, of wombats.

"The first thing that drove me to this is that I have never seen anything this weird in biology. That was a mystery," said Yang. "I didn't even believe it was true at the beginning. I Googled it and saw a lot about cube-shaped wombat poop, but I was skeptical."

Yang and her co-authors studied the digestive tracts of wombats that had been euthanized following motor vehicle collisions in Tasmania, Australia. Carver, the biologist and Australian counterpart to the group of American mechanical engineers, supplied the wombat intestinal specimens.

Near the end of the intestine, they found that feces changed from liquidlike states to solid states made up of small, separated cubes. The group concluded that the varying elastic properties of wombats' intestinal walls allowed for the cube formation.

In the built world, cubic structures -- sugar cubes, sculptures, and architectural features -- are common, and produced by injection molding or extrusion. Cubes, however, are rare in the natural world. Currently, wombats are the only known species capable of producing cubes organically.

"We currently have only two methods to manufacture cubes: We mold it, or we cut it. Now we have this third method," Yang said. "It would be a cool method to apply to the manufacturing process -- how to make a cube with soft tissue instead of just molding it."

So, why do wombats poop cubes? Wombats pile their feces to mark their home ranges and communicate with one another through scent. They pile their feces in prominent places (e.g., next to burrows, or on logs, rocks and small raises) because they have poor eye sight. The higher and more prominently placed the pile of feces, the more visually distinctive it is to attract other wombats to smell and engage in communication. Therefore, it is important that their droppings do not roll away, and cube-shaped poop solves this problem.

Yang hopes that the group's research on wombats will contribute to current understandings of soft tissue transportation, or how the gut moves. She also emphasized that the group's research involved mechanical engineering and biology, and their findings are valuable to both fields. "We can learn from wombats and hopefully apply this novel method to our manufacturing process," Yang said. "We can understand how to move this stuff in a very efficient way."

Carver added, "There is much general interest from the public, both in Australia and internationally, about how and why wombats create cube-shaped feces. Many ideas, some more entertaining than others, have been put forward to explain this, but until this study nobody had ever investigated the cause. This has been a fantastic collaboration which shows the value of interdisciplinary research for making new scientific discoveries."

Presentation E19.1, "How do wombats make cubed poo?" by Patricia J. Yang, Miles Chan, Scott Carver and David L. Hu, will be Sunday, Nov. 18, 5:10 p.m. in Room B306 of the Georgia World Congress Center in Atlanta. Abstract: http://meetings.aps.org/Meeting/DFD18/Session/E19.1

http://bit.ly/2BfOjz0

New dual-action cancer-killing virus

Scientists have equipped a virus that kills carcinoma cells with a protein so it can also target and kill adjacent cells that are tricked into shielding the cancer from the immune system.

It is the first time that cancer-associated fibroblasts within solid tumours - healthy cells that are tricked into protecting the cancer from the immune system and supplying it with growth factors and nutrients - have been specifically targeted in this way.

The researchers, who were primarily funded by the Medical Research Council (MRC) and Cancer Research UK, say that if further safety testing is successful, the dual-action virus - which they have tested in human cancer samples and in mice - could be tested in humans with carcinomas as early as next year.

Currently, any therapy that kills the 'tricked' fibroblast cells may also kill fibroblasts throughout the body - for example in the bone marrow and skin - causing toxicity.

In this study, published in the journal *Cancer Research*, the researchers used a virus called enadenotucirev, which is already in clinical trials for treating carcinomas. It has been bred to infect only cancer cells, leaving healthy cells alone.

They added genetic instructions into the virus that caused infected cancer cells to produce a protein called a bispecific T-cell engager.

The protein was designed to bind to two types of cells and stick them together. In this case, one end was targeted to bind to fibroblasts. The other end specifically stuck to T cells - a type of immune cell that is responsible for killing defective cells. This triggered the T cells to kill the attached fibroblasts.

Dr Joshua Freedman, from the Department of Oncology at the University of Oxford, who was first author on the study said: "We hijacked the virus's machinery so the T-cell engager would be made only in infected cancer cells and nowhere else in the body. The T-cell engager molecule is so powerful that it can activate immune cells inside the tumour, which are being supressed by the cancer, to attack the fibroblasts."

Dr Kerry Fisher, from the Department of Oncology at the University of Oxford, who led the research said: "Even when most of the cancer cells in a carcinoma are killed, fibroblasts can protect the residual cancer cells and help them to recover and flourish. Until now, there has not been any way to kill both cancer cells and the fibroblasts protecting them at the same time, without harming the rest of the body.

"Our new technique to simultaneously target the fibroblasts while killing cancer cells with the virus could be an important step towards reducing immune system suppression within carcinomas and should kick-start the normal immune process.

"These viruses are already undergoing trials in people, so we hope our modified virus will be moving towards clinical trials as early as next year to find out if it is safe and effective in people with cancer."

The scientists successfully tested the therapy on fresh human cancer samples collected from consenting patients, including solid prostate cancer tumours which reflect the complex make-up of real tumours. They also tested the virus on samples of healthy human bone marrow and found it did not cause toxicity or inappropriate T cell activation.

Dr Nathan Richardson, head of molecular and cellular medicine at the MRC said: "Immunotherapy is emerging as an exciting new approach to treating cancers. This innovative viral delivery system, which targets both the cancer and surrounding protective tissue, could improve outcomes for patients whose cancers are resistant to current treatments. Further clinical studies will be crucial to determine that the stimulation of the patient's immune system does not produce unintended consequences".

Dr Michelle Lockley, Cancer Research UK's expert on immunotherapy, said: "Using the power of the body's own immune system to tackle cancer is a growing area of research. This work in human tumour samples is encouraging, but can be complicated - one of the biggest challenges of immunotherapies is predicting how well they will work with the patient's immune system, and understanding what the side effects could be. The next stage will be using clinical trials to test whether this is both a safe and effective way to treat the disease in people."

The virus targets carcinomas, which are the most common type of cancer and start in cells in the skin or in tissues that line or cover internal organs, such as the pancreas, colon, lungs, breasts, ovaries and prostate.