http://bit.ly/2Q7aooi

A fracture anywhere reduces bone density everywhere

New UC Davis Health studies help explain why one break can lead to others

Breaking a bone causes bone density losses throughout the body, not just close to the site of the fracture, and primarily around the time of the fracture, two new studies from UC Davis Health show.

The studies are among the first to associate fractures with systemic bone loss. They also begin the path to finding treatments that preserve long-term skeletal health and reduce susceptibility to additional fractures and, potentially, osteoporosis, which is diagnosed when bone-density losses are severe.

Both investigations were led by Blaine Christiansen, whose research focuses on identifying changes in musculoskeletal tissue due to injury, aging or disease.

"We know one fracture seems to lead to others, but we haven't known why," said Christiansen, associate professor of orthopaedic surgery at UC Davis. "Our work is the first step on the path to identifying the cellular mechanisms of systemic bone loss."

The first study, published in Osteoporosis International, was based on about 4,000 participants in the Study of Osteoporotic Fractures, an observational study of older women that included hip bone mineral density (BMD) measures and fracture history gathered regularly over 20 years.

Outcomes showed that hip BMD decreased over time for all women in the study, but was greatest for those who had fractured a bone ? even if the fracture was not near the hip. BMD reductions averaged between .89 and .77 percent per year for those with fractures, and .66 percent per year for those with no fractures. Those losses were greatest within the first two years of a break.

Published in the *Journal of Bone and Mineral Research*, the second study was conducted using mice with femur fractures and BMD tests in various bones. Once again, bone loss occurred throughout the body, most notably in the spine, and was greatest within the first two weeks of fracture. It also was accompanied by higher levels of inflammatory markers in the blood.

Outcomes of the second study showed interesting age-related recovery differences as well. Younger mice eventually recovered their pre-fracture BMD levels, while older mice did not.

Christiansen next hopes to further characterize the post-fracture inflammatory factors that may contribute to bone loss following fracture.

"It's possible that these factors are key to initiating BMD loss once a bone is broken," Christiansen said. "Ultimately, we hope to develop therapeutic strategies that interrupt those processes and prevent bone loss."

http://bit.ly/2Dxrx9e

Eradicating Helicobacter pylori infections may be a key treatment for Parkinson's disease

A review of the latest literature supports the association between the gut bacteria H. pylori and Parkinson's disease, according to a new report in the Journal of Parkinson's Disease

Amsterdam, NL - While human genetic mutations are involved in a small number of Parkinson's disease (PD) cases, the vast majority of cases are of unknown environmental causes, prompting enormous interest in identifying environmental risk factors involved. The link between *Helicobacter pylori* (*H. pylori*) and gastric ulcers has been known for several decades, but new evidence suggests that this harmful bacterium may play a role in PD as well. A new review in the *Journal of Parkinson's Disease* summarizes the current literature regarding the link between *H. pylori* and PD and explores the possible mechanisms behind the association.

In a comprehensive review of prior studies, investigators uncovered four key findings:

- ***People with PD are 1.5-3-fold more likely to be infected with H. pylori than people without PD.***
- ***H. pylori-infected PD patients display worse motor functions than H. pylori-negative PD patients.***
- ***Eradication of H. pylori improved motor function in PD patients over PD patients whose H. pylori was not eradicated.***
- ***Eradication of H. pylori improved levodopa absorption in PD patients compared to PD patients whose H. pylori was not eradicated.***

"This is an in-depth and comprehensive review that summarizes all the major papers in the medical literature on Parkinson's disease and *H. pylori*, the common stomach bacterium that causes gastritis, ulcers and stomach cancer," explained lead investigator David J. McGee, PhD, Associate Professor, Department of Microbiology and Immunology, LSU Health Sciences Center-Shreveport, Shreveport, LA, USA. "Our conclusion is that there is a strong enough link between the *H. pylori* and Parkinson's disease that additional studies are warranted to determine the possible causal relationship."

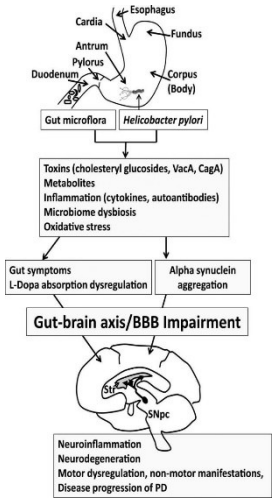

***Diagram illustrating how* H. pylori *may travel along the gut-brain axis and influence the development of PD.* David J. McGee, Xiao-Hong Lu and Elizabeth A. Disbrow**

Investigators also analyzed existing studies to try and find possible testable pathways between the bacterial infection and Parkinson's to lay the groundwork for future research. They found four main possible explanations for the association:

- ***Bacterial toxins produced by H. pylori may damage neurons.***
- ***The infection triggers a massive inflammatory response that causes damage to the brain.***
- ***H. pylori may disrupt the normal gut microbial flora.***
- ***The bacteria might interfere with the absorption properties of levodopa, the medication commonly used to treat the symptoms of Parkinson's disease.***

The onset of PD is often preceded by gastrointestinal dysfunction, suggesting that the condition might originate in the gut and spread to the brain along the brain-gut axis. In the review, investigators note that this has been documented in rats.

Screening PD patients for the presence of *H. pylori* and subsequent treatment if positive with anti-*H. pylori* triple drug therapy, may contribute to improved levodopa absorption and ultimately improvement of PD symptoms, potentially leading to a longer life span in patients with PD.

"Evidence for a strong association among *H. pylori* chronic infection, peptic ulceration and exacerbation of PD symptoms is accumulating," concluded Dr. McGee.

"However, the hypotheses that *H. pylori* infection is a predisposing factor, disease progression modifier, or even a direct cause of PD remain largely unexplored. This gut pathology may be multifactorial, involving *H. pylori*, intestinal microflora, inflammation, misfolding of alpha-synuclein in the gut and brain, cholesterol and other metabolites, and potential neurotoxins from bacteria or dietary sources. Eradication of *H. pylori* or return of the gut microflora to the proper balance in PD patients may ameliorate gut symptoms, L-dopa malabsorption, and motor dysfunction."

http://bit.ly/2Dx5Aa0

High-carbohydrates diet lead to weight loss, according to new study

Diets high in carbohydrates reduce body weight and body fat and improve insulin function in overweight individuals, according to a new study published in Nutrients.

In the 16-week randomized clinical trial, researchers with the Physicians Committee for Responsible Medicine placed participants

in either a plant-based, high-carbohydrate, low-fat diet group or asked them to maintain their current diet. The plant-based diet group avoided all animal products and added oils and limited fat intake to 20-30 grams per day. There were no limits on calories or carbohydrate intake. The control group maintained their current diets, which included meat and dairy products. Neither group altered their exercise routines.

Total carbohydrate intake did not change in the control group, but increased significantly in the plant-based diet group, both as absolute intake and as a percentage of total calories. Participants focused on whole, complex carbohydrates from fruits, vegetables, whole grains, and legumes.

At the end of the trial, body mass index, body weight, fat mass, visceral fat volume, and insulin resistance decreased significantly in the plant-based diet group. There were no significant changes in the control group.

"Fad diets often lead people to fear carbohydrates. But the research continues to show that healthy carbohydrates--from fruits, vegetables, beans, and whole grains--are the healthiest fuel for our bodies," says lead study author Hana Kahleova, M.D., Ph.D., director of clinical research for the Physicians Committee for Responsible Medicine.

The study's results support previous research finding that a plant-based, high-carbohydrate diet can help with weight regulation and body composition and reduce the risk for type 2 diabetes. Another recent study published in The Lancet found that people who consume animal-based, low-carbohydrate diets have a shorter life expectancy, compared with those who consume more carbohydrates and/or more plant-based sources of protein or fat.

Complex carbohydrates are naturally rich in fiber--a nutrient found in plant foods that adds bulk to the diet without adding extra calories. Previous studies have shown that high-fiber diets are effective for weight loss and can help reduce the risk for type 2 diabetes, heart disease, and certain types of cancer.

The study has important implications, because more than 7 in 10 U.S. adults are considered overweight or obese. Approximately 30 million Americans have diabetes, while prediabetes affects 84 million more.

http://bit.ly/2QdE5E2

This Super-Strong Magnet Literally Blew the Doors Off a Tokyo Laboratory

Created one of the most intense magnetic fields ever generated on Earth

By Rafi Letzter, Staff Writer | September 24, 2018 05:34pm ET

There's a magnet in a secure room in central Tokyo. It's an electromagnet, the kind that generates a magnetic field when electrical current flows through it. The last time the scientists who operate it switched it on, it blew open the heavy doors designed to keep it contained. Already, it has created one of the most intense magnetic fields ever generated on Earth. And it keeps getting more powerful.

The magnetic field, which recently reached a strength of 1,200 teslas — a unit of magnetic intensity — was described in a paper published Sept. 17 in the journal Review of Scientific Instruments.

Sparks flew when the Takeyama Lab magnet turned on in a recent experiment. **Shojiro Takeyama**

Twelve hundred teslas is an enormous measurement. The most powerful magnet most people have any chance of encountering in their lifetime is inside an MRI machine — and the most advanced, powerful, sometimes dangerous MRIs in the world clock in at just 3 teslas. In 2004, Popular Mechanics magazine described a machine

billed as "the world's most powerful magnet" — meaning the most powerful magnet that doesn't tear itself to bits whenever it's turned on — and it emitted just 45 teslas. That's less than 4 percent of the power emitted by the magnet created by lead author Shojiro Takeyama and his colleagues.

And crossing the 1,000-tesla mark is a major milestone in an engineering effort that Takeyama said dated back to the 1970s, and which he has led for the last two decades.

To achieve that intensity, Takeyama and his team pump megajoules of energy into a small, precisely engineered electromagnetic coil, the inner lining of which then collapses on itself at Mach 15 — that's more than 3 miles per second (5 kilometers per second). As it collapses, the magnetic field inside gets squeezed into a tighter and tighter space, until its force peaks at a tesla reading unimaginable in conventional magnets. Fragments of a second later, the coil collapses entirely, destroying itself.

The 1,200-tesla experiment required 3.2 megajoules of energy. But Takeyama, a physicist at the University of Tokyo, told Live Science that he believes his device can reach 1,800 teslas if he and his team apply 5 megajoules to it. (They're taking their time getting to that point, he said, partly due to safety concerns.)

"The most similar magnetic-field generation is by chemical explosives," Takeyama said, referring to experiments beginning in the 1960s and continuing until 2001, in which Russian and American researchers detonated explosives around electromagnets in order to squish them, briefly creating very powerful magnetic fields — up to 2,800 teslas.

"They cannot conduct these experiments in indoor laboratories, so they usually conduct everything in the outdoors, like Siberia in a field or somewhere in a very wide place at Los Alamos [New Mexico]," he said. "And they try to make a scientific measurement, but because of these conditions it's very hard to make precise measurements."

Other forms of superstrong magnetic fields require lasers, but Takeyama said that the laser-generated fields are tiny and supershort-lived, even by physics standards, making them similarly problematic for the sorts of experiments in which he and his laboratory colleagues at the University of Tokyo are interested.

The point of building a magnet in the 1,000-plus tesla range, Takeyama said, is to study hidden physical properties of electrons that are invisible under normal circumstances. He and his team will put different materials inside their magnet to study how their electrons behave.

Under those extreme conditions, he said, conventional models of electrons break down. Takeyama doesn't know exactly what happens to electrons in such extreme situations, but said that studying them in the moments before the coil's self-destruction should reveal properties of electrons normally invisible to science. Extremely powerful magnetic fields also have possible applications in fusion engineering, to keep the hot plasmas of a fusion reaction contained and far from their container walls.

The problem with building magnetic fields that powerful is that, as in the case of Takeyama's magnet, they almost, by definition, destroy themselves within moments of their creation. The field — and the process of creating it — inevitably exerts so much energy on the device generating it that at least some element of the device burns out or collapses on itself. Takeyama said that the advantage of his magnetic field is that it's relatively robust compared with fields generated by lasers or explosive devices. It's large enough to contain a substantial amount of material, requires no explosives and has a life span of a few dozen microseconds (millionths of a second). That's short in human terms, but it lasts several times longer than those laser-generated fields.

Also, while the coil itself is destroyed, the surrounding machine survives the process largely intact.

Here's what happened when it was powered up to 3.2 megajoules for the experiment that produced the 1,200-tesla field:

The device is contained and nondestructive compared with those explosive experiments in Siberia and Los Alamos. But still, every time the magnet is used, Takeyama and his team must enter the room and begin the long, laborious process of cleanup and repairs, he said. His research team must fabricate a new magnetic coil to exquisitely precise dimensions for each use. The typical wait time between experiments, he said, is about two to five months.

Outside researchers interested in elusive fusion-power generators have expressed interest in Takeyama's research as possibly useful for their large, magnetic plasma containment systems, he said. However, he said he's not certain how useful his fields might be in that context, nor is that his primary goal.

Down the road, he said, he expects to amp up the power on his machine, eventually maxing it out at the 5-megajoule, 1,800-tesla mark. But he's in no rush to get to that point, he said. First, he and his team want to explore as much as possible what they can learn at the 3.2-megajoule, 1,200-tesla range. And there remains the problem of safety as the energies involved increase.

For now, he said, his team has added some stronger doors to his lab.

http://bit.ly/2xFL95G

Common weed killer—believed harmless to animals—may be harming bees worldwide

Appears to disrupt the microbial community in the bees' digestive system

By Warren Cornwall Sep. 24, 2018 , 3:00 PM

Glyphosate, the world's most widely used herbicide and one long touted as harmless to animals, might be taking a toll on honey bees. The chemical appears to disrupt the microbial community in the bees' digestive system, making them more vulnerable to infection. The discovery adds another potential reason for the alarming decline of honey bees in parts of the world, as well as that of other pollinators that live in colonies, such as bumble bees.

"This is really critical," says Fred Gould, an entomologist at North Carolina State University in Raleigh who was not involved in the work. The study challenges the conventional wisdom that animals are immune to glyphosate because it targets a cellular mechanism particular to plants and some bacteria. "I was surprised."

Glyphosate kills plants by blocking an enzyme they use to make several key amino acids, the building blocks of proteins. Animals don't produce this enzyme, but it is used by some bacteria.

This sparked the interest of Nancy Moran, an evolutionary biologist at the University of Texas in Austin, who has spent a decade examining the gut microbiome—the population of bacteria that inhabit the intestines of animals—of honey bees (*Apis mellifera*). She and colleagues took approximately 2000 bees from a hive and fed some a sugar syrup and others syrup dosed with glyphosate at levels similar to those they might encounter in the environment while foraging for food. Three days after returning to the hive, the guts of glyphosate-fed bees had lower levels of a bacterium known as *Snodgrassella alvi* than those bees that were not exposed. Some of the results were confusing; bees that got the most glyphosate had a more normal looking microbiome after 3 days than those that had lower doses. Moran says it's not clear whether that's because more bees with the higher dose died, leaving behind ones that better withstood the herbicide.

In further tests, bees that consumed glyphosate had five times less of the bacterium. In a petri dish, most strains of *S. alvi* either slowed or stopped growing after a high dose of glyphosate.

This change in a bee's microbial inhabitants appears to make it more vulnerable to lethal infections. In tests on several hundred bees, only 12% of insects fed glyphosate survived infection from *Serratia marcescens*—a bacterium widely found in trace amounts in beehives

and bee guts that can cause infections by invading other parts of a bee's body—compared with 47% not fed glyphosate.

It's not clear why a glyphosate-disrupted microbiome would make the bees more susceptible to infection, Moran says. *S. alvi* lines part of the gut wall, and could create a protective barrier. It also secretes a chemical that could attack invading bacteria, she says.

The findings—reported today in the *Proceedings of the National Academy of Sciences*—add a new factor to a constellation of potential reasons for the decline of honey bees witnessed in recent years, says Gene Robinson, a honey bee geneticist at the University of Illinois in Urbana who was not involved with the study. In recent years, U.S. commercial beekeepers have seen almost a third of their hives fail during the winter, more than twice the historic rate. Researchers believe that pesticides, pathogens, parasites, and nutritional problems all play a role. A major strength of the new paper is that it points to a mechanism—the disruption of gut microbes—for how a pesticide could affect the bees, he says.

The discovery also raises questions about whether glyphosate is affecting the microbiome of other animals, including people. The role of microbes in the human gut has a lot of similarities to bee guts, Moran says. More research is needed; humans have different microbes in their guts, they have vastly larger bacterial populations and are likely exposed to much lower doses of glyphosate than are bees.

The new research is certain to make a controversial herbicide even more of a flashpoint. Some have also warned it could sicken people. Public health agencies have offered conflicting assessments of whether the chemical is a likely carcinogen.

http://bit.ly/2R3L6s8

When supplies of drugs run low, drug prices mysteriously rise, data shows

And the less competition, the higher the price hikes.

Beth Mole - 9/24/2018, 11:12 PM

When nearly 100 drugs became scarce between 2015 and 2016, their prices mysteriously increased more than twice as fast as their expected rate, an analysis recently published in the *Annals of Internal Medicine* reveals. The price hikes were highest if the pharmaceutical companies behind the drugs had little competition, the study also shows.

The authors—a group of researchers at the University of Pittsburgh and one at Harvard Medical School—can't say for sure *why* the prices increased just based off the market data. But they can take a shot at possible explanations. The price hikes "may reflect manufacturers' opportunistic behavior during shortages, when the imbalance between supply and demand increases willingness to pay," they conclude.

"There aren't a lot of industries where if a manufacturer botches the production of a product and is responsible for a reduction in supply that they are able to profit from that... It is the federal government, underinsured, and uninsured patients that are picking up the tab," co-author William Shrank of the University of Pittsburgh noted in an interview with Bloomberg.

Their look into the connection between price increases and shortages adds to a long-held observation among hospitals and analysts that such shortages are costly. When a preferred drug is hard to come by, doctors can turn to less-effective—potentially more-expensive—drugs, as well as delay treatment or cut back on dosages. Together, with the hikes in prices, those changes have led advocates to estimate that drug shortages overall cost $230 million in additional healthcare costs each year.

To get a better handle on how the costs of drugs change under shortages, Shrank and colleagues analyzed data on 617 drug formulations for 90 different drugs that appeared on the Food and Drug Administration's drug shortage database between December

2015 and December 2016. They then pulled pricing figures for those drugs from a database of wholesale acquisition costs.

Overall, they found that the drug prices tended to increase by about seven percent in the 11 months leading up to a shortage—but then increased by 16 percent in the 11 months after a shortage. Moreover, the size of that increase for individual drugs was linked to competition. The scarce drugs that had three or fewer competitors collectively held their price increase rates at about 12 percent *before* shortages. That rate leapt to 27 percent afterward.

On the flip side, drugs with plenty of competition (more than three competitors) saw their rates increase by just 2.5 percent before a shortage and a little under five percent afterward.

Modeling the pricing data, the researchers found that shortages pushed pricing increase rates from an expected nine percent to 20 percent. For drugs with little competition, the rate increases from 17 percent to 30 percent.

To combat potentially exploitative hikes, the authors offer a recommendation:

If manufacturers are observed using shortages to increase prices, public payers could set payment caps for drugs under shortage and limit price increases to those predicted in the absence of a shortage.

Annals of Internal Medicine, 2018. DOI: 10.7326/M18-1137 (About DOIs).

http://bit.ly/2Qqa2vp

Syphilis Cases Surge Among US Newborns, Reaching 20-Year High

A resurgence of syphilis in the United States has led to a dramatic spike in cases of the disease among newborns, according to a new report.

By Rachael Rettner, Senior Writer | September 25, 2018 04:22pm ET

The report found that in recent years, cases of syphilis among newborns — a condition known as congenital syphilis — more than doubled in the U.S., from 362 cases in 2013 to 918 cases in 2017. The latter is the highest number of congenital syphilis cases reported in the U.S. in 20 years, according to the report, from the Centers for Disease Control and Prevention (CDC).

The rise parallels recent increases in syphilis rates among U.S. adults. For nearly two decades, rates of the disease have increased among men, and rates are now rising among women as well. From 2016 to 2017, cases of syphilis increased 21 percent among U.S. women, the report said.

In 2017, congenital syphilis cases were reported in 37 states, but five states accounted for 70 percent of those cases, the CDC said. The five states were California, Arizona, Texas, Louisiana and Florida.

Congenital syphilis can lead to a number of complications, including miscarriage or premature birth, as well as blindness, deafness or even death in newborns, according to the CDC.

The report highlighted the need for all pregnant women to receive early prenatal care, including a syphilis test at their first pregnancy-related doctor's visit.

"Early testing and prompt treatment to cure any infections are critical first steps, but too many women are falling through the cracks of the system," Dr. Gail Bolan, director of the CDC's Division of STD Prevention, said in a statement. "If we're going to reverse the resurgence of congenital syphilis, that has to change."

Syphilis, which is caused by the bacterium *Treponema pallidum*, is a sexually transmitted disease, but it can also pass from mother to baby during pregnancy or delivery. If left untreated, a pregnant woman with syphilis has up to an 80 percent chance of passing the disease to her baby, the CDC said. But the good news is that the infection is easily cured during pregnancy with the right antibiotics.

However, for some women, one test for syphilis during pregnancy may not be enough; the CDC report found that some pregnant women who initially tested negative for syphilis later acquired the infection after their first test. For this reason, women who are at high risk for

syphilis or who live in areas with higher rates of the disease should be tested at the first prenatal visit as well as during the third trimester and at delivery, the CDC said. Anyone, including pregnant women, can lower their risk of syphilis by using condoms properly every time they have sex and by making sure that their partner has also been tested for syphilis, the CDC said.

http://bit.ly/2R47RfI

Ancient Japanese wolf may be rare remnant of ice age wolves

Wolf appears to be a relic of an ancient group of wolves

By Ann GibbonsSep. 25, 2018 , 10:50 AM

JENA, GERMANY—On the island of Honshū in Japan, farmers long appreciated a small gray wolf as a guardian of their crops because its howls warned them of raiders such as wild boars. In folklore, "the Honshū wolf" was seen as a spirit of the forest and honored with shrines. But when the wolves got rabies from dogs in the 19th century, farmers shot and poisoned them until the last wolf died in 1905.

Geoff A Howard/Alamy Stock Photo

Now, only a few stuffed Honshū wolves, like the one shown above, exist in museums. But they were indeed representatives of a wilder era, as graduate student Jonas Niemann of the University of Copenhagen found to his surprise. When he and his colleagues analyzed the genome of a Honshū wolf skeleton from the Natural History Museum in London, they found that this wolf appeared to be a relic of an ancient group of wolves that ranged across the Northern Hemisphere until 20,000 years ago.

The wolf's DNA more closely resembled that of a long-extinct wolf that lived in Siberia more than 35,000 years ago than that of living Eurasian and American wolves, Niemann reported here on Friday at the International Symposium on Biomolecular Archaeology. Most ancient wolves went extinct when the ice sheets that covered the Northern Hemisphere began to melt more than 20,000 years ago and the large mammals the wolves hunted, such as mammoth, died off. But some of their DNA lived on in the Honshū wolf, which could offer a new window on the evolution of wolves as well as dogs, says paleogeneticist Mikkel Sinding of the Greenland Institute of Natural Resources in Nuuk, who extracted the DNA.

http://bit.ly/2NPh7Gq

The soothing effects of strangers

People experience a stronger pain relief if they are treated by a person that belongs to a different social group

Is pain treatment more helpful if it is provided by a person from our own social group, or is the help of a stranger more efficient? A study conducted by researchers from the Universities of Wuerzburg, Amsterdam and Zurich investigated this question and found that people experience a stronger pain relief if they are treated by a person that belongs to a different social group.

The study has been published in the latest issue of the Royal Society of London B: Biological Sciences. It was led by Grit Hein, a psychologist, neuroscientist and professor of Translational Social Neuroscience at the Center of Mental Health of the Würzburg University Hospital who teamed up with Jan B. Engelmann (Amsterdam) and Philippe N. Tobler (Zurich).

"Participants received pain on the back of their hand. In one group of participants, this pain was relieved by a person from their own social group, another group of participants received pain relief from a person from a different group. We measured how the pain relief treatment changed neural pain responses and subjective pain judgments." Grit Hein describes the scientists' approach.

Treatment by a stranger was more efficient

The result: "Before the treatment, both groups showed similarly strong responses to pain," Grit Hein explains. "In contrast, after being treated by what they considered a "stranger", the participants from this group rated their pain less intense than the other group. The effect was not limited to the subjective pain experience: "We also saw a reduction of the pain-related activation in the corresponding brain regions," the scientist says.

While being surprising to the lay person, the finding is in line with a core principle of learning theory according to which people learn particularly well when the results differ significantly from what they had expected. This is called "prediction error learning" in psychological language where the surprise contributes to "rooting" the new experience more effectively in the brain.

Analgesic effect of surprise

Related to the pain experiment, this means the following: "The participants who received pain relief from an outgroup member had not expected to actually get effective help from this person," the neuroscientist explains. And the less the participants had anticipated positive experiences, the bigger their surprise when the pain actually subsided and the more pronounced the reduction of their pain responses. "Of course this finding still needs to be verified outside the laboratory", says Grit Hein, " but it could be relevant for the clinical context where treatment by nurses and doctors from different cultures is common today."

https://wb.md/2P3x748

Antibiotics Safe for Appendicitis, 5-Year Follow-up Data Show

Antibiotics may be a feasible alternative to surgery for patients with uncomplicated acute appendicitis, 5-year follow-up data from a randomized trial show.

Nicola M. Parry, DVM

"Long-term follow up of patients with uncomplicated acute appendicitis suggests that initial treatment with antibiotics rather than surgery may be a feasible alternative," write Paulina Salminen, MD, PhD, from the University of Turku, Finland, and colleagues. The researchers published the results online today in *JAMA*.

Although appendectomy has been the mainstay of treatment for acute appendicitis for more than 100 years, recent advances in diagnostic imaging and antibiotic therapies have allowed clinicians to consider antibiotic treatment as a viable alternative strategy in some cases.

In a recent randomized clinical trial, Salminen and colleagues found that 73% of all patients with acute uncomplicated appendicitis who received antibiotics alone did not require surgery at 1-year follow-up. However, questions remained regarding the long-term outcomes for these patients.

With this in mind, Salminen and colleagues sought to investigate the long-term recurrence rate among trial participants. The randomized Appendicitis Acuta trial was conducted at 6 hospitals in Finland and enrolled 530 adults (329 men; 201 women) with uncomplicated acute appendicitis. Of those, 273 underwent appendectomy (median age, 35 years) and 257 initially received antibiotic treatment (median age, 33 years).

With 5 years of follow-up, 3 patients had died: 2 in the appendectomy group and 1 in the antibiotics group. However, none of the deaths was considered related to the trial.

Among the 257 patients who initially received antibiotics, 100 underwent appendectomy during follow-up. Of those, 70 experienced their recurrent appendicitis within 1 year of the first episode (27.3%; 95% confidence interval [CI], 22.0% - 33.2%; 70/256), and 30 patients required an appendectomy at between 1 and 5 years (16.1%; 95% CI, 11.2% - 22.2%; 30/186).

The cumulative incidence of recurrent appendicitis among patients who initially received antibiotics alone was 34.0% (95% CI, 28.2%

- 40.1%; 87/256) at 2 years, 35.2% (95% CI, 29.3% - 41.4%; 90/256) at 3 years, 37.1% (95% CI, 31.2% - 43.3%; 95/256) at 4 years, and 39.1% (95% CI, 33.1% - 45.3%; 100/256) at 5 years

"Nearly 2/3 of all patients who initially presented with uncomplicated appendicitis were successfully treated with antibiotics alone and those who ultimately developed recurrent disease did not experience any adverse outcomes related to the delay in appendectomy," the authors write.

"These findings demonstrate the feasibility of treating appendicitis with antibiotics and without surgery," Salminen and colleagues conclude.

In an accompanying editorial, Edward H. Livingston, MD, deputy editor at *JAMA*, emphasizes that one of the most important findings from this study is that patients in the antibiotics group who eventually needed surgery experienced no major complication because of delaying surgery.

"The findings from the [Appendicitis Acuta] trial dispel the notion that uncomplicated acute appendicitis is a surgical emergency," he emphasizes. "Given that access to a surgeon is not always available, these results may have implications in many different settings and in many different countries."

Future studies should address factors such as the optimal regimen to use for antibiotic treatment of appendicitis, says Livingston, as well as how to manage suspected recurrent appendicitis in patients who initially receive antibiotics alone.

In the AAPAC trial, patients in the antibiotics group received ertapenem (1 g/day) intravenously for 3 days while in hospital, followed by 7 days of levofloxacin (500 mg, once daily) and metronidazole (500 mg, 3 times daily). However, Livingston explains that this regimen is likely more aggressive than needed, and should be reevaluated.

The next step in appendicitis research should expand on the results from this trial to enhance nonsurgical treatment of appendicitis, he continued. "Further studies should be designed using a noninferiority approach, comparing different antibiotic approaches to that used in the [Appendicitis Acuta] study," he concluded.

This study was supported by the Mary and Georg C. Ehrnrooth Foundation, a government research grant (EVO Foundation) awarded to Turku University Hospital, and a Turku University research grant. Salminen has reported receiving personal fees for lectures from Merck, Lilly, and Orion Pharma. The remaining authors and the editorialist have reported no financial conflicts of interest.

JAMA. Published online September 25, 2018.

http://bit.ly/2Iojl9Z

Reclassification recommendations for drug in 'magic mushrooms'

If phase III clinical trials are successful, researchers suggest categorizing the drug as schedule IV

Psilocybe cubensis*, a common variety of psilocybin-containing mushroom.*
Paul Stamets

In an evaluation of the safety and abuse research on the drug in hallucinogenic mushrooms, Johns Hopkins researchers suggest that if it clears phase III clinical trials, psilocybin should be re-categorized from a schedule I drug--one with no known medical potential--to a schedule IV drug such as prescription sleep aids, but with tighter control. The researchers summarize their analysis in the October print issue of *Neuropharmacology*.

"We want to initiate the conversation now as to how to classify psilocybin to facilitate its path to the clinic and minimize logistical hurdles in the future," says Matthew W. Johnson, Ph.D., associate professor of psychiatry and behavioral sciences at the Johns Hopkins

University School of Medicine. "We expect these final clearance trials to take place in the next five years or so."

Following the Controlled Substances Act of 1970, any drug with the potential for abuse is categorized based on criteria that take into account whether the drug has accepted medical use, and its safety and the potential for abuse. Although preliminary research studies suggest that psilocybin may be effective for smoking cessation and for disorders such as cancer-specific depression and anxiety, it must clear phase III clinical trials before the Food and Drug Administration can be petitioned to reclassify it.

Studies in animals and humans both show low potential for abuse, the researchers say. When rats push a lever to receive psilocybin, they don't keep pushing the lever like they do for drugs such as cocaine, alcohol or heroin. When it comes to human studies, people who have used psilocybin typically report using it a few times across their lifetime.

As for safety, studies show it frequently falls at the end of the scales with the least harm to users and society, say the researchers. Psilocybin also is lowest in the potential for lethal overdose as there is no known overdose level.

"We should be clear that psilocybin is not without risks of harm, which are greater in recreational than medical settings, but relatively speaking, looking at other drugs both legal and illegal, it comes off as being the least harmful in different surveys and across different countries," says Johnson.

That being said, although psilocybin is relatively less harmful than other drugs and not prone to compulsive abuse, the researchers don't recommend releasing psilocybin into patients' hands even with a prescription. "We believe that the conditions should be tightly controlled and that when taken for a clinical reason, it should be administered in a health care setting monitored by a person trained for that situation," says Johnson. The researchers foresee that the process for psilocybin use in the clinic would be similar to how an anesthesiologist prescribes and administers a drug, minimizing the potential for abuse or harm.

Additional authors include Roland Griffiths and Jack Henningfield of Johns Hopkins and Peter Hendricks of University of Alabama, Birmingham.

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COI: Griffiths and Henningfield consult for Hefftner Research Institute and Usona Institute.

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

Searching for the roots of brain cancer

Other than ionizing radiation and genetics, little is known about the factors that influence a person's chances of developing the disease.

Neil Savage

To estimate your chances of developing brain cancer, take a look in the mirror. If you see an older white man, you are in the group that is at highest risk of this disease. If you have ever received radiotherapy for another head or neck condition, or have a close relation who has had brain cancer, your chances of developing such a tumour are greater still. But if you notice that your eyes are red from all the pollen you've inhaled, your risk of brain cancer might not be so high, after all.

A person's chances of developing brain cancer are low, regardless of the category into which they fall. In the United States, the lifetime chance of being diagnosed with a malignant tumour of the brain or spinal cord is less than 1%, according to the American Cancer Society.

Epidemiologists are unable to explain the causes of most brain cancers. They have identified a few genetic factors that place some people at higher risk, as well as an external cause — ionizing radiation. And they have ruled out almost all environmental factors, including those implicated in many other cancers, although non-ionizing radiation from mobile phones has not been eliminated

definitively. Along the way, they have discovered that some factors actually reduce the likelihood of developing brain cancer. Such factors offer tantalizing hints at fresh ways to screen for, or even to treat, the disease.

The International Agency for Research on Cancer (IARC) reported that there were 257,000 new cases of brain or nervous-system cancer worldwide in 2012 — an incidence of more than 3 cases per 100,000 people. Brain cancer is most common in white people, and its incidence is highest in northern Europe, at about 10 cases per 100,000, followed by the United States, Canada and Australia. Most of those cancers — roughly 80% — are gliomas, the most common and deadly type of which is glioblastoma multiforme (GBM). "We haven't gotten very far in terms of what we've learned about exposures or other risk factors, but we do know the demographics are different," says Melissa Bondy, an epidemiologist at Baylor College of Medicine in Houston, Texas.

Relative risk

There are two known risk factors for brain cancer. One is ionizing radiation, usually when delivered to the head or neck as treatment for various conditions that include other brain tumours. The other is a family history. People with certain inherited conditions that promote tumour formation, including neurofibromatosis and tuberous sclerosis, are at an increased risk. Such conditions cause about 5% of gliomas.

As well as those conditions, brain cancer itself can run in families. In 2008, Deborah Blumenthal, a neuro-oncologist at Tel-Aviv Sourasky Medical Center in Israel, analysed the medical and genealogical records of 1,401 people in Utah with brain cancer. She and Lisa Cannon-Albright at the University of Utah, Salt Lake City, found that having an immediate relative with GBM doubled a person's risk of developing the same disease[1]. People with close relatives who had a less aggressive form of astrocytoma had almost four times the risk of developing the same tumour. Blumenthal suggested that both the shared environment and shared genes might be to blame.

In 2015, the international study Gliogene, which Bondy leads, identified the first gene to be associated with familial brain cancer[2]. The gene, known as *POT1*, affects the length of telomeres — repetitive sequences of DNA at the ends of chromosomes that help to protect genes. Bondy is now investigating the part that *POT1* mutations play in brain cancer. But, she points out, only about 5% of brain tumours run in families.

Bondy has also looked at localized variations in the DNA sequence, known as single nucleotide polymorphisms (SNPs), that arise spontaneously in individuals. "Over 12,000 individuals, we've found 25 SNPs that seem to be predictive of risk of glioma," she says. However, researchers are unable yet to say how much having one or more such SNPs increases a person's risk.

Strong links to environmental factors have been difficult for researchers to pin down. "We have studied a lot of different factors, over many decades, and we've ruled out a lot," says Jill Barnholtz-Sloan, a cancer epidemiologist at Case Western Reserve University in Cleveland, Ohio. Researchers have not been able to find a link with obesity, drinking alcohol, or exposure through food or in the workplace to certain metals, chemicals or pesticides. "We've studied all those and haven't found anything," Barnholtz-Sloan says. That might be because potential carcinogens must pass through several obstacles to reach the brain. "It's very well protected, compared to a lot of other organs."

The phone question

A possible risk factor about which researchers remain undecided is radiofrequency electromagnetic fields generated by mobile phones. Some studies have hinted at an association with brain cancer, which was enough for the IARC to classify it as a possible carcinogen in humans, along with 301 other agents. (Notably, the IARC has judged

120 agents to be definitely carcinogenic and a further 82 as being probably carcinogenic.) Studies in male rats exposed discontinuously to high levels of mobile-phone radiation for nine hours a day over a period of up to two years found an increase in malignant schwannoma[3], a rare and usually non-lethal tumour type, in the animals' hearts. The relevance of this finding to glioma in people remains an open question.

Bondy is unconvinced. Since mobile-phone use became widespread in the late 1990s, organizations such as the Central Brain Tumor Registry of the United States have reported only a slight uptick in the incidence of brain cancer, which most researchers attribute to improvements in detection owing to advances in imaging technology. "The rates aren't increasing enough to say that electromagnetic exposure from cell phones increases risk of glioma," Bondy says.

There is also no known physical mechanism by which non-ionizing radiation, which imparts much less energy than its ionizing counterpart, can damage DNA. "Scientists have been looking for adverse health effects of radiofrequency fields since the 1950s, without finding much," says Kenneth Foster, an emeritus bioengineer at the University of Pennsylvania in Philadelphia, who has investigated the effects of such radiation. "If there is any increase in cancer risk from use of cell phones, it is quite small."

But the question is not settled, says Jonathan Samet, an epidemiologist at the Colorado School of Public Health in Aurora, who chaired the IARC working group that classified mobile-phone radiation as a possible carcinogen in 2011. Samet thinks it is notable that the recent studies in rats did find some biological effect, and says that the extensive use of mobile phones makes it worthwhile to continue such research.

Nothing to sneeze at

In the search to provide support for risk factors, epidemiologists have turned up an intriguing finding. Certain conditions — including allergies, diabetes and chickenpox — seem to lower a person's risk of developing a brain tumour. Judith Schwartzbaum, an epidemiologist at the Ohio State University in Columbus, analysed blood samples deposited at a blood bank in Norway since 1972. She found that people who tested positive for the antibody immunoglobulin-E (IgE) were 25% less likely to go on to develop a glioma[4]. Women whose blood contained allergen-specific IgE had their risk of developing GBM cut in half. One hypothesis is that the immune system, already on the alert for the presence of allergens, is somehow able to stop brain cancer from gaining a foothold. Another possibility is that people with strong allergic reactions are better at eliminating carcinogens before they can cause damage to the brain.

Several other studies have found similar results. In 2016, Bondy, Barnholtz-Sloan and their colleagues looked at samples that were collected as part of the Glioma International Case-Control Study (GICC), the largest effort so far to study the disease, and found that having a history of respiratory allergies lowered a person's risk of developing glioma by about 30%[5]. Asthma and eczema also significantly reduced the risk of glioma.

In an attempt to better understand the link between immunity and brain cancer, Schwartzbaum went back to the archived Norway blood samples and measured the levels of various immune-system proteins called cytokines in people with glioma, years before their diagnosis[6]. She expected to find that people who went on to develop glioma had lower levels of cytokine than did those who did not develop the cancer. In blood samples taken 15 years before diagnosis, much to her surprise, she observed little difference. But in samples taken five or fewer years before diagnosis, the mix of cytokines started to change. Whereas the correlation between these proteins in older samples was strong — for instance, if the level of one cytokine increased, that of another might decrease — there was a weaker correlation in samples from people who were only a few years away

from diagnosis. “I think the immune system is responding to the tumour,” Schwartzbaum says.

If she is correct — something that Schwartzbaum hopes to confirm by repeating the study on a different collection of blood samples — the finding might give doctors a way to detect glioma at an earlier stage. How useful that would be is unclear, however. Given the rarity of brain cancer and the lack of an easy follow-up diagnostic test, broader screening programmes might not be practical. And even if they were, researchers would still need to show that early detection leads to improved outcomes.

There might be more of a pay-off from teasing out other intriguing associations. In 2017, Schwartzbaum confirmed the presence of an inverse relationship between glioma and blood-glucose levels in people with diabetes[7]. “A lot of people believe that it’s due to medication,” she says. She plans to look at a large data set to determine whether metformin, a drug that is commonly prescribed to treat diabetes and that also seems to interrupt certain processes involved in tumour growth, is associated with a reduced risk of brain cancer.

Another finding to emerge from the GICC was that catching chickenpox lowers a person’s risk of glioma by 21%[8]. When combined with the allergy findings, this “suggests the immune system is suppressing the tumour”, Schwartzbaum says. Working out the mechanism behind that suppression could eventually lead researchers to fresh targets for treatments. It is unclear whether the varicella-zoster-based vaccine used to prevent chickenpox has the same effect on the risk of developing glioma, but if it did, the vaccination might be recommended to help prevent brain cancer, akin to the way in which the human papilloma virus vaccine is used to lower the risk of cervical cancer.

As doctors and researchers develop a better appreciation of the diversity of brain cancer, it is becoming more challenging for epidemiologists to tease out relevant risks. Categorizing such cancers into subtypes that might have different causes, and then cross-checking for potential risks when several factors might be interacting, could require thousands or even tens of thousands of cases. “It’s likely an interplay between genetics and things in your environment and lifestyle, and the mathematics of that is complicated,” says Barnholtz-Sloan.

Schwartzbaum hopes that molecular biology could yet reveal some unknown risk factors. Large studies, including the Million Veterans Project, conducted by the US Department of Veterans Affairs, although not geared specifically to studying brain cancer, could uncover useful evidence. But only, Schwartzbaum says, if there are indeed more risk factors to be found. “Maybe it’s just bad luck — you get a mutation and that’s it,” she says. “But I’d like to make sure that’s true, because if we can find something, maybe we can prevent it.”

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https://go.nature.com/2Qe1YeA

Why Chinese medicine is heading for clinics around the world

For the first time, the World Health Organization will recognize traditional medicine in its influential global medical compendium.

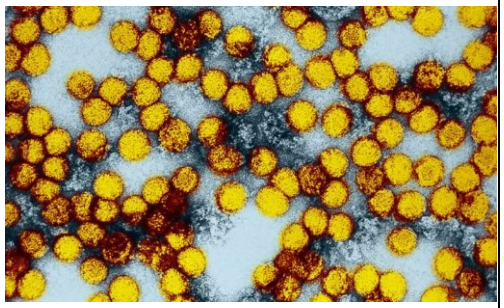
http://bit.ly/2OYeY7U

Zika and yellow fever—vaccines without eggs

New methods with which viruses for vaccines can be replicated in significantly higher concentrations than before

A team led by researchers from the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg is developing methods with which viruses for vaccines can be replicated in significantly higher concentrations than before. The

researchers produce the pathogens in cell cultures in small bioreactors. The production of vaccines currently requires about half a billion chicken eggs per annum, which causes some problems.



The production of vaccines often suffers from complications and bottlenecks.

Yellow fever viruses under an electron microscope. Researchers at the Max Planck Institute for Dynamics of Complex Technical Systems are multiplying the pathogens in bioreactors. This technique could soon also be used in the production of vaccines. **Alamy / CDC / BSIP**

Because production must be planned years in advance, changes in vaccination recommendations, quality defects or even economic calculations by the few companies in the vaccine market have far-reaching consequences for the supply of the protective substances. In April 2017, for example, the US Center for Disease Control announced that the only licensed vaccine against yellow fever would no longer be available in the United States by the end of 2018. Although an alternative was offered which is not licensed in the USA, the limited availability of an effective vaccine could be dangerous in the event of an epidemic. For example, thousands of people became infected with the disease in 2016 during a yellow fever epidemic in Angola and the Congo. The World Health Organisation's stock of vaccine became so limited that the helpers had to vaccinate those at risk with only one fifth of the usual dose.

A combined approach for ideal virus production

A team led by Yvonne Genzel and Alexander Nikolay from the Max Planck Institute for Dynamics of Complex Technical Systems is working on preventing such problems from occurring in the future. Researchers are combining several approaches for the production of flaviviruses under ideal conditions, including the pathogen that causes yellow fever. First they multiply animal cells in a bioreactor filled with nutrient solution, which serve as hosts for the viruses. The cells multiply in suspension, i.e. floating in the nutrient solution. A device that regularly sucks in and pumps back part of the solution is connected to the bioreactor. A module containing dozens of membrane tubes permeable to the nutrient medium retains the cells but filters spent nutrient solution and waste out of the reactor. During this perfusion process, a probe continuously monitors the concentration of the cells, adjusting the supply of fresh culture medium. Researchers have achieved cell concentrations In the bioreactor up to 75 times higher than the usual standard.

The researchers then infect the cells with yellow fever viruses. In doing so, they use another trick to achieve the highest possible virus concentration. The scientists use a pathogen that they have previously adapted to multiply particularly well in animal cells.

Alexander Nikolay prepares a bioreactor for an experiment at the Max Planck Institute for Dynamics of Complex Technical Systems. In a container of this size, the researchers will be able to produce enough viruses for several million doses of vaccine within just a few weeks. **Max Planck Institute for Dynamics of Complex Technical Systems**

Read more at: https://phys.org/news/2018-09-zika-yellow-fevervaccines-eggs.html#jCp

Higher virus concentrations than any other known method

"Our progress is very promising," says Yvonne Genzel, who heads a team in the Bioprocess Technology working group at the Max Planck Institute in Magdeburg. "The new perfusion method makes it possible to produce viruses in extremely large quantities in a small space. This has enabled us to achieve higher virus concentrations for zika and yellow fever than any previous method has been able to

deliver". Perfusion methods might be particularly suitable for the production of large quantities of viruses if the virus yield per cell is very low. "It would be good if this technology could soon be used on a large scale by vaccine manufacturers," explained Udo Reichl, Director of the Max Planck Institute for Dynamics of Complex Technical Systems and head of the Bioprocess Technology working group. "The method should make it possible to adapt production to demand more flexibly and finally find an efficient and economical production process for viruses that are difficult to multiply".

Flaviviruses are usually transmitted to humans via mosquitoes and trigger infectious diseases that can be fatal, such as yellow fever. At present an infection with flavivirus cannot be cured, medicines only relieve the symptoms. However, vaccination can protect against some of the pathogens.

A live vaccine against yellow fever has been available since 1937, but the manufacturing method has not changed fundamentally since the first production processes were established. Pharmaceutical companies are still multiplying the viruses in chicken embryos. They then produce live vaccines from viruses without disease-causing properties. They need eggs that are not contaminated by foreign substances and other pathogens and the production of a vaccine in this way takes about 12 months.

Viruses for 10 million vaccine doses after two weeks

With the new production method, the number of yellow fever viruses that multiply in a bioreactor with one litre capacity in two weeks is equal to the number required for ten million vaccine doses. "Unfortunately, the viruses cannot be harvested directly through the hollow fibre membrane because the membrane becomes blocked over time," said Yvonne Genzel. "This is why we are also testing other perfusion systems without membranes".

Her team is also investigating how perfusion methods work with other pathogens such as the flu virus, the Japanese encephalitis virus and the modified vaccinia Ankara virus. The latter is a promising candidate to introduce genetic material into the cells of living organisms in gene therapy. Cancer treatment requires extremely high virus concentrations so that doctors can use this method to treat previously incurable tumours. If the perfusion method proves its worth in the planned research, viruses could become more readily available for many applications.

Explore further: *Researchers map the potential spread of yellow fever virus to cities around the world*

More information: *Alexander Nikolay et al. Process intensification of EB66® cell cultivations leads to high-yield yellow fever and Zika virus production, Applied Microbiology and Biotechnology (2018). DOI: 10.1007/s00253-018-9275-z*

http://bit.ly/2OcWdRh

Phobos May Have Come from Massive Impact on Mars

Phobos may be more similar to the Martian crust than it appears

The Martian moons **Phobos** and Deimos have been suggested to be **captured asteroids** based on the similarities between the dark, red, nearly featureless spectra of these bodies and **D-class asteroids**. However, the capture hypothesis suffers from difficulties associated with the shapes and inclinations of the Martian moons' orbits. A new look at old data from **NASA's Mars Global Surveyor** lends support to the idea Phobos (and likely Deimos) formed after a large impact on the planet threw a lot of rock into orbit. The dataset held unplumbed clues to the stuff Phobos is made of, which may be more similar to the Martian crust than it appears.

***Martian moon Phobos*: NASA / JPL-Caltech / University of Arizona.**

Planetary researchers study the mineral composition of objects by breaking the light they reflect into component colors with a spectrophotometer, creating distinctive visual 'fingerprints.'

By comparing the spectral fingerprints of planetary surfaces to a library of spectra for known materials, they can infer the composition of these distant objects.

Most of the research into the composition of asteroids has examined their spectra in visible light and in near-infrared light, which is just beyond human vision on the red side of the visible spectrum.

Phobos and D-class asteroids look much the same — that is, both their spectra are nearly featureless because they are so dark.

D-class asteroids are nearly black as coal because, like coal, they contain carbon. This dark aspect of Phobos led to the hypothesis that the moon is a captive asteroid that flew a little too close to Mars.

But planetary scientists looking at the orbits of the Martian moons argued they could not have been captured. They believe the moons must have formed at the same time as Mars, or resulted from a massive impact on the planet during its formative millennia.

"If you talk to the people who are really good at orbital dynamics and figuring out why certain bodies orbit the way they do, they say that, given the inclination and the details of Phobos' orbit, it's almost impossible that it was captured," said Dr. Tim Glotch, a geoscientist at Stony Brook University in New York.

"So you have the spectroscopists saying one thing and the dynamicists saying something else."

Dr. Glotch and colleagues decided to look at the problem in a different light: the mid-infrared, which is in the same range as body temperature.

They compared the mid-infrared spectra of Phobos — collected in 1998 by the Thermal Emission Spectrometer carried on the Mars Global Surveyor — to samples of a meteorite that fell to Earth near Tagish Lake, British Columbia, which some scientists have suggested is a fragment of a D-class asteroid, and other rock types.

In the lab, they subjected their samples to Phobos-like conditions of cold vacuum, heating them from above and below to simulate the extreme changes in temperature from the sunny to the shady sides of airless objects in space.

"We found, at these wavelength ranges, the Tagish Lake meteorite doesn't look anything like Phobos, and in fact what matches Phobos most closely, or at least one of the features in the spectrum, is ground-up basalt, which is a common volcanic rock, and it's what most of the Martian crust is made out of," Dr. Glotch said.

"That leads us to believe that perhaps Phobos might be a remnant of an impact that occurred early on in Martian history."

The study does not argue Phobos is made entirely of material from Mars, but the new results are consistent with the moon containing a portion of the planet's crust, perhaps as an amalgamation of debris from the planet and the remnants of the impacting object.

"The Tagish Lake meteorite is unusual, and perhaps not the best example of a D-class asteroid available for a compelling comparison with Phobos," said Dr. Marc Fries, a planetary scientist and curator of cosmic dust at NASA's Johnson Space Center, who was not involved in the study.

"The new study was unlikely to be able to produce a definitive answer because Phobos is subject to space weathering, which affects its reflectance spectrum and is difficult to replicate in the lab."

The findings were published online this week in the *Journal of Geophysical Research: Planets.*

Timothy D. Glotch et al. MGS-TES spectra suggest a basaltic component in the regolith of Phobos. Journal of Geophysical Research: Planets, published online September 24, 2018; doi: 10.1029/2018JE005647

http://bit.ly/2xKPDbd

People can die from giving up the fight

New research into 'give-up-itis'

People can die simply because they've given up, life has beaten them and they feel defeat is inescapable, according to new research.

The study, by Dr John Leach, a senior research fellow at the University of Portsmouth, is the first to describe the clinical markers for 'give-up-itis', a term used to describe what is known medically as psychogenic death.

It usually follows a trauma from which a person thinks there is no escape, making death seem like the only rational outcome.

If not arrested, death usually occurs three weeks after the first stage of withdrawal.

Dr Leach said: "Psychogenic death is real. It isn't suicide, it isn't linked to depression, but the act of giving up on life and dying usually within days, is a very real condition often linked to severe trauma."

He describes in clinical detail the five stages leading to progressive psychological decline and suggests give-up-itis could stem from a change in a frontal-subcortical circuit of the brain governing how a person maintains goal-directed behaviour.

The likely candidate in the brain is the anterior cingulate circuit, responsible for motivation and initiating goal-directed behaviours.

He said: "Severe trauma might trigger some people's anterior cingulate circuit to malfunction. Motivation is essential for coping with life and if that fails, apathy is almost inevitable."

Death isn't inevitable in someone suffering from give-up-itis and can be reversed by different things at each stage. The most common interventions are physical activity and/or a person being able to see a situation is at least partially within their control, both of which trigger the release of the feel-good chemical dopamine.

"Reversing the give-up-itis slide towards death tends to come when a survivor finds or recovers a sense of choice, of having some control, and tends to be accompanied by that person licking their wounds and taking a renewed interest in life," he said.

The five stages of give-up-itis are:

1. **Social withdrawal** - usually after a psychological trauma. People in this stage can show a marked withdrawal, lack of emotion, listlessness and indifference and become self-absorbed.

Prisoners of war have often been described in this initial state, having withdrawn from life, of vegetating or becoming passive.

Dr Leach said withdrawal can be a way of coping, to pull back from any outward emotional engagement to allow an internal re-alignment of emotional stability, for example, but if left unchecked it can progress to apathy and extreme withdrawal.

2. **Apathy** - an emotional or symbolic 'death', profound apathy has been seen in prisoners of war and in survivors of shipwreck and aircraft crashes. It's a demoralising melancholy different to anger, sadness or frustration. It has also been described as someone no longer striving for self-preservation. People in this stage are often dishevelled, their instinct for cleanliness gone.

Dr Leach said one prisoner of war who was also a medical officer described being in this stage as waking each morning but being unable to summon the energy to do anything. Others describe it as a severe melancholy, where even the smallest task feels like the mightiest effort.

3. **Aboulia** - a severe lack of motivation coupled with a dampened emotional response, a lack of initiative and an inability to make decisions.

People at this stage are unlikely to speak, frequently give up washing or eating and withdraw further and deeper into themselves.

At this stage, a person has lost intrinsic motivation - the ability or desire to start acting to help themselves - but they can still be motivated by others, through persuasive nurturing, reasoning, antagonism and even physical assault. Once external motivators are removed, the person reverts to inertia.

Dr Leach said: "An interesting thing about aboulia is there appears to be an empty mind or a consciousness devoid of content. People at

this stage who have recovered describe it as having a mind like mush, or of having no thought whatsoever. In aboulia, the mind is on stand-by and a person has lost the drive for goal directed behaviour."

4. **Psychic akinesia** - a further drop in motivation. The person is conscious but in a state of profound apathy and unaware of or insensitive to even extreme pain, not even flinching if they are hit, and they are often incontinent and continue to lie in their own waste. A lack of pain response is described in a case study in which a young woman, later diagnosed with psychic akinesia, suffered second-degree burns while visiting the beach, because she hadn't removed herself from the sun's heat.

5. **Psychogenic death** - Dr Leach describes this final stage as the disintegration of a person.

He said: "It's when someone then gives up. They might be lying in their own excreta and nothing - no warning, no beating, no pleading can make them want to live."

In concentration camps, people who reached this stage were often known to be near death by fellow prisoners when they took out a hidden cigarette and began smoking it. Cigarettes were highly valuable in the camps and could be traded for important things such as food.

Dr Leach said: "When a prisoner took out a cigarette and lit it, their campmates knew the person had truly given up, had lost faith in their ability to carry on and would soon be dead."

The progress from stage four, psychic akinesia, to stage five, psychogenic death, generally takes three to four days and shortly before death, there's often a false dawn - a flicker of life, for example, when someone suddenly enjoys a cigarette.

Dr Leach said: "It appears briefly as if the 'empty mind' stage has passed and has been replaced by what could be described as goal-directed behaviour. But the paradox is that while a flicker of goal-directed behaviour often takes place, the goal itself appears to have become relinquishing life."

http://bit.ly/2NS3Qqw

Educating the next generation of medical professionals with machine learning is essential

Teaching hospitals have not yet come to grips with educating students and trainees on AI and ML

Boston - Artificial intelligence (AI) driven by machine learning (ML) algorithms is a branch in the field of computer science that is rapidly gaining popularity within the healthcare sector. However, graduate medical education and other teaching programs within academic teaching hospitals across the U.S. and around the world have not yet come to grips with educating students and trainees on this emerging technology.

"The general public has become quite aware of AI and the impact it can have on health care outcomes such as providing clinicians with improved diagnostics. However, if medical education does not begin to teach medical students about AI and how to apply it into patient care then the advancement of technology will be limited in use and its impact on patient care," explained corresponding author Vijaya B. Kolachalama, PhD, assistant professor of medicine at Boston University School of Medicine (BUSM).

Using a PubMed search with 'machine learning' as the medical subject heading term, the researchers found that the number of papers published in the area of ML has increased since the beginning of this decade. In contrast, the number of publications related to undergraduate and graduate medical education have remained relatively unchanged since 2010.

Realizing the need for educating the students and trainees within the Boston University Medical Campus about ML, Kolachalama designed and taught an introductory course at BUSM. The course is intended to educate the next generation of medical professionals and

young researchers with biomedical and life sciences backgrounds about ML concepts and help prepare them for the ongoing data science revolution.

The authors believe that if medical education begins to implement ML curriculum, physicians may begin to recognize the conditions and future applications where AI could potentially benefit clinical decision making and management early on in their career and be ready to utilize these tools better when beginning practice. "As medical education thinks about competencies for physicians, ML should be embedded into information technology and the education in that domain," said Priya Sinha Garg, MD, associate dean ad interim for Academic Affairs at BUSM.

The authors hope this perspective article stimulates medical school and residency programs to think about the progressing field of AI and how to use it in patient care. "Technology without physician knowledge of its potential and applications does not make sense and will only further perpetuate healthcare costs."

These findings appear as a perspective in the journal *NPJ Digital Medicine*.

Funding was provided by the American Heart Association through a Scientist Development Grant (17SDG33670323); the Hariri Institute for Computing and Computational Science & Engineering at Boston University through a Research Award; the National Center for Advancing Translational Sciences, National Institutes of Health, through BU-CTSI Grant (1UL1TR001430); the Whitaker Cardiovascular Institute at Boston University School of Medicine through a pilot grant award.

http://bit.ly/2Ooc2nW

Low-dose contraceptive pill protects against ovarian cancer

Study finds reduced cancer rates even after contraceptive use ceases.

Andrew Masterson reports.

Newer oral contraceptives use less oestrogen, but still deliver anti-cancer benefits.

A Danish study involving almost two million women has found that low-dose oestrogen contraceptive pills are associated with a reduced rate of ovarian cancer.

The news will come as a relief to users and clinicians alike. The protective effect against cancer of oral contraceptives has long been established, but most studies in the field used data arising from older-style pills, which contained comparatively high doses of oestrogen.

Over the past few years, contraceptive pill manufacturers have switched to a new formula, with different progestogens and much lower levels of oestrogen. This gave rise to the not unreasonable speculation that the reduced quantity might also lessen the protective anti-cancer effect.

Now, however, the latest study, by researchers led by Lisa Iversen from the University of Aberdeen in Scotland, dispels the concern.

The researchers used Danish prescribing and cancer registries to track the health of 1.9 million women aged between 15 and 49 for the years 1995 to 2014. They divided the women into three categories: those who had never used oral contraceptives, those who were using the pills or had stopped within the past 12 months, and those who had stopped for longer than a year.

After taking into account other potential influences, they found that the rate of ovarian cancer among women who had never used the contraceptives was 7.5 per 100,000 – more than double that found in the other two cohorts.

There was no evidence of a similar protective effect among women who used progestogen-only pills, but that might because this group comprised only 14% of the sample and was thus too small to produce meaningful results.

The study was observational, so cannot be used to draw any conclusions regarding the mechanics of the protective effect. Nevertheless, Iverson and her colleagues conclude that oral

contraceptives prevented an estimated 21% of cancer cases among the user groups.

"Based on our results, contemporary combined hormonal contraceptives are still associated with a reduced risk of ovarian cancer in women of reproductive age, with patterns similar to those seen with older combined oral products," say the authors.

"The reduced risk seems to persist after stopping use, although the duration of benefit is uncertain. Presently, there is insufficient evidence to suggest similar protection among exclusive users of progestogen-only products."

The study is published in the journal *The BMJ*.

http://bit.ly/2zEOCmo

Ancient DNA reveals the secrets of a devastating European disease

Comparison with modern strains offers glimpses of the pathogen's evolutionary history.

Kiona N. Smith - 9/27/2018, 6:40 AM

Many epidemics of fever ravaged Europe from ancient times through the early 20th century. But one disease stands out in historical accounts because authors describe patients appearing to recover before relapsing into fever again and again. This disease has been around for so long that Hippocrates described a series of such fevers that struck the city of Thasos in the wake of an especially harsh winter, and outbreaks have persisted through last century.

PNAS

The disease tended to show up when times were hardest. Over the centuries, records describe epidemics of a nearly identical illness, usually on the heels of war or famine, with isolated cases popping up between times among the poor. One such epidemic struck during the Great Irish Famine of 1846 to 1852. Another ravaged Central Europe and Russia in the aftermath of World War I, killing at least five million people.

For years, historians have blamed those epidemics, termed louse-borne relapsing fever (LBRF), on *Borrelia recurrentis*, a twisting, spiral-shaped bacterium transmitted only by the human body louse. The logic was simple: *B. recurrentis* causes the only relapsing fever we know of that's carried by lice and capable of spreading fast enough to cause an epidemic. Although it seems to make frequent and horrible appearances in the historical record, LBRF has been totally invisible in the archaeological record. A new study changes that and provides evidence that *B. recurrentis* is indeed at fault.

An isolated case

Paleopathologist Meriam Guellil of the University of Oslo and her colleagues managed to assemble a nearly complete *B. recurrentis* genome from sequences of DNA recovered from the skeleton of a woman buried in a medieval graveyard in Oslo. She had been buried with her child, who was between seven and nine years old, near the southern edge of the graveyard—the one farthest from the church. This revealed something about her socioeconomic status even before anyone found evidence of a louse-borne pathogen on her remains.

She must have had a difficult life, and radiocarbon dating indicates that it came to an end around 1430 to 1465 CE. Based on how much bacterial DNA showed up in the shotgun sequencing performed by Guellil and her colleagues, the woman probably died with a lot of *B. recurrentis* in her system, so it's likely that the fever killed her.

"Although at the time of the burial... the town was still affected by the economic decline caused by the Black Death in the mid-1300s, which probably left parts of the population vulnerable to disease and malnourishment," wrote Guellil and her colleagues, "the results

reported in this study probably represent an isolated case of the disease."

That's not enough to confirm that louse-borne relapsing fever caused all those historical epidemics, but it at least proves that the disease was present in medieval Europe. The real surprise, however, is how the medieval European version of LBRF differs from the modern strains that still impact people living in Ethiopia, Eritrea, Somalia, and Sudan. At some point in its evolutionary history, *B. recurrentis* appears to have split into two lineages—and they've evolved different adaptive strategies, the medieval DNA suggests.

Different ways to downsize a genome

B. recurrentis causes relapses because its genetic code enables the bacteria to run through a random sequence of different variants of two proteins, called antigens, on its surface. The variations change the shape of its antigens, allowing it to keep dodging the host's immune responses. The result is a fever that seems to clear up, then flares up again as the immune system tries to respond to a new set of antigens.

The genes that code for the antigen variants are stored on several plasmids, strands of DNA that can replicate or move around separately from the bacteria's chromosome. The more places in the bacterial genome that encode an antigen variant, the larger the number of them it can randomly produce to thwart a host's immune system—at least in theory. But compared to modern African strains, the medieval strain is missing copies of six loci, mostly at a particular site on some plasmids.

But this method of hiding from the immune system is only one possible evolutionary solution. Other pathogens facing similar challenges tend to evolve smaller genomes and greater virulence. Guellil and her colleagues compared the genomes of the medieval strain of *B. recurrentis* to the modern African strains, as well as DNA sequences from a close relative, a tick-borne pathogen called *B. duttoni* that also causes a relapsing fever. Compared to its tick-borne cousin, all the louse-borne relapsing fever strains had fewer intact copies of the antigen variation genes.

"But this difference is even more pronounced in the medieval strain," wrote the researchers. Modern strains, meanwhile, have also downsized their genomes over the countless generations since their last common ancestor with the medieval European strain, but they've done it differently.

One of the major differences between the medieval strain and the modern strains is a genetic sequence called OppA-1, which is involved in metabolism—or would be, if it worked. In modern strains, it has been reduced to an imperfect, nonfunctional copy called a pseudogene, thanks to a stop codon in the middle of its sequence. In the medieval strain and in its close relative *B. duttoni*, OppA-1 still works.

Adaptive trade-offs

But everything has consequences, and for the medieval European strain of *C. recurrentis*, the price of a smaller genome was probably fewer antigen variants. That may have meant that the medieval European version of LBRF brought fewer relapses, on average, than the modern African versions. But Guellil and her colleagues say it's impossible to be sure, because there's not much modern data on untreated cases of the fever, and historical sources aren't always specific about the number of relapses patients suffered.

One clue, however, may lie in the LBRF's tick-borne cousin, *B. duttoni*, which has more intact loci for antigen variation than modern *B. recurrentis*. It tends to produce more relapses in untreated patients. As for OppA-1, Guellil and her colleagues wrote that "We can only speculate about the effect of this mutation on the ecological life cycle of the disease."

Based on their comparison of the medieval bacterial genome with modern strains, the researchers suggest that the two lineages have

adapted to different environments. Humans may have helped shape that adaptation by putting pressure on the vector—maybe by changing hygiene or housing practices—or its host, but paleopathologists don't have enough data yet to be sure.

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http://bit.ly/2OZJNcm

Crash diets are highly effective – new evidence

Latest* research *suggests it isn't always the case that crash dieting isn't the best way to lose weight

Nerys M Astbury*

If you've ever tried to lose weight, you've probably heard that crash dieting isn't the best way to go about it. Although you may lose lots of weight initially, you won't be able to keep the weight off and may even end up being heavier than you were before. But our latest research suggests that this isn't always the case.

Most people are aware that being overweight is bad for their health, so it's not surprising that about half of the UK population is trying to lose weight at any given time. But many people struggle to stick to traditional diets long enough to achieve results.

Some people opt for a quicker, more drastic solution: crash dieting. These diets, otherwise known as total diet replacement (TDR) programmes, involve drastically reducing calorie intake to between 800-1,200 calories per day. (The usual calorie intake for a woman is 2,000 calories, and for a man it's 2,500 calories.) People on these diets consume nothing but specially formulated soups, shakes and bars for up to 12 weeks.

Although lots of retailers sell these TDR products, they are more effective when combined with support and encouragement from a dietitian or trained counsellor. This professional support helps dieters develop the skills to stick with the programme and keep the weight off once the programme is complete.

However, in the UK, GPs don't tend to refer people who are looking to lose weight to these programmes. This is because NICE, the agency that evaluates treatments for the NHS, doesn't recommend TDR programmes, perhaps because there wasn't enough evidence to support TDR when NICE published their guidance. But recent studies suggest that it may be time for NICE to reevaluate the evidence.

Time to reevaluate crash diets

For our study, which is published in the BMJ, we recruited 278 obese patients. Half were randomly assigned to a 12-week TDR programme, while the other half were assigned to see the practice nurse for advice on how to lose weight ("usual care").

After one year, those assigned to receive the TDR programme lost an average of 11kg, while those in the usual care group lost an average of 3kg. Using a tool that helps GPs estimate a patient's risk of having a heart attack or stroke in the next ten years, the people in the TDR group had significantly reduced their risk score.

The TDR group also had significantly greater improvements in blood glucose control than the usual care group. Perhaps most important of all, participants in the TDR group reported bigger increases in quality of life than people in the usual care group.

More people in the TDR group reported side effects, but the number of more serious side effects was similar across groups. Side effects that were more common in the TDR group than in the usual care group included constipation, headache, fatigue and dizziness.

This new evidence suggests that TDR is a safe and effective way to lose a large amount of weight. For now, though, TDR programmes are not available on the NHS. Those interested in losing weight using TDR have to pay for it themselves, which means that many people who could benefit from this treatment may be unable to access it.

Senior Researcher - Diet and Obesity, University of Oxford

Disclosure statement

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http://bit.ly/2IoQ3rP

The warm glow of kindness is real -- Sussex study confirms

The 'warm glow' of kindness is real -- even when there's nothing in it for you

Psychologists at the University of Sussex have confirmed that the warm glow of kindness is real, even when there's nothing in it for you. In their study, published in *NeuroImage*, they undertook a major analysis of existing research showing the brain scans relating to over 1000 people making kind decisions. For the first time, they split the analysis between what happens in the brain when people act out of genuine altruism - where there's nothing in it for them - and when they act with strategic kindness - when there is something to be gained as a consequence.

Many individual studies have hinted that generosity activates the reward network of the brain but this new study from Sussex is the first that brought these studies together, and then split the results into two types of kindness - altruistic and strategic. The Sussex scientists found that reward areas of the brain are more active - i.e. use up more oxygen - when people act with strategic kindness, when there is an opportunity for others to return the favour.

But they also found that acts of altruism, with no hope of personal benefit, activate the reward areas of the brain too, and more than that, that some brain regions (in the 'subgenual anterior cingulate cortex') were more active during altruistic generosity, indicating that there is something unique about being altruistic with no hope of gaining something in return.

Dr Daniel Campbell-Meiklejohn, the study's lead and Director of the Social Decision Laboratory at the University of Sussex, said:

"This major study sparks questions about people having different motivations to give to others: clear self-interest versus the warm glow of altruism. The decision to share resources is a cornerstone of any cooperative society. We know that people can choose to be kind because they like feeling like they are a 'good person', but also that people can choose to be kind when they think there might be something 'in it' for them such as a returned favour or improved reputation. Some people might say that 'why' we give does not matter, as long as we do. However, what motivates us to be kind is both fascinating and important. If, for example, governments can understand why people might give when there's nothing in it for them, then they can understand how to encourage people to volunteer, donate to charity or support others in their community."

Jo Cutler, the PhD student who co-authored the study at the University of Sussex, added:

"The finding of different motivations for giving raises all sorts of questions, including what charities and organisations can learn about what motivates their donors. Some museums, for example, choose to operate a membership scheme with real strategic benefits for their customers, such as discounts. Others will ask for a small altruistic donation on arrival. Organisations looking for contributions should think about how they want their customers to feel. Do they want them to feel altruistic, and experience a warm glow, or do they want them to enter with a transactional mind-set?"

"Given that we know there are these two motivations which overlap in the brain, charities should be careful not to offer something which feels like a token gesture, as this might undermine a sense of altruism. Sending small gifts in return for a monthly donation could change

donors' perceptions of their motivation from altruistic to transactional. In doing so, charities might also inadvertently replace the warm glow feeling with a sense of having had a bad deal."

"The same issues could also apply when we think about interactions between family, friends, colleagues or strangers on a one-to-one basis. For example, if after a long day helping a friend move house, they hand you a fiver, you could end up feeling undervalued and less likely to help again. A hug and kind words however might spark a warm glow and make you feel appreciated. We found some brain regions were more active during altruistic, compared to strategic, generosity so it seems there is something special about situations where our only motivation to give to others is to feel good about being kind."

Jo Cutler and Dr Campbell-Meiklejohn analysed 36 existing studies relating to 1150 participants whose brains were scanned with fMRI scans over a ten-year period.

http://bit.ly/2xLb3VD

Oumuamua Traced to Four Possible Home Stars

Four stars identified as possible homes of 'Oumuamua

In October 2017, a fast moving, cigar-shaped comet of extrasolar origin was **discovered** close to the Earth with the Pan-STARRS1 telescope in Hawai'i. Officially named 1I/2017 U1 ('Oumuamua), the **comet** was presumably **ejected** from a forming planetary system, probably by a gravitational kick from a giant exoplanet. Now, using data from ESA's star-mapping Gaia satellite, **Dr. Coryn Bailer-Jones** of the Max Planck Institute for Astronomy and co-authors have identified four stars as possible homes of 'Oumuamua.

Comets are leftovers of the formation of planetary systems, and it is possible that 'Oumuamua was ejected from its home star's realm while planets were still taking shape there.

To look for its home, astronomers had to trace back in time not only the trajectory of the interstellar comet, but also of a selection of stars that might have crossed paths with this object in the past few million years.

To this aim, Dr. Bailer-Jones and his colleagues dived into the data from Gaia's second release.

The Gaia data contain positions, distance indicators and motions on the sky for more than a billion stars in our Milky Way Galaxy; most importantly, the data set includes radial velocities — how fast they are moving towards or away from us — for a subset of seven million, enabling a full reconstruction of their trajectories.

This artist's impression shows the first interstellar comet 'Oumuamua. **M. Kornmesser / ESO.**

The astronomers looked at these seven million stars, complemented with an extra 220,000 for which radial velocities are available from the astronomical literature.

As a result, they identified four stars whose orbits had come within a couple of light years of 'Oumuamua in the near past, and with relative velocities low enough to be compatible with likely ejection mechanisms.

All four had their 'close' encounter with 'Oumuamua between one and seven million years ago.

However, none of these stars is known to either harbor planets or to be part of a binary stellar system; a giant planet or companion star would be the preferred mechanism to have ejected the small body.

"All four of them are dwarf stars," Dr. Bailer-Jones and co-authors said.

"The one that came closest to 'Oumuamua, at least about one million year ago, is HIP 3757, a reddish dwarf star some 81 light-years away. It approached within about 1.96 light-years."

"Given the uncertainties unaccounted for in this reconstruction, that is close enough for 'Oumuamua to have originated from its planetary system. However, the comparatively large relative speed (around 56,000 mph, or 25 km/s) makes it less probable for this to be 'Oumuamua's home."

"The next candidate, HD 292249, is similar to our Sun and is approximately 135 light-years away. It was a little bit less close to the object's trajectory 3.8 million years ago, but with a smaller relative speed of 22,400 mph, or 10 km/s."

"The two additional candidates met 'Oumuamua 1.1 and 6.3 million years ago, respectively, at intermediate speeds and distances."

While future observations of these four stars might shed new light on their properties and potential to be the home system of 'Oumuamua, the astronomers are also looking forward to future releases of Gaia data.

The team's paper will be published in the *Astronomical Journal*.

C.A.L. Bailer-Jones et al. *2018. Plausible home stars of the interstellar object 'Oumuamua found in Gaia DR2.* AJ, *in press; arXiv: 1809.09009*

http://bit.ly/2zFA59T

Gene drive used to turn all female mosquitos sterile

In the lab, mosquito populations don't evolve resistance to this approach.

John Timmer - 9/27/2018, 8:15 PM

We've known for a long time that we can limit malaria infections by controlling the mosquitos that transmit them. But that knowledge hasn't translated into control efforts that have always been completely successful. Many of the approaches we've used to control mosquitos have caused environmental problems, and mosquito populations are large enough that they have evolved resistance to many of our pesticides.

That made the development of what are called "gene drive" constructs exciting (if a bit scary). They have the potential to rapidly spread genes throughout a population—including a mosquito population. But the prospect of a modern genetic control of mosquito populations has run up against the very old problem of evolution, as the gene drives often stall due to genetic changes that allow mosquito populations to escape their impact.

Now, a team has figured out a way to possibly avoid this problem: use gene drive to target a gene that is fundamental to how mosquitos develop as male or female. In doing so, it makes the females sterile and, at least in the lab, causes mosquito populations to collapse.

The obvious question

What's gene drive? Essentially, it's a tool for converting an entire population to a single genotype over several generations.

Normally, the spread of genotypes within a population is slow, as each individual carrier will pass it on to only half its offspring, and the chance that two carriers will end up mating are small. The only way to speed things up is to have the genotype provide a powerful advantage in survival or mating success, but that's about the last thing you want to give to mosquitos. Gene drive changes that, accelerating the spread of any chosen genotype, even if it harms the organism carrying it.

The method works using the enzymes involved in gene editing. DNA carrying the genes for these enzymes are placed together with a gene that encodes a short RNA that directs the editing to the location of your choice within an organism's genome. All of this then gets inserted into that same spot where the gene editing system will target the DNA. Typically, this spot resides within one of the organism's genes.

In the next generation, this gene-editing DNA will reside on one chromosome, and the organism's normal DNA will be present on that chromosome's partner. The gene editing system will recognize the normal DNA and make a cut in it. The cell will then attempt to repair this cut using the DNA from this region on the other copy of the

chromosome. But that other copy will have all the genes of the gene editing system inserted in it, so the repaired chromosome will end up with these as well. As a result, both copies of the chromosome will end up carrying the DNA-editing system.

Also as a result, all of their offspring will end up inheriting the engineered gene from this parent. And, in each of these offspring, the process will repeat, converting all the chromosomes to the engineered version. If you start a population where only 12 percent carry the gene-drive system, it will be present in 100 percent of the population in about a dozen generations.

Targeting sex

This process has a lot of potential for things like mosquito control. You can take a population and potentially eliminate its resistance to existing pesticides. Or you can make it sensitive to a chemical that doesn't normally work as a pesticide. Or, in some of the more extreme versions, you can simply kill off all the members of one sex. There has just been one small problem: so far, initial attempts to use gene drive in this manner haven't worked out so well. The problem has been that trying to kill off a population places a strong evolutionary pressure on said population, selecting for animals where the editing doesn't work. This typically involves changes to the DNA at the site the editing system targets, changes that mean the system no longer recognizes it. And, at least with the targets chosen so far, these sorts of changes appear to either already be present in the population at low levels or arise frequently enough that resistance to the gene drive spreads quickly through the population.

These sorts of changes may even occur more often when gene-drive systems are present, since the gene-editing system doesn't always neatly edit and may create deletions of the DNA it targets.

The goal behind the new work is to find a gene where the changes that would make it immune to editing would also damage the gene. To do so, the researchers took advantage of our knowledge of how insects determine sex, largely generated in the fruit fly *Drosophila*. That work has identified a gene called *doublesex* that is essential for both males and females to develop properly.

The male and female activities are somewhat separate. If you simply damage the entire gene, then both sexes are affected and will develop as a confused intermediate of male and female traits. But there's a specific part of the gene that is needed for female development. If it is damaged, then females develop as a mix of traits, while males develop perfectly normally. Because this part is so essential for the gene's function, changes to the DNA there aren't well tolerated.

Driven

This is precisely the area that the researchers, from Imperial College in the UK, targeted with their gene drive system. Males that carry one or two copies of the edited version of the *doublesex* gene develop perfectly normally and are fertile. Females with only one copy also develop normally. In all these cases, these animals will experience gene editing, and all their offspring will end up receiving a copy of the edited version of the gene from them. And females where both copies have been edited develop with a mix of male and female traits and can't reproduce.

Thus, once this gene-drive construct starts to spread, every mosquito is likely to either spread it further or be sterile.

The authors tested this on two groups of mosquitos by mixing in males carrying the gene-drive construct until these unlucky fellows were 12.5 percent of the total population. In one cage, only seven generations were needed for every mosquito to inherit the gene-drive-carrying chromosome. All the females were sterile, and the population collapsed—there was no generation eight. In the second group, this took until generation 11, but that population collapsed as well.

The researchers checked, and they did find a few altered versions of the *doublesex* gene that could no longer be edited. But all of these

deleted part of the female-specific portion of the gene and, therefore, caused female sterility as well. The researchers also sequenced African mosquito populations and found only a single naturally occurring variant at the site where gene editing takes place. Tests show that it wouldn't interfere with the editing. So, as far as they can tell, the evolution of resistance isn't an issue here.

That doesn't mean it can never be. The researchers plan to try their method out in much larger populations to determine if very rare events allow resistance. And they cite a similar approach that targets a different gene involved in the development of the two sexes yet still suffered from frequent resistance. Figuring out exactly how these approaches differed will be important for this to move forward.

Even aside from that, the gene drive isn't ready for use in the field. *Doublesex* is so central to insect sex determination that every species we have looked at has a version, and the ones in closely related species are similar enough that the gene-drive construct could potentially hop species. While targeting other mosquitos might not be a terrible thing, we probably want to have a clear idea of potential issues before releasing anything like this into the wild.

Back to basics

The work also highlights the potential value of the foundational research behind these developments. We didn't actually know what the mosquito version of *doublesex* did before this work. Instead, all of our knowledge had been generated in the fruit fly *Drosophila*; the authors note that this work helps clarify the poorly understood mosquito version of the sex determination pathway. And *Drosophila* isn't a major agricultural pest or a disease vector. People were just studying it in order to have a better understanding of how biology operates.

That's precisely the sort of open-ended, impractical research that finds itself at risk whenever budgets get tight and funding has to be cut. (In fact, fruit-fly research was specifically singled out by Sarah Palin as having "little or nothing to do with the public good.") But science has a funny way of finding uses for knowledge that was developed without any purpose in mind—just like the gene-editing technology itself, which grew out of trying to understand how bacteria protect themselves from viruses.

Nature Biotechnology, 2018. DOI: 10.1038/nbt.4245 (About DOIs).

http://bit.ly/2DHLsSQ

Early Parkinson's patients waiting too long to seek medical evaluation

Too many early PD patients wait too long before seeking medical attention, or start taking symptomatic medications before they are required

The time between diagnosis and the institution of symptomatic treatment is critical in the effort to find a cure for Parkinson's Disease (PD). A paper published in npj Parkinson's Disease notes too many early PD patients wait too long before seeking medical attention, or start taking symptomatic medications before they are required, thereby dramatically shrinking the pool of candidates for clinical trials.

Parkinson's disease is a disorder of the central nervous system that affects movement. Symptoms include tremors, stiffness, and slow and small movement. The pace of progression varies among patients, making the months following diagnosis crucial to researchers studying the disease's progression.

"The critical time of about one year from when the patient can be diagnosed with early PD based on mild classic motor features until they truly require symptomatic therapy can be considered the Golden Year," said lead author Robert A. Hauser, MD, director of the Parkinson's & Movement Disorder Center at the University of South Florida. "It is during this early, untreated phase, that progression of clinical symptoms reflects the progression of the underlying disease."

Hauser says that in order to determine whether or not a potential disease slowing therapy is actually working, they must be able to compare the therapy to a placebo without interference from symptomatic treatment. Otherwise, they won't know if the therapy is slowing the disease's progression or if they are just seeing the effects of symptomatic treatment.

This requires patients to seek assessment soon after they notice the onset of tremor or slow movement. In addition, physicians should consider referring patients to clinical trials soon after diagnosis and delay prescribing symptomatic medication until it's necessary. If a patient waits until symptomatic treatment is necessary, the opportunity to participate in these crucial clinical trials is lost.

http://bit.ly/2NUmFQ3

Cancer hijacks the microbiome to glut itself on glucose

Leukemia undercuts the ability of normal cells to consume glucose, thus leaving more glucose available to feed its own growth

Cancer needs energy to drive its out-of-control growth. It gets energy in the form of glucose, in fact consuming so much glucose that one method for imaging cancer simply looks for areas of extreme glucose consumption - where there is consumption, there is cancer. But how does cancer get this glucose? A University of Colorado Cancer Center study published today in the journal Cancer Cell shows that leukemia undercuts the ability of normal cells to consume glucose, thus leaving more glucose available to feed its own growth.

"Leukemia cells create a diabetic-like condition that reduces glucose going to normal cells, and as a consequence, there is more glucose available for the leukemia cells. Literally, they are stealing glucose from normal cells to drive growth of the tumor," says Craig Jordan, PhD, investigator at University of Colorado Cancer Center, division chief of the Division of Hematology and the Nancy Carroll Allen Professor of Hematology at the University of Colorado School of Medicine.

Like diabetes, cancer's strategies depend on insulin. Healthy cells need insulin to use glucose. In diabetes, either the pancreas under-produces insulin or tissues cannot not respond to insulin and so cells are left starved for energy while glucose builds up in the blood. The current study shows that leukemia goes about creating similar conditions of glucose buildup in two ways.

First, tumor cells trick fat cells into over-producing a protein called IGFBP1. This protein makes healthy cells less sensitive to insulin, meaning that when IGFBP1 is high, it takes more insulin to use glucose than it does when IGFBP1 is low. Unless the supply of insulin goes up, high IGFBP1 means that the glucose consumption of healthy cells goes down. (This protein may also be a link in the chain connecting cancer and obesity: The more fat cells, the more IGFBP1, and the more glucose is available to the cancer.)

Of course, cancer has a second strategy that ensures insulin production does not go up to meet the need created by increased IGFBP1. In fact, cancers turn insulin production down. In large part, they do this in the gut.

"In the course of doing this systemic analysis, we realized that some of the factors that help regulate glucose are made by the gut or bacteria in the gut. We looked there and found that the composition of the microbiome in leukemic animals was different than in control mice," Jordan says.

One major difference in the guts of leukemic mice was the lack of a specific kind of bacteria known as bacteroids. These bacteroids produce short-chain fatty acids that in turn feed the health of cells lining your gut. Without bacteroids, gut health suffers. And the current study shows that without bacteroids, gut health suffers in ways that specifically aid cancer.

One way is the loss of hormones called incretins. When blood glucose gets high, for example after you eat, your gut releases incretins, which tamp down blood glucose, reducing it back into the normal range. Working through the gut, leukemia inactivates these incretins, allowing blood glucose to remain higher than it should. Leukemia also nixes the activity of serotonin. Serotonin is well-known as a "feel good" chemical that helps to regulate mood and is found in many antidepressants. But serotonin is also essential for the manufacture of insulin in the pancreas, and by attacking serotonin, leukemia reduces insulin production (and thus, down the line, glucose use).

The result of less insulin secretion and less insulin sensitivity is that cancer undercuts healthy cells' use of insulin from both sides: Healthy cells need more insulin, just as there is less insulin available. Less insulin use by healthy cells leaves more glucose for the cancer. "It's a classic parasite trick: Take advantage of something the host does and subvert it for your own purposes," Jordan says.

Interestingly, just as a parasite might eat a host's food leading to malnourishment, cancer's energy theft may play a role in the fatigue and weight loss common in cancer patients.

"The fairly prevalent observation is that cancer patients have a condition called cachexia, basically wasting away - you lose weight. If cancers are inducing systemic changes that result in depletion of normal energy stores, this could be part of that story," Jordan says.

However, Jordan and colleagues including first author Haobin Ye, PhD, not only showed how leukemia dysregulates healthy cells' glucose consumption, but also showed how to "re-regulate" this consumption.

"When we administered agents to recalibrate the glucose system, we found that we could restore glucose regulation and slow the growth of leukemia cells," Ye says.

These "agents" were surprisingly low-tech. One was serotonin. Another was tributyrin, a fatty acid found in butter and other foods. Serotonin supplementation replaced the serotonin nixed by leukemia and tributyrin helped to replace the short-chain fatty acids that were absent due to loss of bacteroids.

The group calls the combination Ser-Tri therapy. And they show that it is more than a theory. Ser-Tri therapy led to the recovery of insulin levels and reduction of IGFPB1. And leukemic mice treated with Ser-Tri therapy lived longer than those without. Twenty-two days after leukemia was introduced in mice, all of the untreated mice had died, while more than half of the mice treated with Ser-Tri were still alive.

The continuing line of work shows that cancer may depend on the ability to out-compete healthy cells for limited energy. Healthy tissues have strategies to regulate insulin, glucose and other factors controlling energy consumption; cancer cells have strategies to subvert this regulation with the goal of making more energy available for their own use.

"We now have evidence that what we observed in our mouse models is also true for leukemia patients." Ye says.

Understanding these mechanisms that cancer uses to unbalance the body's system of energy in their favor is helping doctors and researchers learn to thumb the scale in favor of healthy cells.

"This furthers the notion that you can do things systemically to disfavor leukemia cells and favor normal tissue," Jordan says. "This could be part of limiting growth of tumors."

http://bit.ly/2QkyOup

Hitchhikers hinder medication shelf life

Why some biopharmaceuticals have a longer shelf life than others is a problem that has baffled scientists and manufacturers alike.

Karen B. Roberts

Even the same medication, produced by different manufacturers, can vary in its storage life.

University of Delaware Professors Kelvin Lee and Abraham Lenhoff offer insight on one way this can happen in a special class of drugs called monoclonal antibodies, which comprise a large fraction of biopharmaceuticals.

Traditional small molecule medicines, such as ibuprofen or aspirin, are manufactured using well-defined, discrete chemical reactions between various chemical compounds. Biopharmaceuticals, on the other hand, are much larger and more complex molecules that are manufactured by growing cells that produce a desired protein (often, an antibody) that is purified to create the medicine.

Biopharmaceuticals can be used to treat cancers and autoimmune or inflammatory disorders, such as rheumatoid arthritis and Crohn's disease. Adalimumab, for example, is a monoclonal antibody that blocks inflammation caused by rheumatoid arthritis by binding to the signaling protein that triggers the swelling.

The human body makes millions of antibodies in small quantities. Antibodies are what protect you from infection, and to some extent, from disease. For example, a chicken pox vaccine helps the body learn to make an antibody against the chickenpox virus. If you get chickenpox after being vaccinated, the body marshals its antibody troops and sends them off to find, and bind, to the virus; then signals the immune system to eliminate it from the body.

"Once you get the cell to start making the drug for you, then you grow lots of cells, purify the drug, formulate it and ship it out to doctor's offices and hospitals. This is simplified, of course, but it's generally how these classes of medicines are made," said Lee, the Gore Professor of Chemical Engineering and director of the Manufacturing USA National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) at UD.

The trouble is that cells don't make just the desired antibody (i.e., the medicine), cells produce thousands of other proteins, too. When a medication is manufactured, these other proteins are removed through a process called purification. However, some proteins may stick to the antibody and piggyback their way through the manufacturing process. Manufacturers have developed methods to separate the piggybacking molecules in different ways, at different times during manufacturing, but problems can occur if the hitchhiking protein "looks" or behaves like the target medication.

Added to this, antibody-based drugs often are mixed with chemical additives to keep the medication safe and stable for a period of time, say six- or 12-months. One commonly used stabilizer is polysorbate. The polysorbate's job is to keep the protein antibody in solution.

One challenge the biopharmaceutical industry has observed is that the level of polysorbate found in some drug products can decrease over time. This hitch can shorten a medication's shelf life. For many years, there was no discernable reason for why the polysorbate degraded in some cases, but not in other cases.

Uncovering the problem, driving new solutions

In previous National Science Foundation-funded work, Lee and Lenhoff were collaborating to understand which contaminating proteins, or impurities, might be especially difficult to remove from a drug product. Lee specializes in analyzing complex mixtures and identifying all of the different proteins inside, a field called proteomics. Lenhoff, the Allan P. Colburn Professor of Chemical Engineering, is an expert in separating mixtures of proteins.

Through a series of experiments, the research teams identified a few dozen proteins that seemed likely to be impurities that would be difficult to remove. One protein that emerged as interesting for its potential to remain throughout the manufacturing process as an impurity was lipoprotein lipase.

Lipases are enzymes that chew up fats. Lipoprotein lipase is a common enzyme found in the human body that breaks down triglycerides, a type of fat found in the blood with a known association to heart disease and cholesterol problems.

"Lipoprotein lipase is one example of a protein that associates with antibodies and sometimes can't be separated from antibodies using standard approaches. Thus, it may ultimately make its way through the manufacturing process to the other end," said Lee.

The researchers became curious whether lipoprotein lipase could contribute to polysorbate degradation and focused additional experiments on lowering the amount of lipoprotein lipase to determine what, if any, effect it had on polysorbate. It turned out that lowering the amount of lipoprotein lipase that was present lowered the rate of degradation of polysorbate.

"We knew through the work of others in the field as early as 2010 that the amount of polysorbate degradation seemed to be related to problems people see in the stability of drug," explained Lee. "Now, our published research shows a clear link between the presence of lipoprotein lipase and polysorbate degradation, which has been a key problem that the industry has faced for several years."

The researchers developed a method to reduce the amount of lipoprotein lipase that's produced by the cells, in order to reduce the amount that might show up downstream as an impurity in relevant antibody-based drug formulations. They patented the idea with the help of UD's Office of Economic Innovation and Partnerships (OEIP). Two former UD doctoral students, Kristen Valente and Nick Levy, both of whom now work in the biopharmaceutical industry, are named on the patent.

While the technique only applies to medications that may experience polysorbate degradation, the researchers consider it an incremental step that can help inform the manufacturing industry.

"It's a quality control issue, and when you are talking about people's lives at stake, you really pay a lot of attention to that," said Lenhoff. Lee agreed though he conceded that what happens next remains uncertain.

"When the technology gets adopted, or by who, I do not know," he said. "But, now there are some clear solutions that people could follow for potentially improving manufacturing a stable supply of medicines that might experience polysorbate degradation."

http://bit.ly/2Qhk9QA

NASA wants to begin hunting for intelligent aliens who, like us, create technology

The search for technosignatures goes a step further, focusing on radio or laser emissions

Chabeli Herrera, Orlando Sentinel

For decades, the search for life in outer space has focused on finding tiny microbes that would do little to satisfy a growing appetite for connection with beings that more closely resemble us.

It's been the appetizer to the main course, a search for sophisticated creatures that truly deliver on the answer to one of humanity's central questions: Are we alone?

Now, thanks to new interest in Congress for further scientific research, NASA is changing its focus to search for life advanced enough to, like us, create technology.

The signs are called technosignatures, as compared with biosignatures, like in microbes, that show signs of life. Technosignatures come primarily as radio signals that allow scientists to infer the existence of technological life in the universe.

A bill proposed in the U.S. House in April recommended that NASA receive $10 million to partner with private sector and philanthropic organizations to search for alien life. It wouldn't actually allocate the funds, and would still have to pass in the House and Senate, but it

represents the first time in 25 years that the federal government has considered using funds to search for extraterrestrial life.

The original program, called SETI, or the search for extraterrestrial intelligence, lost federal funding in 1993 after a year of research didn't turn up a "single green little fellow," said then U.S. Sen. Richard Bryan of Nevada.

Unlike SETI, NASA argues that the search for technosignatures goes a step further, focusing on radio or laser emissions, not just communication signals. Our own radio and television broadcasts have been drifting into space, so we may be able to receive signals from other beings, the agency said.

And signs of large structures or an atmosphere full of pollutants—like our own—could prove that there is a civilization like Earth's elsewhere in the universe.

Whether NASA will find life outside our solar system is anyone's guess. Astronomer Frank Drake's Drake formula postulates that there could be 10,000 intelligent civilizations in the galaxy. Italian physicist Enrico Fermi's Fermi paradox asserts that if there was intelligent life out there, we would have met it already.

But recent discoveries by the Kepler mission of multiple exoplanets, including some that have similarities with Earth, and the TESS mission, which recently launched a satellite that has already found two new exoplanets, have increased public interest in finding alien life.

It'll have to be more an irregular radio signal to pass the test, though. NASA said that to answer the question of our place in the universe, it will need "unmistakable signs" of life.

https://wb.md/2NbQhTQ

FDA Freezes Imports From Chinese Maker of Tainted Valsartan

Inspection of the company's facility uncovered numerous manufacturing and quality control issues

Megan Brooks

The US Food and Drug Administration (FDA) has banned imports of active pharmaceutical ingredients (API) and finished drug products produced by China's Zhejiang Huahai Pharmaceuticals (ZHP), the company at the center of the tainted valsartan crisis.

The FDA's "import alert," issued September 28, follows a recent inspection of the company's Chuannan facility in Linhai, China, which uncovered numerous manufacturing and quality control issues, the FDA said.

The import alert is designed to "protect US patients" while the company "fully determines how impurities were introduced into its API and remediates its quality systems," the FDA said.

The import alert freezes all API and finished drug products made by ZHP from legally entering the United States.

Valsartan is an angiotensin II receptor antagonist used to treat hypertension and heart failure. This past July, some valsartan products manufactured by ZHP were found to be contaminated with *N*-nitrosodimethylamine (NDMA), a potential carcinogen, which led US and European regulators to pull all affected valsartan products from the market.

The European Medicines Agency (EMA) announced today that an inspection by European Union (EU) authorities in collaboration with the European Directorate for the Quality of Medicines found that Zhejiang Huahai did not comply with good manufacturing practice in the manufacture of valsartan at the same Chuannan site in Linhai.

The latest European inspection, which focused on the manufacture of valsartan and was completed in September, found several weaknesses, including deficiencies in the way the company investigated the presence of NDMA and another impurity *N*-nitrosodiethylamine (NDEA) in its valsartan products, the EMA said.

"As a result, a statement of non-compliance for the manufacture of valsartan has been issued and the site is no longer authorized to

produce valsartan (and its intermediates) for EU medicines. This means that marketing authorization holders in the EU are prohibited from using valsartan from the site for the production of medicines," the EMA said.

This action comes after valsartan medicines from ZHP were recalled in the EU and the company's certificate of compliance with European standards for quality testing for valsartan was suspended.

"EMA and national authorities in the EU are now actively considering all available evidence, including the outcomes of the European and US inspections, as part of the ongoing process of evaluating the Zhejiang Huahai manufacturing site. This will determine what further EU action may be required for other active substances produced by the site," the agency said.

Last week, the EMA announced it was expanding its review of impurities in valsartan following the detection of very low levels of NDEA in another active substance, losartan, made by Hetero Labs in India. As a result, the agency's review now includes medicines containing four other "sartans": andesartan, irbesartan, losartan, and olmesartan.

The FDA has also recalled some valsartan-containing products manufactured by Hetero Labs, labeled as Camber Pharmaceuticals, after they were found to contain NDMA.

NDMA has also been detected in some valsartan medications made by a second Chinese drug maker, Zhejiang Tianyu Pharmaceuticals in Taizhou, China.

The FDA maintains an updated list of valsartan products under recall and not under recall on its website.

http://bit.ly/2On4TUX

Pregnant Women Who Get a Flu Shot Protect Their Babies, Too

When pregnant women with the flu are sicker than nonpregnant individuals and the odds of more severe illness and even death increase as well

By Yasemin Saplakoglu, Staff Writer

Getting the flu is never a pleasant experience, but for pregnant women, the illness can be particularly bad. That's because pregnant women are considered one of the "high-risk" groups who are more likely to develop complications from the flu.

Despite this risk, last flu season, just 49.1 — less than half — of the pregnant women in the U.S. got a flu vaccine, according to the Centers for Disease Control and Prevention (CDC).

"When [pregnant] women come in and they say, 'Do I really need to get the flu shot,' my answer is yes," Dr. Laura Riley, Given Foundation professor and chair of the Department of Obstetrics and Gynecology at Weill Cornell Medicine, said at a news conference on Sept. 27.

The reason is that pregnancy changes the immune system, Riley said. In a healthy pregnancy, "your immune system isn't working exactly the way we need it to work" to fight off the virus. So, when pregnant women get the flu, they get sicker than nonpregnant individuals. And as the pregnancy progresses into the second and third trimesters, the odds of more severe illness and even death increase as well. [Flu Shot Facts & Side Effects (Updated for 2018-2019)]

A changed immune system isn't the only thing that makes pregnant women more vulnerable to the flu. Because a woman's lung volume decreases as the pregnancy progresses (and the fetus grows and takes up more space), it becomes more difficult to clear respiratory infections, Riley said.

And catching the flu endangers not only the mother but also the unborn child: If the mother has a prolonged fever due to the flu, it can lead to birth defects, Riley said. But another, more common problem is that women who get the flu during pregnancy are more

likely to have a preterm birth than pregnant women who don't get the flu. This is a problem "we see every year," Riley said, and problems associated with preterm births can become a "lifelong issue" for some babies.

The flu vaccine, Riley said, leads to the creation of antibodies in the body that then cross the placenta into the fetus. These antibodies protect the baby from the flu in the infant's first six months of life.

Indeed, the CDC and the American College of Obstetricians and Gynecologists recommend that every pregnant woman get a flu shot. They can do so at any trimester, Riley said.

Women's immune systems remain in this altered state for a couple of weeks after giving birth, so it's recommended that postpartum women get vaccinated if they haven't already done so, she added.

Studies have shown that pregnant women who received a flu vaccination were 40 percent less likely to be hospitalized during pregnancy than pregnant women who weren't vaccinated, Riley said. "Pregnant women naturally want to protect their babies," she said, and the vaccine is "effective" and "safe."

Last year's flu season was the worst in at least four decades, with around 80,000 deaths and 900,000 hospitalizations, according to the CDC.

https://nyti.ms/2zFbfa4

Tiny Device Is a 'Huge Advance' for Treatment of Severe Heart Failure

A clip used to repair damaged heart valves sharply reduced deaths among patients with a grim prognosis.

By Gina Kolata

Almost two million Americans have severe heart failure, and for them even mundane tasks can be extraordinarily difficult.

With blood flow impeded throughout their bodies, patients may become breathless simply walking across a room or up stairs. Some must sleep sitting up to avoid gasping for air.

Drugs may help to control the symptoms, but the disease takes a relentless course, and most people with severe heart failure do not have long to live. Until now, there has been little doctors can do.

But on Sunday, researchers reported that a tiny clip inserted into the heart sharply reduced death rates in patients with severe heart failure.

Doctors performed a procedure to install a device called a MitraClip, which helps repair the heart's mitral valve, in a hospital in Aurora, Colo. **Kent Nishimura/The Denver Post, via Getty Images**

In a large clinical trial, doctors found that these patients also avoided additional hospitalizations and described a drastically improved quality of life with fewer symptoms.

The results, reported at a medical meeting in San Diego and published simultaneously in the New England Journal of Medicine, were far more encouraging than heart specialists had expected.

"It's a huge advance," said Dr. Howard Herrmann, the director of interventional cardiology at the University of Pennsylvania, which enrolled a few patients in the study. "It shows we can treat and improve the outcomes of a disease in a way we never thought we could."

If the device is approved by the Food and Drug Administration for treatment of severe heart failure, as expected, then insurers, including Medicare, most likely will cover it.

In heart failure, the organ itself is damaged and flaccid, often as a consequence of a heart attack. The muscle pumps inefficiently, and in an attempt to compensate, the heart enlarges and becomes misshapen.

The enlarged organ tugs apart the mitral valve, which controls blood flow from the left atrium into the left ventricle. The distorted valve functions poorly, its flaps swinging apart. Blood that is supposed to be pumped into the body backs up into the heart and lungs.

A vicious cycle ensues: The heart enlarges, so the mitral valve leaks. The leaky mitral valve makes the heart enlarge even more, as it tries to compensate, and heart failure worsens.

In the new study, a device called the MitraClip was used to repair the mitral valve by clipping its two flaps together in the middle. (The clip is made by Abbott, which funded the study; outside experts reviewed the trial data.)

The result was to convert a valve that barely functioned into one able to regulate blood flow in and out of the heart.

Until today, researchers were not sure that fixing the mitral valve would do much to help these patients. A smaller study in France with similar patients failed to find a benefit for the MitraClip.

But that research included many patients with less severe valve problems, the procedure was not performed as adeptly, and the patients' medications were not as well optimized as in the new study.

In the new trial, 614 patients with severe heart failure in the United States and Canada were randomly assigned to receive a MitraClip along with standard medical treatment or to continue with standard care alone.

Among those who received only medical treatment, 151 were hospitalized for heart failure in the ensuing two years. Sixty-one died. In contrast, just 92 who got the device were hospitalized for heart failure during the period, and 28 died.

The results have left leading researchers unexpectedly optimistic. The trial sends "a very, very powerful message," said Dr. Gilbert Tang, a heart surgeon at Mount Sinai Medical Center, which enrolled a patient in the trial.

"This is a game changer. This is massive," said Dr. Mathew Williams, director of the heart valve program at NYU Langone Health, which had a few patients in the study.

Estimates of how many heart failure patients in the United States are like those in the trial range from 1.6 million to 2.5 million, Dr. Williams said. But, he adds, the number who might ultimately be treated will be less than the number who could be treated.

The device itself costs about $30,000, not counting the cost of the hospital and doctors: a surgeon, an interventional cardiologist and an echocardiologist, among others, all in the operating room.

Cardiologists said the study was impeccably executed.

The doctors inserting the device first had to demonstrate their expertise doing so. An independent group of experts ascertained that patients' medical care was optimal; all too often, heart failure patients do not receive ideal treatment.

Patients with severe heart failure often are gravely ill, too sick to have open-heart surgery to have mitral valves replaced. "It's not worth the risk," said Dr. Gregg Stone of Columbia University Medical Center and NewYork-Presbyterian Hospital, the study's principal investigator.

(Dr. Stone reported no relevant conflicts, but said that Columbia University gets royalties from the sale of the MitraClip.)

But the new procedure is much less invasive than open-heart surgery. A cardiologist threads the device to the heart through a blood vessel in the groin. Once it reaches the heart, the MitraClip is guided to the valve, and the device is used to clip the two flaps together.

Not every cardiologist is equipped to insert the clip. "These are difficult procedures that require training and dedication," Dr. Herrmann said.

During the procedure, for example, a tiny echocardiogram camera is placed into the patient's esophagus behind the heart to show where the catheter with the clip is going.

Doctors must watch an X-ray screen and an echocardiogram as they guide the clip to the mitral valve. When the clip arrives, “you have to see where you are grasping to get a good result,” Dr. Tang said.

The device is already approved by the F.D.A. for patients too frail for surgery, but whose hearts are fine except for a mitral valve that does not function properly.

Cardiologists predicted the F.D.A. would quickly approve the device for patients with severe heart failure, as well. It already is used in Europe for these patients, but there had been no rigorous studies showing it helped.

The new trial promises to alter prospects for many people with severe heart failure who had relatively few options. “This will change how we treat these patients,” Dr. Williams said.

It’s possible, he added, that many would fare even better with the valve repair procedure if they were not so frail when they got it.

“Maybe we need to start intervening earlier,” he said.