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Many kidneys discarded in the United States would be transplanted in France

New study, led by Penn Medicine and Paris Transplant Group, found French transplant centers are far more likely to transplant kidneys from older donors

PHILADELPHIA -- French organ transplant centers are far more likely to accept "lower-rated" kidneys, like those from older organ donors, than centers in the United States, according to a first-of-its kind analysis published today in JAMA Internal Medicine. French transplant centers would have transplanted more than 60 percent - about 17,500 kidneys - of the nearly 28,000 deceased-donor kidneys discarded in the United States between 2004 and 2014, according to the research team from Penn Medicine and the Paris Transplant Group.

"These findings highlight the striking disparities in organ acceptance between the two countries and suggest that many of the 90,000 Americans awaiting a kidney transplant could reap major benefits from a more aggressive approach," said study co-author Peter Reese, MD, MSCE, an associate professor of Medicine and Epidemiology in the Perelman School of Medicine at the University of Pennsylvania. "Our study provides fresh evidence that organs from older deceased donors are a valuable, underused resource - particularly for people on the waitlist who otherwise may not receive a transplant at all."

The lack of organs available for kidney transplantation is a major global health problem. In the United States, an estimated 37 million adults have chronic kidney disease and more than 720,000 people have end-stage renal disease, meaning their kidneys have failed, and they require either a transplant or dialysis in order to survive. In July, the Trump administration signed an executive order - shaped, in part, by research published by experts at Penn Medicine - to improve kidney care and increase the number of transplants. In recent years, innovative solutions, including the use of Hepatitis C-infected organs, have helped to increase the supply of transplantable kidneys. Yet, every year, 5,000 Americans die while waiting for a kidney transplant.

To identify best practices for kidney allocation and organ use, researchers analyzed the acceptance and use of deceased-donor kidneys in France and the United States between 2004 and 2014. During that timeframe, centers in the United States discarded about 18 percent of the 156,089 deceased-donor kidneys recovered - about two times as high as the discard rate in France. Researchers found that, over the 10-year-period, transplant centers in France addressed the need for organs by accepting lower-rated kidneys, such as those from older donors. For example, the average age of a kidney donor in France was 56 years old - 17 years older than the average age of a donor in the United States.

Although donor age is a risk factor for organ failure, studies have shown that kidneys from donors in their 50s or 60s may extend life for transplant candidates, particularly older recipients. Previous research found that transplant candidates older than 65 lived longer if they reduced their wait time by accepting kidneys from an "extended criteria" donor - those older than 60, or older than 50 with comorbidities, such as high blood pressure.

Researchers noted the significant need for viable kidneys suitable for older adults in the United States, where the percentage of transplant recipients older than 60 has increased from 22 percent in 2004 to 32 percent in 2017. More than 35,000 people older than 60 in the United States remain on the waitlist for a kidney. By adopting a similar model to France, the United States could provide more than 10,000 years of life with a functioning kidney transplant to its patients each year.

"This study demonstrates that there is more the U.S. can do to prevent the deaths of thousands of Americans each year who are waiting for a transplant," said coauthor Dr. Alexandre Loupy, nephrologist at the Department of Nephrology and Kidney Transplantation at Necker Hospital in Paris and Head of the Paris Transplant Group. "Our findings reinforce how collaboration between countries can lead to a concrete, new direction on how to help address a global health problem and advance care for wait-listed kidney patients in the United States."

The work was supported, in part, by the Health Resources and Services Administration (234-2005-37011C), the French national research agency ATIP Avenir, Fondation Bettencourt Schueller and the French organ allocation authority.

http://bit.ly/2HxjTeu

How Do You Convince 125 Million People to Embrace Wolves?

It would be good for Japan's forests and farms (less so the deer).

by Allan Richarz

If asked to imagine deer in Japan, one's mind may turn to thoughts of docile herbivores gently eating out of tourists' hands in Nara. Less likely to come to mind are the unchecked herds of hulking 300-pound deer picking clean growing swaths of Japan's forests and farmland. But that is increasingly the reality facing Japan, with deer responsible for millions of dollars in crop damage each year.

A wolf walking through snow at Asahiyama Zoo in Asahikawa, Hokkaido. ***Shayne Hill Xtreme Visuals / Getty Images***

It is a situation retired professor Naoki Maruyama hopes to fix. The chairman of the Japan Wolf Association, Maruyama believes that the reintroduction of wolves—extinct in Japan for the better part of a century—can help curb the damage caused by deer and restore ecological balance to affected regions of the country.

Historically, owing to migration via land bridges from Asia and Russia, Japan was home to *Ezo* wolves—found on the northern island of Hokkaido—and *Honshu* wolves, which inhabited the three other main islands. Changing agricultural needs and fear of rabies in local communities, combined with aggressive hunting policies, gradually led to the extinction of the Ezo wolf in 1889 and Honshu wolf in 1905. Over the intervening century, the wolves' former prey—deer and boar—flourished.

For Maruyama, the idea of reintroducing wolves first came to him in 1988, with the discovery of wild wolves in Poland's Bieszczady National Park, where they had previously been wiped out by hunting in the 1960s. "As a researcher on the social ecology and conservation management of deer," Maruyama wrote in an email, "I realized the importance of the existence of predator wolves."

His calls for the reintroduction of wolves in Japan were rebuffed, however, by the country's ecological societies. Ultimately, "we gave up on appealing to the academy," Maruyama continued, "and decided to appeal directly to the public." And so the Japan Wolf Association was formed in 1993.

An Ezo wolf (a.k.a. Hokkaido wolf), which is believed to have become extinct in the late 19th century. **Public Domain**

There are a number of concerns surrounding Japan's large deer population, which itself was on the verge of disappearing in the years following World War II. In Hokkaido, home to an estimated 600,000 deer, some 2,000 car accidents involving deer occur each year, leading to government-led culls on the island. Deer, with their voracious appetites for up to 5-pounds of plant matter per day, have

also caused ecological issues, among them "crop damage, bark stripping, soil erosion … and reduced tree diversity," according to *Pacific Standard*. Such is the extent of the problem that even Nara's famed deer have been slated for culling.

In 2015, Japan's Ministry of Agriculture, Forestry and Fisheries released a report indicating that of the 8,000 hectares of forest damaged by wildlife in 2015, 77 percent—totaling some $53 million—could be attributed to deer. This is almost double the amount of damage recorded in 1998. News reports further indicate that 20 of the Japanese main islands' 30 national parks have sustained damage from deer.

A herd of deer strolls past a shop in Nara. Alexander Spatari / Getty Images

For the Japan Wolf Association and similar organizations, reintroducing wolves would likely involve the importation of similar subspecies from Mongolia and China. The more immediate challenge, however, is in convincing the public of the merits, and value, in reintroducing wolves. While wolves have traditionally been viewed favorably in Japanese mythology—often portrayed as messengers of deities and protectors of travelers—Maruyama noted in an email the lingering impact of *Little Red Riding Hood*—of wolves as dangerous, man-hungry predators—on contemporary Japanese opinions of wolves.

Maruyama cites surveys conducted by Kunihiko Otsuki, a director of the JWA board, showing increased support for the plan and decreased opposition among respondents from 1993-2016. At the same time, he notes the difficulty in countering persistent public indifference to the issue. Opposition has steadily dropped from 44 percent to 11 percent, but JWA surveys note a consistent high level of indifference—45 percent of respondents to the JWA's most recent survey in 2016 had no opinion on reintroducing wolves—relative to those with firm pro or anti-wolf-reintroduction views. Said Maruyama, "It is much more difficult to persuade people who are simply not interested than persuading those who oppose [the reintroduction of wolves]."

Compounding the issue is opposition from other ecological and animal welfare groups in Japan, as well as from the government. They note the considerable industrialization that has taken place in the country since wolves were last spotted over a century ago, and the encroachment of development on natural areas. Proximity of humans to wolves, accordingly, could become an issue for both alike.

Critics worry that wolves will come into contact with humans. The JWA says there are regions sparsely populated enough that human-wolf contact would be unlikely. "[Wolves] are not an alien species," says Maruyama, and would fall into similar hunting patterns of wolves elsewhere.

***Howling wolves in Asahikawa.* 浪武 / Alamy**

Supporters of reintroducing wolves point to successful reintroduction programs elsewhere, such as in Yellowstone National Park in 1995. Professor Maruyama has also noted that returning wolves have an ancillary impact of controlling the park's elk population.

For the JWA, work continues on building public support for their initiative. "We have 570 members," wrote Maruyama, "but [we] are aging like the rest of Japanese society." Indeed, recruiting young members to carry on the JWA's work is the organization's most pressing, and flummoxing challenge. Maruyama, who is 76, says

"we have held dozens of seminars, lectures, forums, and symposiums all over the country," but youth engagement remains low. "If you can't understand the feelings of Japanese people, including young people, there is no way to reach them."

To that end, on August 1 the organization launched a year-long poster advertising campaign on the well-trafficked Keihan Electric Railway, timed to coincide with heavy rail use by students and office workers on summer holidays and promote the idea that "wolves are not scary."

http://bit.ly/328SiYQ

Most of California's Big Earthquakes Are Preceded by Ghostly 'Foreshocks' Weeks in Advance

Foreshocks — the tiny, sometimes imperceptible tremors that precede massive earthquakes — are way more common than we thought.

By Brandon Specktor Planet Earth

How do earthquakes begin? It's an ancient question — and while scientists have ruled out the vengeful gods blamed over the past few millennia, agreeing that tremors are more a matter of grinding plate tectonics than of Poseidon's wrath, many facets of this seismic puzzle remain murky.

One ongoing mystery is the phenomenon of foreshocks, small, sometimes imperceptible tremors that can precede larger quakes in the same area by several days or weeks. Studies have found that anywhere from 10% to 50% of large earthquakes follow these minishocks. This has led many researchers to wonder whether foreshocks are a geophysical fluke or a standard feature of big quakes that modern instruments just aren't sensitive enough to detect with certainty.

A study published July 30 in the journal Geophysical Research Letters offers compelling new evidence for the second hypothesis. Using the most comprehensive catalogue of earthquake activity in Southern California ever assembled, a team of researchers found that roughly 72% of large (magnitude 4.0 or greater) quakes in the region between 2008 and 2017 followed distinct foreshocks that hit up to a month before the event.

"We're hoping that these observations will help inform improved physical models of how earthquakes get started," lead study author Daniel Trugman, a seismologist at Los Alamos National Laboratory in New Mexico, told Live Science. "With this improved physical understanding, we'll eventually be able to improve earthquake forecasting as well."

Trugman and his colleagues began their hunt for foreshocks by compiling a catalogue of some 284,000 earthquakes detected by various monitoring stations around Southern California between 2008 and 2017. Using a technique called quake template matching (QTM), the researchers trained a computer to recognize the distinct waveform these quakes created, then scoured the records for hints of smaller quakes showing those same vibrational patterns, hints that lay hidden in the constant, rumbling background noise of Earth. The team turned up more than 1 million additional earthquakes, many of them magnitude 0.0 or less (seismologists measure earthquake magnitude on a logarithmic scale, so a magnitude 0.0 quake would be about 10,000 times weaker than a magnitude 4.0 quake). In total, the researchers expanded their catalogue to include 1.81 million earthquakes, or an average of one quake every 3 seconds over the last 10 years, Trugman said.

From this expanded list, the researchers picked 46 quakes with magnitude 4.0 or higher to study for foreshock activity. But first, the team had to calculate the average number of earthquakes near each fault line in Southern California.

"If you pick any point in Earth's crust, especially near an active fault zone, there's going to be a background rate of seismicity," Trugman said. "To show that there are foreshocks, you have to

demonstrate that there are more earthquakes than you'd expect leading up to the larger event."

Armed with these seismic averages, the researchers showed a statistically significant increase in foreshock activity shortly before 33 of the 46 big quakes. Foreshocks activity spiked anywhere from three to 35 days before a mainshock hit, with the average increase in rumbling occurring about 16 days before the big event.

"The results suggest that foreshock occurrence in nature is more prevalent than previously thought," the researchers concluded in their study. And what about the 28% of quakes that lacked a surge in foreshock activity? Trugman said it's likely that many of those quakes did see foreshocks as well but the researchers just couldn't define them with "99% certainty." "There are a number of cases where there is an increase in seismic activity, but we're not sure it's statistically significant," Trugman said. As seismic-monitoring equipment improves, so too should foreshock detection, he said.

Still, Trugman added, some of the big quakes clearly missed such a spike in foreshocks before the heavy rumbling began. And, on the flipside, a vast majority of the tiny quakes he and his team discovered did not precede large earthquakes at all, meaning that simply seeing an increase in seismic activity along a given fault line is not a reliable predictor of a bigger earthquake to come.

"What we show in this paper is that most if not all mainshocks are preceded by elevated seismic activity that cannot be explained as simple background seismicity," Trugman said. "But that is a very different statement from saying that 'most upticks in seismicity are foreshocks that signal that a mainshock is impending'." This all shows that the processes that initiate earthquakes are "quite variable," Trugman said, reminding us that seismologists are still a good ways away from being able to forecast earthquakes with any certainty. Perhaps we shouldn't let Poseidon off the hook yet after all.

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Some CBD extracts are totally legal, DEA confirms

Agency says it still wants to expand cannabis research and notes that CBD is now legal.

Beth Mole

The US Drug Enforcement Administration cleared the air around cannabis Monday, reaffirming its plans to expand cannabis research and confirming that *some* products containing the popular cannabis-derived component cannabidiol (CBD) are now legal.

Three years ago, the agency said it wanted to expand cannabis research by letting more entities grow marijuana. Right now, there's only one approved grower—the University of Mississippi. It has had an exclusive deal to be the federal government's cannabis supplier for more than 50 years.

With the recent boom in cannabis products and legalization by states, federally funded researchers have been clamoring for more cannabis products than Ole Miss can supply, particularly products that resemble those that patients and consumers can buy at dispensaries.

In August 2016, the DEA said it would oblige and began accepting applications from entities to be new growers.

But little has changed since then. The agency has collected 33 applications but has yet to process any of them, according to Reuters.

One applicant, the Arizona-based Scottsdale Research Institute, got so frustrated that it asked a federal court earlier this year to step in and compel the agency to move on the applications. In doing so, it referred to the existing Ole Miss supply as "sub-par."

Today, the DEA finally announced that it is "moving forward" and "providing notice of pending applications from entities applying to be registered to manufacture marijuana for researchers."

In the announcement, DEA Acting Administrator Uttam Dhillon said specifically:

DEA is making progress in the program to register additional marijuana growers for federally authorized research, and will work with other relevant federal agencies to expedite the necessary next steps. We support additional research into marijuana and its components, and we believe registering more growers will result in researchers having access to a wider variety for study.

But there's a catch. Before the agency will approve any of the applications, it says it wants to roll out new rules to evaluate and oversee any potential new growers.

"The new rules will help ensure DEA can evaluate the applications under the applicable legal standard and conform the program to relevant laws," the DEA explained. When the DEA will give any applicant a green light remains unclear.

In the meantime, the DEA took the opportunity to point out that some cannabis products are now legal and no longer in need of DEA authorization to grow or make.

As Ars has noted before, the Agriculture Improvement Act of 2018 changed the federal definition of marijuana to exclude hemp, a strain of cannabis that contains CBD but has low levels of the psychoactive cannabinoid Tetrahydrocannabinol (THC), which gives cannabis-users a "high."

As such, hemp and hemp-derived CBD preparations that have 0.3% THC or less are not controlled substances, the DEA confirmed. "DEA registration is not required to grow or research" them.

The confirmation will be good news to the CBD industry, which has exploded recently.

But any manufacturers making health claims about the CBD-containing products will still receive scrutiny from the Food and Drug Administration. Additionally, individual state laws and restrictions may apply.

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Greater left ventricular mass increases risk of heart failure

Left-ventricular hypertrophy, is a stronger predictor of coronary artery disease-related death

OAK BROOK, Ill. - Elevated left ventricular mass, known as left-ventricular hypertrophy, is a stronger predictor of coronary artery disease-related death and heart failure than coronary artery calcium score, according to a new study published in the journal *Radiology*.

In the study led by Nadine Kawel-Boehm, M.D., a senior staff radiologist at Hospital Graubünden in Chur, Switzerland, a team of researchers analyzed data collected in the Multi-Ethnic Study of Atherosclerosis (MESA) sponsored by the National Heart, Lung, and Blood Institute. MESA is an ongoing, multi-center study of a diverse, population-based sample of 6,814 men and women age 45-84 with no known heart disease.

According to Dr. Kawel-Boehm, there is little research on predicting the long-term risk of cardiovascular events in ethnically diverse patients who have MRI-identified left ventricular (LV) hypertrophy, a condition in which the muscle mass of the heart's main pumping chamber is increased.

"Previous studies have used ECG or echocardiography, which have lower sensitivity in the diagnosis of LV hypertrophy, and typically follow patients for only several years," she said. "The MESA study used MRI, which is the gold standard for quantifying LV mass, and had a long follow-up of 15 years."

The researchers studied otherwise healthy individuals from the community in the MESA study. 4,988 MESA participants underwent a baseline cardiac MRI between 2000 and 2002 and participated in follow-up over a 15-year period. MRI showed that 247 participants in the study group had LV hypertrophy.

The mean age of all participants at baseline was 62 years, and 52 percent were women. Thirty-nine percent were white, 13 percent were Asian, 26 percent were African American and 22 percent were Hispanic.

At the 15-year follow-up, the research team found that 290 patients had a significant coronary heart disease (CHD) event, including 207 myocardial infarctions--or heart attacks, and 95 CHD deaths. Cardiovascular disease-related deaths occurred in 57 patients, and 215 patients had heart failure. A statistical analysis of the data demonstrated that LV hypertrophy was an independent predictor of significant CHD events, including myocardial infarction, coronary artery disease-related death and heart failure.

According to the analysis, 22 percent of the study participants with LV hypertrophy had a significant CHD event, compared to 6 percent of participants without LV hypertrophy.

Patients with LV hypertrophy had 4.3 times the risk of coronary artery disease-related death compared to participants without LV hypertrophy. Deaths from coronary and non-coronary related cardiovascular causes were more strongly related to LV hypertrophy than to coronary artery calcium scoring done with a CT scan. "In contrast to the widely used coronary artery calcium by CT, which measures a condition not known to regress under medical therapy, an elevated LV mass is potentially reversible under treatment," Dr. Kawel-Boehm said.

As a result of the long length of the study follow-up, Dr. Kawel-Boehm said the researchers were able to determine that the risk of cardiovascular events began to increase in participants with LV hypertrophy particularly after five years.

"Our results provide further evidence and motivation for regular follow up and management of individuals with left ventricular hypertrophy," she said. "A higher LV mass quantified by imaging may matter more in some instances than a high calcium score."

"Left Ventricular Mass at MRI and Long-Term Risk of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis (MESA)." Collaborating with Dr. Kawel-Boehm were Richard Kronmal, Ph.D., John Eng, M.D., Aaron Folsom, M.D., Gregory Burke, M.D., J. Jeffrey Carr, M.D., M.Sc., Steven Shea, M.D., M.S., João A. C. Lima, M.D., and David A. Bluemke, M.D., Ph.D.

http://bit.ly/32bWXcq

Vaccine against deadly superbug Klebsiella effective in mice

The life-threatening bacterial infections are spreading

Scientists have produced and tested, in mice, a vaccine that protects against a worrisome superbug: a hypervirulent form of the bacteria Klebsiella pneumoniae. And they've done so by genetically manipulating a harmless form of *E. coli*, report researchers at Washington University School of Medicine in St. Louis and VaxNewMo, a St. Louis-based startup.

Klebsiella pneumoniae causes a variety of infections including rare but life-threatening liver, respiratory tract, bloodstream and other infections. Little is known about how exactly people become infected, and the bacteria are unusually adept at acquiring resistance to antibiotics. The prototype vaccine, details of which are published online Aug. 27 in *Proceedings of the National Academy of Sciences*, may offer a way to protect people against a lethal infection that is hard to prevent and treat.

"For a long time, Klebsiella was primarily an issue in the hospital setting, so even though drug resistance was a real problem in treating these infections, the impact on the public was limited," said co-author David A. Rosen, MD, PhD, an assistant professor of pediatrics and of molecular microbiology at Washington University. "But now we're seeing Klebsiella strains that are virulent enough to cause death or severe disease in healthy people in the community. And in the past five years, the really resistant bugs and the really virulent bugs have begun to merge so we're beginning to see drug-resistant, hypervirulent strains. And that's very scary."

Hypervirulent strains of Klebsiella caused tens of thousands of infections in China, Taiwan and South Korea last year, and the bacteria are spreading around the world. About half of people infected with hypervirulent, drug-resistant Klebsiella die. Two types in particular - known as K1 and K2 - are responsible for 70 percent of the cases.

Rosen; senior author Christian Harding, PhD, a co-founder of VaxNewMo; first author Mario Feldman, PhD, an associate professor of molecular microbiology at Washington University and a co-founder of VaxNewMo; and colleagues decided to create a vaccine against the two most common strains of hypervirulent Klebsiella. The bacterium's outer surface is coated with sugars so the researchers designed a glycoconjugate vaccine composed of these sugars linked to a protein that helps make the vaccine more effective. Similar vaccines have proven highly successful at protecting people against deadly diseases such as bacterial meningitis and a kind of pneumonia.

"Glycoconjugate vaccines are among the most effective, but traditionally they've involved a lot of chemical synthesis, which is slow and expensive," Harding said. "We've replaced chemistry with biology by engineering *E. coli* to do all the synthesis for us."

The researchers genetically modified a harmless strain of *E. coli*, converting it into tiny biological factories capable of churning out the protein and sugars needed for the vaccine. Then they used another bacterial enzyme to link the proteins and sugars together.

To test the vaccine, the researchers gave groups of 20 mice three doses of the vaccine or a placebo at two-week intervals. Then they challenged the mice with about 50 bacteria of either the K1 or the K2 type. Previous studies had shown that just 50 hypervirulent Klebsiella bacteria are enough to kill a mouse. In contrast, it takes tens of millions of classical Klebsiella - the kind that affects hospitalized people - to be similarly lethal.

Of the mice that received the placebo, 80 percent infected with the K1 type and 30 percent infected with the K2 type died. In contrast, of the vaccinated mice, 80 percent infected with K1 and all of those infected with K2 survived.

"We are very happy with how effective this vaccine was," Feldman said. "We're working on scaling up production and optimizing the protocol so we can be ready to take the vaccine into clinical trials soon."

The goal is to get a vaccine ready for human use before the hypervirulent strains start causing disease in even larger numbers of people.

"As a pediatrician, I want to see people get immunity to this bug as early as possible," Rosen said. "It's still rare in the United States, but given the high likelihood of dying or having severe debilitating disease, I think you could argue for vaccinating everybody. And soon we may not have a choice. The number of cases is increasing, and we're going to get to the point that we'll need to vaccinate everybody."

Conflict of Interest Statement: Mario F. Feldman and Christian M. Harding have a financial stake in VaxNewMo LLC, a for-profit entity developing bioconjugate vaccines against Streptococcus pneumoniae and Klebsiella pneumoniae using patented technology derived from the data presented in this and other published manuscripts.

http://bit.ly/2HwHjRa

Could Smoking Marijuana Help Men's Fertility?

The results of a new study surprised even the researchers.

By Rachael Rettner 2 days ago Health

Men who smoke marijuana may have a better chance of having a baby with their female partner, compared with those who don't use the drug, a surprising new study suggests.

The study, which was published Aug. 14 in the journal Human Reproduction, involved several hundred couples undergoing fertility treatment with in vitro fertilization (IVF). The researchers found that women who reported currently using marijuana had a

higher likelihood of pregnancy loss, compared with women who didn't use marijuana.

In contrast, couples whose male partner said he currently used marijuana had better chances of having a child, compared with couples whose male partner didn't currently use marijuana.

This finding was unexpected, according to the authors, from the Harvard T.H. Chan School of Public Health in Boston. The researchers had hypothesized that marijuana smoking wouldn't be related to fertility outcomes in either men or women, as has been the case in previous studies.

But the new result agrees with findings in an earlier study from the same group of researchers. In that study, men who reported ever having smoked marijuana had higher sperm counts, on average, than those who had never used the drug.

Still, the new findings don't mean that men should start smoking marijuana to boost their fertility. Only a small number of participants said they smoked marijuana around the time of their fertility treatments, which reduces the strength of the results. At most, they suggest that marijuana may not have a harmful effect on men's fertility, the authors said. On the other hand, the researchers don't think their findings should be taken as evidence that marijuana has a beneficial effect for men undergoing fertility treatment.

There is an urgent need for "additional research to clarify the role of marijuana use on human reproduction and on the offspring's health," the authors concluded.

Despite the growing use and legalization of marijuana around the world, scientists know little about how the drug impacts fertility. And few studies have included both men and women.

In the new study, the researchers analyzed information from 200 couples who underwent fertility treatment at Massachusetts General Hospital between 2005 and 2017. The researchers also included data from an additional 220 women who underwent fertility treatment, but did not have a partner in the study.

Participants were asked whether they were currently using marijuana, had used the drug in the past or had never used it.

Overall, 44% of the women and 61% of the men in the study reported they had smoked marijuana at some point in their lives. But just 12 women (3%) and 23 men (12%) in the study said they were currently using marjuana.

Among the small number of women who said they currently smoked marijuana and became pregnant during the study, more than 50% experienced a pregnancy loss, compared with just 26% of the women who were past marijuana users or who had never used the drug.

This finding suggests that marijuana use among women "may be related to worse infertility treatment outcomes," the authors said. But they caution that since very few women in the study were current marijuana users, it's possible that this finding was due to chance.

On the other hand, among couples whose male partner was a current marijuana user, 48% eventually had a live birth, compared with just 29% of couples whose male partner was a past marijuana user or who had never used it. The link held even after the researchers took into account some factors that could affect fertility, including the participants' age, ethnicity, body mass index (BMI), tobacco smoking history, coffee intake, alcohol use and cocaine use.

More and more patients are asking about the reproductive effects of marijuana, but doctors have had few studies to share when advising patients.

"At least weekly, I have patients asking me about the effects of marijauna on male fertility," said Dr. Neel Parekh, a urologist specializing in male fertility and men's health at the Cleveland

Clinic's Glickman Urological & Kidney Institute. "There just isn't a great answer we can give them yet."

In this sense, the new study is "a step in the right direction," Parekh told Live Science.

However, the new study by itself isn't enough for doctors to recommend that men smoke marijuana prior to fertility treatment.

Parekh noted that, with only 23 men in the study reporting current use of marijuana, "It's hard to make that big of a statement saying marijuana is going to improve success rates" with fertility treatment.

But Parekh agreed with the authors that, rather than showing a benefit per se, the study suggests that smoking marijuana may not hurt the chances of success with fertility treatment when the male partner uses it.

The study authors note that their work included couples undergoing fertility treatment, and so the findings may not apply to couples trying to conceive without medical assistance. Indeed, Parekh noted that some forms of IVF use only a single sperm to fertilize an egg, and so with these treatments, a man's sperm count isn't usually a big deal. But when couples are trying to conceive naturally, sperm count matters more.

In addition, the new study only asked about marijuana smoking and not other forms of marijuana use.

More robust studies are now needed to look at this issue, said Parekh, and he expects to see more research in this area in the coming years.

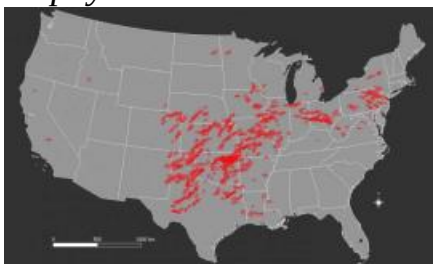
http://bit.ly/324qDs6

Scientists forecasted late May tornado outbreak nearly four weeks before it ripped through U.S.

A team of scientists reports that they accurately predicted the nation's extensive tornado outbreak of late May 2019 nearly four weeks before it began.

by Tom Parisi, American Geophysical Union

The team's study, detailing factors that went into the forecast, is newly published in the AGU journal, *Geophysical Research Letters*.



"This is the first documented successful long-range forecast for an extended period of tornado activity in the U.S.," said lead author Victor Gensini, a professor of meteorology at Northern Illinois University.

The 757 tornado warnings (red polygons) issued by NOAA's National Weather Service from May 17 to May 30 of this year. NIU

Gensini said extended-range predictions are the "new frontier of forecasting."

"In our field, there's a big push to accurately predict all kinds of extreme weather events well in advance," Gensini said.

"If we can better anticipate when and where these extreme events may be occurring, it gives us a better chance to mitigate their impacts. We think any additional lead time could be extremely valuable to emergency response teams, insurance companies, and numerous other sectors of industry."

May 17 through May 29 proved to be an unusually active period of severe weather in the United States—even for a time of the year known to produce violent storms.

During the 13-day stretch, 374 tornadoes occurred, more than tripling the 1986-2018 average of 107 for this period. In total, 757 tornado warnings were issued by NOAA's National Weather Service, and seven fatalities were reported. The outbreak contributed significantly to the second highest monthly (E)F1+ tornado count (220) on record for May since reliable tornado counts began in the early 1950s.

NIU

The central and southern Great Plains, along with the lower Great Lakes region, including Pennsylvania and Ohio, were particularly hard hit by the tornadic storms.

Five years ago, Gensini and colleagues formed an Extended Range Tornado Activity Forecast (ERTAF) team to conduct research on sub-seasonal, or extended-range, forecasting. Its current members include Paul Sirvatka of the College of DuPage and current study co-authors David Gold of IBM-Global Business Services, John T. Allen of Central Michigan University and Bradford S. Barrett of the United States Naval Academy.

Studies in recent years by the team and other scientists used historical weather-pattern records to develop methodologies for predicting the likelihood of severe weather across the continental United States weeks in advance.

From April 28 on, the ERTAF team highlighted the likelihood of an active period of severe weather three to four weeks into the future. The prediction was especially notable given the pre-season expectation of below-average frequencies of U.S. tornadoes due to the presence of weak El Niño conditions in the tropical Pacific Ocean.

"It's important to note that this was a single successful extended-range forecast—we're not going to get every one of these correct," Gensini said. "But our work does create a pathway to forecasting severe weather with these extended lead times. These are usually forecasts of opportunity, meaning that they are not always possible."

Gensini said the ERTAF team, which posts forecasts on its website every Sunday evening during tornado season, has had many other successful forecasts that were two to three weeks in advance. They chose to publish on this example because of the magnitude of the storms and textbook nature of the chain of events.

"This is the first extended-range forecast that has been fully scientifically dissected," Gensini said. "We wanted to make sure it's documented."

The forecast process is complex. It looks for signals in two atmospheric indices—the Madden-Julian Oscillation, an eastward moving disturbance of winds, rain and pressure, and the Global Wind Oscillation, a collection of climate and weather information that measures atmospheric angular momentum, or the degree of waviness in the jet stream.

Recurring modes within both oscillations occasionally provide enhanced predictability of future potential for severe weather frequency, the researchers said.

The conditions that resulted in the tornado outbreak began thousands of miles away as thunderstorms over the Indian Ocean and Maritime Continent. The storms progressed into the equatorial Pacific, leading to an enhancement of the jet stream—a key signal the scientists were looking for. The jet stream then crashed like a wave, breaking over western North America into a wavy pattern.

"This process often leads to a thermal trough over the western U.S. that connects downstream to a thermal ridge, creating a rollercoaster-like jet stream pattern," Gensini said. "Those types of weather patterns have long been known to be most favorable for tornado outbreaks."

From beginning to end, the pattern progressed as the researchers expected.

"It doesn't always happen that way, and we have a lot of work to do to make this methodology robust, but every year we learn something new," Gensini said.

More information: *Vittorio A. Gensini et al. Extended U.S. Tornado Outbreak During Late May 2019: A Forecast of Opportunity, Geophysical Research Letters (2019). DOI: 10.1029/2019GL084470*

Journal information: Geophysical Research Letters

Provided by American Geophysical Union

http://bit.ly/2Llq78T

Stunning ancient skull shakes up human family tree

New fossil could reshuffle an ancient relationship

By Michael Price

For months, herder Ali Bereino had been trying to get a job working for a team of fossil hunters in northeastern Ethiopia. The Afar man hung around, watching and learning. One day in February 2016, Bereino dug a burrow to keep his baby goats safe from hyenas. He noticed teeth protruding from the hard-packed sand and pulled out a jawbone, which he brought to the team's leader, Ethiopian paleoanthropologist Yohannes Haile-Selassie of the Cleveland Museum of Natural History in Ohio. Shoveling aside nearly half a meter of old goat droppings and sieving through sediment, the team unearthed the nearly complete skull of an enigmatic human ancestor, the oldest member of the genus that eventually led to our own.

***A skull (left) shows that* Australopithecus anamensis *(artist's reconstruction, right) had a small brain and a protruding face.* (Left to right): Jennifer Taylor/Cleveland Museum Of Natural History/Dale Mori And Liz Russell; John Gurche And Matt Crow/Cleveland Museum Of Natural History**

After 3 years of analysis, researchers have dated the fossil to 3.8 million years old and identified it as *Australopithecus anamensis*, a hominin long thought to be the direct predecessor of the famed "Lucy" species, *A. afarensis*. The new fossil could reshuffle that ancient relationship, the authors argue this week in two papers in *Nature*.

Researchers hail the skull as one of the most significant hominin discoveries in decades. "It's a spectacular find," says Carol Ward, an evolutionary anatomist at the University of Missouri School of Medicine in Columbia. "A number of teams—mine included—have been looking for an australopith skull like this. … This is the specimen we've been waiting for."

Still, not everyone is convinced it clarifies the relations of the australopithecines, a genus of upright apes that lived between 4.2 million and 2 million years ago throughout eastern and southern Africa.

A. anamensis was first identified in 1995, mostly on the basis of 4-million-year-old teeth and jaws from Kenya. Given the dates, plus several telltale anatomical similarities, most researchers concluded that *A. anamensis* gradually transitioned into and was replaced by *A. afarensis*, which lived from about 3.7 million to 3 million years ago.

The new Ethiopian specimen, named MRD after Miro Dora, the site where it was found, was probably a male with a brain size of about 370 cubic centimeters, about that of a chimpanzee. He had jutting cheekbones, elongated canine teeth and oval-shaped earholes—all features that strongly suggest membership in *A. anamensis* rather than the bigger-brained, flatter-faced *A. afarensis*, Haile-Selassie says. The team dated the skull using the radioactive decay of isotopes of argon in the surrounding sediments.

Fred Spoor, a paleoanthropologist at the Natural History Museum in London, says features such as MRD's projecting cheekbones and primitive earholes resemble those of later hominins, including South Africa's *A. africanus* and Kenya's *Kenyanthropus platyops*. The similarities, he says, may make some researchers wonder whether *A. anamensis*—and not *A. afarensis*, as thought—was the ancestor of those later hominins.

MRD's anatomy also helps pin down the identity of a puzzling 3.9-million-year-old forehead bone found in Ethiopia in 1981; Haile-Selassie says the comparison suggests the skull fragment belonged to *A. afarensis*. If he's correct, Lucy's species would predate the

new *anamensis* skull. Haile-Selassie concludes that the two species overlapped for about 100,000 years. The team still thinks *A. afarensis* descends from *A. anamensis*, but suggests Lucy's species branched off *anamensis*, rather than simply replacing it.

Ward and William Kimbel, a paleoanthropologist at Arizona State University in Tempe, agree that the new skull belongs to *A. anamensis*, but both say it will take more fossils to convince them that two distinct species of australopithecines roamed the Afar region at the same time. "That issue rests on the comparison of the new specimen with the single frontal" bone, which is the only *A. afarensis* specimen suspected of such antiquity, Kimbel says. "It's difficult to make a strong argument because we have only the two specimens."

In a statement, Tim White, a paleoanthropologist at the University of California, Berkeley, who served as Haile-Selassie's doctoral adviser years ago, praised the discovery but says the studies' evolutionary implications are "a bridge too far." He thinks individual variation alone can account for the differences between the two specimens, and that the idea that *afarensis* replaced *anamensis* still makes sense.

Regardless of how things shake out for hominin taxonomy, the finding proved a boon for Bereino. "Obviously, it guaranteed him a hire," Haile-Selassie says.

http://bit.ly/2PnkOo1

Exposing how pancreatic cancer does its dirty work

Organ-on-chip study reveals mechanism by which the disease destroys and replaces nearby blood vessels, driving malignancy

Pancreatic cancer is one of the most insidious forms of the disease, in which an average of only 9% of patients are alive five years after diagnosis.

One of the reasons for such a dismal outcome is that pancreatic cancer cells are able to escape from tumors and enter the bloodstream very early in the disease, meaning that by the time the cancer is discovered, it has usually already spread. Paradoxically, pancreatic tumors appear to almost lack blood vessels altogether, which prevents cancer drugs from reaching and killing them and has puzzled scientists and clinicians trying to understand how the disease progresses.

Now, a new study from Harvard's Wyss Institute for Biologically Inspired Engineering, Boston University, and the University of Pennsylvania has finally shed light on this mystery. Using both in vitro and in vivo models of pancreatic cancer and vasculature, it found that the tumor cells invade nearby blood vessels, destroy the endothelial cells that line them, and replace those cells with tumor-lined structures.

This process seems to be driven by the interaction between the protein receptor ALK7 and the protein Activin in pancreatic cancer cells, pointing to a possible target for future treatments. The research is published in *Science Advances*.

"Our study really brings to light the importance of 'rescuing' the vasculature prior to treating pancreatic cancer, because this disease is actively destroying our only route for delivering drugs to metastatic tumors," said co-first author Duc-Huy Nguyen, Ph.D., a postdoctoral associate at Weill Cornell Medicine who performed the research while a graduate student at the University of Pennsylvania.

"If we could prevent the cancer's ablation of the surrounding endothelium by developing an inhibitor specific to the ALK7-Activin pathway, we could preserve the existing blood vessels and deliver drugs to patients to shrink down the tumor mass, which it is currently impossible to do."

Catching a killer

Studying the interactions between pancreatic cancer and blood vessels has historically been very difficult, as it would require

multiple, invasive tissue biopsies from human cancer patients, and imaging the disease over time in the internal organs of living mouse models is technically very challenging.

The researchers took a different approach by using organs-on-chips: clear, flexible, plastic chips about the size of a USB stick containing microfluidic channels embedded in a collagen matrix that can be lined with living cells kept alive via a constant flow of nutrient-rich media.

To replicate a pancreatic cancer tumor, the team seeded one channel with mouse pancreatic cancer cells, and a neighboring channel with human endothelial cells.

They observed that after about four days, the pancreatic cancer cells began to invade the collagen matrix toward the blood vessel channel, and eventually wrapped themselves around the channel, spread along its length, and finally invaded it.

During the invasion process, the endothelial cells in direct contact with the cancer cells underwent apoptosis (cell death), leading to a blood vessel channel that was composed exclusively of cancer cells. They saw the same pattern when using human pancreatic cancer cells in the organ-on-chip, and in living mouse models of pancreatic cancer, suggesting that this process may also occur in humans.

Identifying the weapon

The researchers suspected that the mechanism by which pancreatic cancer cells ablate endothelial cells had something to do with the TGF-? signaling pathway, a cascade of molecular interactions that has been implicated in multiple types of cancers.

They introduced a TGF-? inhibitor into their organ-on-chip cancer model for seven days, and saw that the ablation of endothelial cells was significantly reduced. When pancreatic cancer cells were implanted into mice who were subsequently given the same inhibitor molecule, their tumors displayed a higher density of blood vessels, confirming that the inhibitor also reduced ablation in vivo.

To further hone in on the specific TGF-? receptor(s) driving the ablation process, the team created a co-culture device in which they grew pancreatic cells surrounded by endothelial cells so they could investigate exactly what was happening at the interface between the two cell types.

They identified three candidate receptors - ALK4, ALK5, and ALK7 - and genetically deleted the gene coding for each receptor, first in the endothelial cells, then in the pancreatic cancer cells. They found that only by deleting ALK7 from the cancer cells could they significantly reduce ablation of endothelial cells and slowed cancer cell growth.

The ALK7 receptor has two known binding partners, the proteins Activin and Nodal, and when the researchers exposed in vitro cancer cells to compounds that inhibit each partner, only the Activin inhibitor reduced endothelial ablation, suggesting that the interaction between ALK7 and Activin is the major driver of pancreatic cancer's growth and metastasis.

This was further confirmed by knocking out ALK7 expression in cancer cells and then implanting them into mice, which resulted in slower-growing in vivo tumors with higher blood vessel density and fewer apoptotic endothelial cells.

"Not only has our study revealed a major insight into pancreatic cancer biology that could be used to drive the development of new treatments, our cancer-on-a-chip platform opens a new door to being able to more carefully study the interactions between blood vessels and other types of cancers, which could be extremely useful in teasing out these important but complex interactions," said co-first author Esak (Isaac) Lee, Ph.D., who was a Postdoctoral Fellow at the Wyss Institute and Boston University when the research was carried out and is now an Assistant Professor at Cornell University.

The team is actively looking into developing their platform to further understand additional cellular interactions in cancer,

including between cancer and immune cells, and between cancer and the perivascular cells that surround and support blood vessels.

"This study really demonstrates the power of using 3D and 2D organotypic models to replicate disease states in vitro and identify precise mechanisms, and their superiority over traditional in vitro and in vivo approaches," said corresponding author Chris Chen, M.D., Ph.D., an Associate Faculty Member at the Wyss Institute who is also a Professor of Biomedical Engineering and Director of the Tissue Microfabrication Laboratory at Boston University.

"We are really just beginning to scratch the surface, and we're excited to see what other kinds of insights we can uncover with this platform that could lead to new and better treatments."

"This elegant use of organ-on-a-chip technology by Chris Chen and his team provides an entirely new perspective as to why pancreatic cancer is such a malignant form of this disease, as well as potential new molecular targets that may lead to an entirely new class of anti-cancer therapeutics that act by preventing cancer cell colonization of blood vessels rather than targeting angiogenesis, immune cells, or the cancer cells themselves," said Wyss Institute Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at HMS, the Vascular Biology Program at Boston Children's Hospital, and Professor of Bioengineering at Harvard's John A. Paulson School of Engineering and Applied Sciences (SEAS).

Additional authors of the paper include former Wyss Institute Postdoctoral Fellow Styliani Alimperti, Ph.D.; Jeroen Eyckmans, Ph.D. at the Wyss Institute and Boston University; Robert Norgard and Ben Stanger, M.D., Ph.D. at the Perelman School of Medicine at the University of Pennsylvania; former Boston University graduate student Alec Wong, M.S.; and Jake June-Koo Lee, M.D., Ph.D. at Harvard Medical School. This research was supported by the National Institutes of Health, the Lymphatic Education and Research Network, and the Harvard Ludwig Center.

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

A robo-thread wiggles through some of the body's most intricate spaces

Robots that are roughly half a millimetre wide veer around sharp corners and down tiny corridors.

A thread-shaped robot can worm through narrow spaces under the control of magnetic fields, raising hopes of its use in convoluted human organs.

Guided by a magnetic field, a wiry robot wends through a replica of the blood vessels in the human brain. **Kim et al., Sci. Robot. 4, eaax7329 (2019).**

Doctors use snake-like robots in procedures on the heart, but these commercially available devices are too large for more tortuous body parts. To address this gap, Xuanhe Zhao at the Massachusetts Institute of Technology in Cambridge and his colleagues created soft, thread-like robots less than 1 millimetre wide. The robots contain microscopic magnetic particles and are coated with a water-rich lubricating gel. A magnet some distance away directs the robot's course.

The team showed that the robots can smoothly navigate through a series of closely spaced hoops. The devices can also glide through twisting passageways simulating blood vessels in a life-sized replica of the human brain.

Sci. Robot. (2019)

http://bit.ly/2NIdbWH

Stone tools suggest the first Americans came from Japan

Stone tools at the Cooper's Ferry site resemble tools from Ice Age sites in Japan.

Kiona N. Smith

Evidence from the Cooper's Ferry archaeological site in Western Idaho shows that people lived in the Columbia River Basin around

16,000 years ago. That's well before a corridor between ice sheets opened up, clearing an inland route south from the Bering land bridge. That suggests that people migrated south along the Pacific coast. Stone tools from the site suggest a possible connection between these first Americans and Northeast Asian hunter-gatherers from the same period.

Route closed due to ice

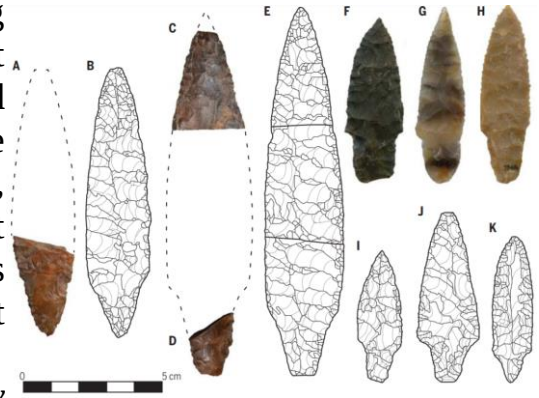
A piece of charcoal unearthed in the lowest layer of sediment that contains artifacts is between 15,945 and 15,335 years old, according to radiocarbon dating. More charcoal, from the remains of an ancient hearth pit, dated to between 14,075 and 15,195 years old. A few other pieces of bone and charcoal returned radiocarbon dates in the 14,000- to 15,500-year-old range. In higher, more recent layers, archaeologists found bone and charcoal as recent as 8,000 years old, with a range of dates in between.

This makes clear that people had been using the Cooper's Ferry site for a very long time, but it's hard to say whether they stuck around or just kept coming back. "Because we did not excavate the entire site, it is difficult to know if people occupied the site continuously starting at 16,000 years ago," Oregon State University archaeologist Loren Davis told Ars. "I expect that this site was used on a seasonal basis, perhaps as a base camp for hunting, gathering, and fishing activities."

Either way, the local Nimiipuu (Nez Perce) people know the site as the location of an ancient village called Nipéhe. "We worked with archaeologists and student interns from the Nez Perce Tribe who visited to get tours of the excavation and to participate in excavations at the site," said Davis.

Davis and his colleagues used a statistical model to calculate how old the very oldest layers of artifacts at the site should be. "The Bayesian model makes predictions about the age of the lower portion of [the excavated layers] based on the chronological trend of known radiocarbon ages in the upper and middle third," Davis explained. According to the model, the very oldest artifacts at Nipéhe are probably between 16,560 and 15,280 years old.

That's about 2,000 to 1,500 years before the great continent-spanning ice sheets of the Pleistocene began to break up. That break-up opened an ice-free corridor southward from the Bering land bridge between the towering sides of the Cordilleran and Laurentian ice sheets. According to computer simulations, that corridor was closed and buried under several kilometers of ice until at least 14,800 years ago, and possibly even later. And that has some important implications for when, and how, people first set foot in the Americas.



Comparison of Cooper's Ferry projectile points with late Pleistocene age Tachikawa-type stemmed points from the Kamishirataki 2 site on Hokkaido, Japan. (A) Stemmed projectile point haft fragment from LU3 (B) Illustration of Japanese Upper Paleolithic stemmed projectile point from the Kamishiritaki 2 site (C) Blade fragment of projectile point from LU3 (D) Stemmed projectile point haft fragment from LU3 (E) Illustration of Japanese Upper Paleolithic stemmed projectile point from the Kamishiritaki 2 site as one possible comparison for the reconstructed stemmed projectile point shown in (C) and (D). (F) Stemmed projectile point from PFA2 (73-627). (G) Stemmed projectile point from PFA2 (73-628). (H) Stemmed projectile point from PFA2 (73-626). (I to K) Illustrations of Japanese Upper Paleolithic stemmed projectile points from the Kamishiritaki 2 site **Davis et al. 2019**

The coastal route

If the ice-free corridor wasn't open, the only way to get south of the ice sheets would have been to skirt along the Pacific coast on foot or by boat, moving among locations where the edges of the 4km (2.5 miles) thick glaciers didn't quite reach the Pacific Ocean. Much

of Ice Age coastline is now underwater, largely thanks to the melting of those huge glaciers. But there have been a few recent archaeological finds that support the idea that the first humans in the Americans moved south along the coast much earlier than previously thought.

Genetic evidence, which uses predictable rates of genetic mutations to tell how long ago populations separated from each other, suggests that sometime between 17,500 and 14,600 years ago, the people living south of the ice sheets split up into two major groups, which moved generally northward and generally southward. That lines up well with the timing at Nipéhe.

At this point, there's not really much debate about whether people had arrived in the Americas before the rise of the Clovis culture, the collection of tools and weapons once thought to represent the oldest human activity in the Americas. Clovis appears starting around 13,250 years ago, so some groups were clearly present earlier. Most of the debate now is focused on the route these earlier people took to reach the thawed, habitable parts of North America.

Davis and his colleagues say Nipéhe is strong evidence for the coastal route. "This does not preclude subsequent human migrations through the [ice-free corridor] at a later time, as suggested by paleogenomics," they wrote, "but such possible population movements do not represent the initial peopling of the Americas."

This is what the Columbia River basin would have looked like 16,000 years ago. **Davis et al. 2019**

A Japanese connection?

Buried in the Ice Age layers at Nipéhe, Davis and his colleagues found animal bones and discarded stone tools, including bifaces (two-sided handaxes; think of them as prehistoric multi-tools), blades, sharp stone flakes, and fragments of two projectile points. The tool collection didn't look a thing like the fluted projectile points that have become the archaeological calling card of the Clovis culture.

To make a Clovis-style projectile point, the flint-knapper has to chip off a flake from one or both faces at a point right at the base of the object. That creates a small groove (also called a flute), which makes it easier to fit the point onto the shaft of a spear or arrow. But at Nipéhe (and at a few other pre-Clovis sites in the Americas), people took the opposite approach: they shaped the base of the point into a stem to attach to the spear or arrow shaft. Some of the younger stone tools from Nipéhe are about the same age as the Clovis culture, but they're clearly a separate technology.

Stemmed projectile points aren't a recent technology, even by archaeological standards; people figured out that stems made points easier to haft by around 50,000 years ago in Africa, Asia, and the Levant. But there are different ways to shape a chunk of flint into a stemmed point, and the ones at Nipéhe look strikingly similar to stemmed points from Northeast Asia. Similarities are especially strong with items from the Japanese island of Hokkaido, which have turned up at sites dating between 16,000 and 13,000 years ago. (As an interesting side note, stemmed projectile points from a 13,500-year-old site in Kamchatka, in east Russia, were made with a distinctly different style.)

Other aspects of the stone tools at Nipéhe also resemble the ones being made and used on Hokkaido at around the same time and slightly earlier. Davis and his colleagues claim that similarity is no coincidence. They suggest that the similar stone tool technology is evidence of a cultural link between the earliest Americans—who arrived on the Pacific coast and migrated southward before moving inland south of the ice sheets—and people in Northeastern Asia.

The dates line up well; many of the Hokkaido sites with stemmed points are older than Nipéhe, while others are around the same age. That suggests that it's possible for the culture to have originated in Japan and then spread to North America—although it's impossible to guess how many generations removed the people of Nipéhe may have been from their relatives in Hokkaido by the time they dug their hearth pit in Western Idaho.

Davis told Ars that archaeologists need to consider the possibility that two distant cultures happened to come up with the same stone-tool-making techniques at around the same time. But that seems unlikely. "These archaeological patterns require further study," he and his colleagues acknowledged in their paper.

Science, 2019. DOI: 10.1126/science.aax9830 (About DOIs).

http://bit.ly/2ZCax7q

New science blooms after star researchers die, study finds

Deaths of prominent life scientists tend to be followed by a surge in highly cited research by newcomers

Written by Peter Dizikes, MIT News Office

The famed quantum physicist Max Planck had an idiosyncratic view about what spurred scientific progress: death. That is, Planck thought, new concepts generally take hold after older scientists with entrenched ideas vanish from the discipline.

"A great scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it," Planck once wrote.

Now a new study co-authored by MIT economist Pierre Azoulay, an expert on the dynamics of scientific research, concludes that Planck was right. In many areas of the life sciences, at least, the deaths of prominent researchers are often followed by a surge in highly cited research by newcomers to those fields.

Indeed, when star scientists die, their subfields see a subsequent 8.6 percent increase, on average, of articles by researchers who have not previously collaborated with those star scientists. Moreover, those papers published by the newcomers to these fields are much more likely to be influential and highly cited than other pieces of research.

"The conclusion of this paper is not that stars are bad," says Azoulay, who has co-authored a new paper detailing the study's findings. "It's just that, once safely ensconced at the top of their fields, maybe they tend to overstay their welcome."

The paper, "Does Science Advance one Funeral at a Time?" is co-authored by Azoulay, the International Programs Professor of Management at the MIT Sloan School of Management; Christian Fons-Rosen, an assistant professor of economics at the University of California at Merced; and Joshua Graff Zivin, a professor of economics at the University of California at San Diego and faculty member in the university's School of Global Policy and Strategy. It is forthcoming in the *American Economic Review*.

To conduct the study, the researchers used a database of life scientists that Azoulay and Graff Zivin have been building for well over a decade. In it, the researchers chart the careers of life scientists, looking at accomplishments that include funding awards, published papers and the citations of those papers, and patent statistics.

In this case, Azoulay, Graff Zivin, and Fons-Rosen studied what occurred after the unexpected deaths of 452 life scientists, who were still active in their disciplines. In addition to the 8.6 percent increase in papers by new entrants to those subfields, there was a 20.7 percent decrease in papers by the rather smaller number of scientists who had previously co-authored papers with the star scientists.

Overall, Azoulay notes, the study provides a window into the power structures of scientific disciplines. Even if well-established scientists are not intentionally blocking the work of researchers with alternate ideas, a group of tightly connected colleagues may wield considerable influence over journals and grant awards. In those cases, "it's going to be harder for those outsiders to make a mark on the domain," Azoulay notes.

"The fact that if you're successful, you get to set the intellectual agenda of your field, that is part of the incentive system of science, and people do extraordinary positive things in the hope of getting to that position," Azoulay notes. "It's just that, once they get there, over time, maybe they tend to discount 'foreign' ideas too quickly and for too long." Thus what the researchers call "Planck's Principle" serves as an unexpected -- and tragic -- mechanism for diversifying bioscience research.

The researchers note that in referencing Planck, they are extending his ideas to a slightly different setting than the one he himself was describing. In his writing, Planck was discussing the birth of quantum physics -- the kind of epochal, paradigm-setting shift that rarely occurs in science. The current study, Azoulay notes, examines what happens in everyday "normal science," in the phrase of philosopher Thomas Kuhn.

The process of bringing new ideas into science, and then hanging on to them, is only to be expected in many areas of research, according to Azoulay. Today's seemingly stodgy research veterans were once themselves innovators facing an old guard.

"They had to hoist themselves atop the field in the first place, when presumably they were [fighting] the same thing," Azoulay says. "It's the circle of life."

Or, in this case, the circle of life science.

The research received support from the National Science Foundation, the Spanish Ministry of Economy and Competitiveness, and the Severo Ochoa Programme for Centres of Excellence in R&D.

http://bit.ly/2HCl5NE

Blocking specific protein could provide new treatment for deadly form of prostate cancer

Study provides rationale for clinical trial evaluating CDK7 inhibitors

PHILADELPHIA - Blocking a kinase known as CDK7 sets off a chain reaction that results in the death of prostate cancer cells that have spread and are resistant to standard therapies, according to a new study from researchers in the Abramson Cancer Center at the University of Pennsylvania. The team identified the role of CDK7 as the on/off switch that controls Med-1, a process that works in partnership with the androgen receptor to drive prostate cancer growth. Researchers show turning the switch off eventually leads to the death of cancer cells in mice. Cancer Discovery published the findings today.

Androgen deprivation therapy is a standard approach to treating prostate cancer, but over the course of treatment, a majority of patients will eventually become resistant to the therapy, allowing the cancer to grow and spread. This is referred to as metastatic castration-resistant prostate cancer (CRPC). There are two drugs approved by the U.S. Food and Drug Administration for these cases, but patients see little or no long-term survival benefit from these therapies.

Since the androgen receptor (AR) continues to be the main the driver of cancer growth in CRPC, taking away its function is still critical. Given the disease's resistance to therapies that try to take on AR directly, a new approach is needed. While these cancers do not have additional mutations or other genetic overexpression, the Penn team was still able to identify a new target thanks to what researchers called "AR's co-pilot."

"We know that AR does not work alone; that it needs Med-1 as its partner," said the study's senior author Irfan A. Asangani, PhD, an

assistant professor of Cancer Biology in the Perelman School of Medicine at the University of Pennsylvania. "Our study found a way to turn off Med-1, leaving AR without its co-pilot which means the cancer cannot grow and the cells eventually die."

Using an inhibitor to turn off CDK7 led to the death of CRPC cells in both the lab setting and in animal models. Researchers also saw very limited off-target effects of this approach, since healthy cells have redundancies in place to deal with the loss of Med-1, meaning only the cancer cells end up dying off.

"Our theory is that these cancer cells are addicted to Med-1 and AR but other cells are not, so we're essentially cutting them off from their addiction," Asangani said.

CDK7 inhibitors are already being tested in phase I clinical trials for other cancers - including leukemia, lung cancer, glioblastoma, and breast cancer - but Asangani said this study shows the rationale for testing them in CRPC.

Reyaz ur Rasool, Ramakrishnan Natesan, and Qu Deng are co-first authors on the study. Other Penn authors include Shweta Aras, Priti Lal, Samuel Sander Effron, Erick Mitchell-Velasquez, Jessica M. Posimo, Lauren E. Schwartz, Daniel J. Lee, and Donita C. Brady.

http://bit.ly/2LiLukA

Fossil colour studies are changing our idea of how dinosaurs looked

What colour were the dinosaurs? If you have a picture in your head, fresh studies suggest you may need to revise it.

by Gareth Willmer, From Horizon Magazine

New fossil research also suggests that pigment-producing structures go beyond how the dinosaurs looked and may have played a fundamental role inside their bodies too.

The latest findings have also paved the way for a more accurate reconstruction of the internal anatomy of extinct animals, and insight into the origins of features such as feathers and flight.

Much of this stems from investigations into melanin, a pigment found in structures called melanosomes inside cells that gives external features including hair, feather, skin and eyes their colour—and which, it now turns out, is abundant inside animals' bodies too.

"We've found it in places where we didn't think it existed," said Dr. Maria McNamara, a palaeobiologist at University College Cork in Ireland. "We've found melanosomes in lungs, the heart, liver, spleen, connective tissues, kidneys… They're pretty much everywhere." The discoveries in her team's newest research, published in mid-August, were made using advanced microscopy and synchrotron X-ray techniques, which harness the energy of fast-moving electrons to help examine fossils in minute detail.

In-depth fossil analysis could help us understand the true functions of colour.
Aline Dassel/Pixabay, licensed under Pixabay licence

Using these, the researchers found that melanin was widespread in the internal organs of both modern and fossil amphibians, reptiles, birds and mammals—following up a finding they made last year that melanosomes in the body of existing and fossil frogs in fact vastly outnumbered those found externally.

What's more, they were surprised to discover that the chemical make-up and shape of the melanosomes varied between organ types—thus opening up exciting opportunities to use them to map the soft tissues of ancient animals.

Secondary

These studies also have further implications. For one, the finding that melanosomes are so common inside animals' bodies may overhaul our very understanding of melanin's function, says Dr. McNamara. "There's the potential that melanin didn't evolve for

colour at all," she said. "That role may actually be secondary to much more important physiological functions."

Her research indicates that it may have an important role in homeostasis, or regulation of the internal chemical and physical state of the body, and the balance of its metallic elements.

"A big question now is does this apply to the first, most primitive vertebrates?" said Dr. McNamara. "Can we find fossil evidence of this? Which function of melanin is evolutionarily primitive—production of colour or homeostasis?"

At the same time, the findings imply that we may need to review our understanding of the colours of ancient animals. That's because fossil melanosomes previously assumed to represent external hues may in fact be from internal tissues, especially if the fossil has been disturbed over time.

Dr. McNamara says her research has also shown that melanosomes can change shape and shrink over the course of millions of years, potentially affecting colour reconstructions.

Further complicating the picture is that animals contain additional non-melanin pigments such as carotenoids and what is known as structural colour, which was only recently identified in fossils. In 2016, a study by Dr. McNamara's team on the skin of a 10-million-year-old snake found that these could be preserved in certain mineralised remains.

"These have the potential to preserve all aspects of the colour-producing gamut that vertebrates have," said Dr. McNamara.

She hopes over time that these findings and techniques will together help us to much more accurately interpret the colours of ancient organisms—though in these early days, she doesn't have examples of animals for which this has already changed.

Deep time

Many of the significant strides in this area have come out of a project that Dr. McNamara leads called ANICOLEVO, which set out to look into the evolution of colour in animals over deep time—or hundreds of millions of years.

The project's starting point was that previous animal colour studies largely omitted in-depth fossil analysis, leaving a significant gap by basing what we know about colour mainly on modern organisms.

But it has since led to even wider investigation. Dr. McNamara says it is providing fresh hints on the kinds of biological structures and processes that are essential for survival in terrestrial and aquatic environments. "It looks like we'll be able to look into much broader, exciting questions about what it means to be an animal," she said.

Two fossils found in China showed that flying reptiles known as pterosaurs had feathers, indicating the structures evolved earlier than previously thought. **Zixiao Yang**

Part of her research on two fossils found in China even showed that flying reptiles known as pterosaurs had feathers, potentially taking the evolution of these structures back a further 80 million years to 250 million years ago. The fossils contained preserved melanosomes with diverse shapes and sizes, one of the tell-tale signs of feathers.

"We were able to show for the first time that not only were dinosaurs feathered, but an entirely different group of animals, the pterosaurs, also had feathers," said Dr. McNamara.

Another project she worked on, called FOSSIL COLOUR, compared the chemistry of colour patterns between fossil and modern insects. Again, says Dr. McNamara, these don't entirely map onto each other.

"It's already clear that the fossilisation process has altered the chemistry somewhat, so we're doing experiments to try to

understand these changes." What's evident is that there's lots still to find out about colour. "We're just at the tip of the iceberg when it comes to fossil colour research," said Dr. McNamara.

Thermoregulation

Other researchers agree that there's more to animal colour than meets the eye. Dr. Matthew Shawkey, an evolutionary biologist at Ghent University in Belgium, said that looking into properties and functions beyond colour's use for visual means like signalling and camouflage will be critical to understanding its true significance.

"For example, how do colours affect thermoregulation? Flight? Such functions may be complementary to, or even more significant, than purely visual functions," he said.

Dr. Shawkey is looking into such questions, with one of his recent studies indicating that the wing colour of birds may play an important role in flight efficiency by leading to different rates of heating.

"What started as a novelty of deciphering dinosaur colours has turned into a very serious field which is studying the origins of key pigment systems, how the evolution of colourful structures may have helped drive major evolutionary transitions like the origin of flight, and how colour is related to ecology and sexual selection," said Dr. Steve Brusatte, a vertebrate palaeontologist and evolutionary biologist at the University of Edinburgh, UK.

Ultimately, we may be able to find out more about colour than once thought possible. "When I was growing up, so many of the dinosaur books I read in school said that we would never know what colour they were," said Dr. Brusatte. "But as is so often the case in science, it was silly to treat this as impossible."

He said he is excited to see what comes next, with the field just in its infancy: "Palaeontologists now have a whole new window into understanding the biology and evolution of long-extinct organisms."

http://bit.ly/2MMDRWX

Human Cortical Organoids Model Neuronal Networks

After growing in culture for a few months, the mini-brains produced rhythmic neural activity that strengthened over time.

Abby Olena

Cortical organoids—three-dimensional bundles of neurons and glia grown in a dish from induced pluripotent stem cells—look a lot like tiny brains. And while the gene expression, cell types, and organization found in these spherical structures have similarities to the developing cortex, it's not clear whether they're also an appropriate model in which to explore how neural networks form.

ABOVE: 10-month-old human cortical organoids **MUOTRI LAB, UCSD**

In a study published today (August 29) in *Cell Stem Cell*, researchers have shown that organoids derived from human stem cells produce brain waves that become more complex as development progresses. The synchronized neural activity can be blocked by drugs, a sign that cells were communicating with each other and forming functional neural circuits within the miniature brains.

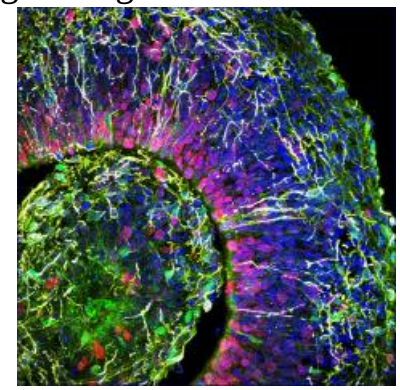
The authors draw parallels between organoids' neural patterns and those of the brains of preterm infants and point to them as evidence that cortical organoids could be used to study neural networks, perhaps in organoids created from the cells of patients with neurological or psychiatric disorders. Others in the field caution that what these oscillations really mean is still an open question.

"The idea of organoids developed from fibroblasts that will give us patient-specific information is really exciting," says John Huguenard, an electrophysiologist at Stanford University who was not involved in the study. "I'm a little less excited about the nature

of the activity that they're seeing. It's a sign that they're going in the right direction, [but] we're just not quite there yet."

Previous work has shown that neurons in cortical organoids are capable of firing here and there. Alysson Muotri, a biologist at the University of California, San Diego, tells *The Scientist* that he was initially skeptical that these organoids could create more sophisticated neural networks, at least in part because they're missing some cell types found in the developing brain.

To explore this question, he and his team grew organoids from induced pluripotent stem cells derived from fibroblasts of healthy adult men and verified that cell types typically found in the cortex were organized into layers resembling those present in the developing brain. Then they plated the mini-brains on special culture dishes containing multi-electrode arrays used to record neural activity.



A cross-section of a human brain organoid **MUOTRI LAB, UCSD**

When their cultures were about two months old, the researchers started to see some small oscillations—rhythmic spikes in action potentials across multiple neurons in the vicinity of the electrode arrays—that came and went. As the organoids matured, the neural activity continued to increase in frequency and complexity and could be disrupted with drugs that block synaptic activity, indicating that neural networks were present.

The authors next examined possible parallels between the organoids' brain waves and the human brain. Using a collection of electroencephalogram (EEG) data from premature babies aged 24 to 38 weeks, they trained a machine learning program to determine the age of the subject based on the neural activity detected by the EEGs. When the research team fed the computer information from the brain organoids, it was unable to distinguish the data coming from an EEG from that collected by the multielectrode arrays from the organoids starting at about 25 weeks.

Muotri says that the result could mean that the electrical activity of the organoids follows a similar developmental trajectory as the human brain and that, in the future, this model system could be used to study conditions where neural networks function differently, such as epilepsy.

"I am happy to see that they also see similar network bursts to what we have shown previously, but they show that this activity does become more mature in this paper," Madeline Lancaster, a developmental biologist the MRC Laboratory of Molecular Biology in the UK who did not participate in the study, writes in an email to *The Scientist*. "While the coordinated neural activity is interesting, it's important to keep in mind what exactly is being measured," she adds, explaining that brain waves are long-range coordinated firing of neurons with particular frequency that can immediately be detected without extensive data analysis using a simple EEG. Here, the authors are measuring very short-range network bursts using a multi-electrode array. Then, by extensively filtering the data, they are able to show particular frequencies, she says. "It should be stressed though that this is not the same as a brain wave."

"It's an intriguing and interesting report, but I think we have to be cautious about the comparisons that are made between the activity in the organoids and normal brain activity captured by EEG in premature human infants," says Arnold Kriegstein, a stem cell biologist at the University of California, San Francisco, who was not involved in the work. He explains that, unlike developing brains in vivo, the organoids lack connections to other brain areas and are also missing inhibitory neurons, which underlie much of the EEG activity in the human brain. These and other issues raise questions

about the mechanisms behind these oscillations and whether the circuits forming are anything like those of a real cortex.

"It's still premature to use this kind of activity as a measure of normal versus abnormal activity in disease states," Kriegstein says. "In the absence of more information about the evolution of normal activity, as well as more information about where this activity in the organoids comes from, how it's generated, and what it depends upon, it's going to be very difficult to decide how this could be altered in a disease."

C.A. Trujillo et al., "Complex oscillatory waves emerging from cortical organoids model early human brain network development," **Cell Stem Cell,** *doi:10.1016/j.stem.2019.08.002, 2019.*

http://bit.ly/2Lel4BI

Vaping-illness investigations turn to contaminants, counterfeits: report

Adulterated liquids containing THC still appear to be a lead suspect.

Beth Mole

State and federal investigations into the puzzling burst of severe lung illnesses linked to e-cigarette use—aka vaping—are focusing in on black-market and counterfeit products, according to a report by the Washington Post.

Unknown adulterants and dubious solvents—such as oils and diluting "cutting agents"—in vaping liquids are now the prime suspects behind the illnesses, which have has led to 215 possible cases in 25 states. One person in Illinois has died. Investigators say that in many of the cases, people bought suspect products on the black market or in "pop-up" shops.

Solvents in counterfeit and black-market vaping liquids "can vary a lot," an unnamed official at the Centers for Disease Control and Prevention told the Post. The official added that solvents sold for mixing home-made vaping liquids may also be mislabeled.

"What's likely causing the harm is something that they are putting in to make it easy or cheap to mix," former Food and Drug Administration commissioner Scott Gottlieb told the Post.

Gottlieb, who led a crackdown on e-cigarette makers while at the FDA, said that mainstream e-cigarette products such as those from Juul or Blu are unlikely to be involved in the cases. While such products may cause chronic problems, he said, the recent flare-up of cases involve acute illnesses—ones that haven't been seen before and are spread unevenly across the country.

Abrupt illnesses

Those sickened often suffer gradual breathing difficulties, coughing, fatigue, chest pain, and weight loss, which leads to hospitalization. Some have also experienced vomiting and diarrhea.

Many cases seem linked to vaping liquids containing THC, or tetrahydrocannabinol, the primary psychoactive ingredient in marijuana. Investigators say that they're also looking into suspect nicotine-containing liquids.

Shady THC-containing liquids seem to be the primary suspects in investigations in several states, including Utah, Pennsylvania, and California.

"We suspect adulterated or contaminated products, because these [marijuana] products have been out there for some time, and we've not seen these cases until this summer," Phillip Lamberty, a pulmonologist and critical care specialist at the University of Pittsburgh Medical Center (UPMC), told the Post. Lamberty treated three vaping-linked cases recently, at least two of which were linked to THC-containing products. One was bought online and the other from an illicit drug dealer.

Sketchy sales

The UPMC health system, which includes 40 hospitals, has seen at least 14 patients with vaping-linked illnesses. Several patients said they bought the black-market brand "Dank Vapes" products online.

In California's King County, health officials linked all seven cases in the county to "pop-up" shops selling marijuana vaping cartridges. "The patients had switched from regular retailers to the pop-up shops," elaborated Nancy Gerking, the county's assistant director of public health. The patients "found a difference between the potency of the products," she added. "They had to use twice as much, so they were taking twice as much of the product into their lungs."

Some health officials have suggested that consumers stop using all vaping products until the culprit(s) are clearly identified. However, e-cigarette makers and other health experts have pushed back, noting that the issue is clearly with dubious products, not vaping generally.

http://bit.ly/2ZJ4qqC

Internal bleeding after heart attack may trigger suspicion of cancer

Bleeding a few after discharge from hospital for heart attack linked with subsequent cancer diagnosis

Paris, France -Bleeding during the first six months after discharge from hospital for a heart attack is linked with a subsequent cancer diagnosis, according to research presented today at ESC Congress 2019 together with the World Congress of Cardiology.(1)

"Our results suggest that patients should seek medical advice if they experience bleeding after discharge for a heart attack," said study author Isabel Munoz Pousa of Alvaro Cunqueiro Hospital, Pontevedra, Spain. "Particularly if the bleeding is of gastrointestinal, pulmonary or genitourinary origin, without any obvious reason, and occurs in the first six months. If the cause is cancer, early detection can improve prognosis."

Following discharge for an acute coronary syndrome (heart attack or unstable angina), patients are typically treated with dual antiplatelet therapy for around one year. This treatment inhibits the formation of blood clots but raises the risk of bleeding. Previous research has suggested that post-discharge bleeding may have negative consequences. This study examined its association with a new diagnosis of cancer.

The researchers retrospectively reviewed the hospital records of 3,644 acute coronary syndrome patients discharged with dual antiplatelet therapy from Alvaro Cunqueiro Hospital. Patients were followed-up for a median of 56.2 months for bleeding events and cancer. The researchers analysed associations between bleeding and the absolute risk of a new cancer diagnosis.

Bleeding occurred in 1,215 patients (33%) during follow-up and 227 patients (6%) had a new diagnosis of cancer. After adjustment for factors known to influence bleeding or cancer, post-discharge bleeding was associated with a threefold higher risk of new cancer diagnosis. The median time from bleeding to cancer was 4.6 months. The link with cancer increased as the severity of bleeding worsened.

Spontaneous bleeding with no apparent cause was linked with a four times higher risk of cancer diagnosis while there was no relation with bleeding due to trauma such as injury or bladder catheterisation.

Regarding the location, blood in the faeces was associated with a nearly fourfold risk of cancer diagnosis, while coughing up blood or blood in the urine were linked with four and eight-times greater risks, respectively.

There was a relationship between bleeding and cancer regardless of whether patients were still on dual antiplatelet therapy or not.

Ms Munoz Pousa said: "Most of the bleeding episodes in the study were mild. The bleeding events more strongly related with a new cancer diagnosis were severe haemorrhages of unknown cause requiring surgery - for example digestive bleeding needing endoscopic treatment. We found a higher incidence of cancer in the

first six months after discharge regardless of whether patients were taking dual antiplatelet therapy or not."

She added: "A possible explanation is that there is a pre-existing subclinical lesion in an organ that is triggered to become cancer by antiplatelet drugs or a stressful situation such as heart attack. This hypothesis needs to be tested and patients should ensure they take antiplatelets as prescribed to avoid having another heart attack."

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Disclosures: None.

Acknowledgements: Isabel Muñoz Pousa thanks Dr Sergio Raposeiras Roubín, Dr Emad Abu-Assi, and Dr Andrés Íñiguez Romo for their help and support for the study.

References and notes

(1) The abstract "Association between bleeding after acute coronary syndrome and newly diagnosed cancers" will be presented during Poster Session 1: Cardio-oncology I on Saturday 31 August at 11:00 to 16:00 CEST in the Poster Area.

http://bit.ly/2LhTLXo

Preventative artery repair provides major benefit after serious heart attack

No major downside to the additional procedures

HAMILTON, ON - A major international study has shown that opening all clogged arteries with stents after a serious heart attack is much better than opening only the single clogged artery that caused the heart attack.

About half of all heart attack victims are found to have additional clogged arteries in addition to the one that caused their heart attack. Previously, doctors focused on opening the one artery responsible for the heart attack, leaving the other blockages for treatment with medication alone. The new study, a collaboration of 130 hospitals in 31 countries, has shown that opening all the blockages is better than treating only the one blockage causing the heart attack. This led to a 26 per cent reduction in the patient's risk of dying or having a recurrent heart attack.

The study, known as the COMPLETE trial, was published today in the New England Journal of Medicine and presented as a late-breaking clinical science session at the European Society of Cardiology Congress together with the World Congress of Cardiology in Paris, France.

"Given its large size, international scope and focus on patient-centered outcomes, the COMPLETE trial will change how doctors treat this condition and prevent many thousands of recurrent heart attacks globally every year," said study leader Dr. Shamir R. Mehta of the Population Health Research Institute (PHRI) of McMaster University and Hamilton Health Sciences.

He said that although it had been known that opening of the single blocked artery that caused the heart attack with stents was beneficial, it was unclear whether additional stents to clear the other clogged arteries further prevented death or heart attack. In most cases, doctors would just treat the additional blockages with medication alone.

"This study clearly showed that there is long term benefit in preventing serious heart-related events by clearing all of the arteries. There was also no major downside to the additional procedures," said Mehta.

The COMPLETE study, led by the PHRI and funded by the Canadian Institutes of Health Research, involved 4,041 patients and is the first large, randomized, international trial to show a reduction in major outcomes with this approach.

"The benefits emerged over the long term and were similar when the additional stent procedures were done anytime in the first 45 days after the heart attack," said Mehta who is also a PHRI senior scientist, a professor of medicine at McMaster University and an interventional cardiologist of Hamilton Health Sciences.

Over the median of three years, a second heart attack or cardiovascular death dropped to 7.8 per cent of the patients who had the complete revascularization compared to 10.5 per cent of those who had a stent only for the artery that caused the first heart

attack, a highly significant difference, said Mehta. The benefit was even more sizable when factoring in other untoward events such as severe chest pain necessitating a repeat stenting procedure.

There was no difference between the groups on whether they experienced side effects, including stroke and major bleeding.

http://bit.ly/2ZNi97j

Part cow, part… bacterium? Biotech company makes heifer of gene-editing blunder

Gene-edited cow project on the butcher block after bacterial genes found.

Beth Mole - 9/1/2019, 10:00 PM

A Minnesota-based gene-editing company is left red in the face after it took on bull genetics—and got slammed.

The company, Recombinetics, set out years ago to genetically engineer Holstein dairy cattle to come without their troublesome horns, which farmers typically remove to keep themselves and other cows safe. In 2015, the company seemed to have succeeded, unveiling two hornless bulls, Spotigy and Buri. Recombinetics touted them as a bona fide, 100%-bovine success story.

Though Spotigy was sacrificed for research, Buri lived on to sire 17 offspring—one of whom graced the cover of Wired, as MIT Technology Review notes. And, until just a few months ago, Brazil was set to create a herd of hornless Holsteins from shipments of Buri's sperm, Wired reported.

But the plans were bucked after scientists at the Food and Drug Administration stumbled upon an utterly damning find earlier this year—Buri isn't all bull: he's a wee bit bacterium.

Bullish edits

When Recombinetics edited the cow cells that would later give rise to Buri, the company did so using bacterial DNA-editing machinery—which inadvertently got stitched into Buri's genome.

The machinery involved are called TALENs (transcription activator-like effector nucleases), which are enzymes that can be customized to snip a targeted spot in a genetic code. That break in the code can then be patched up with a desired DNA sequence—say, a stretch of DNA that leads to hornlessness, swiped from other, hornless cattle breeds.

Recombinetics' scientists used a standard method to get the TALENs into the cow cells—they delivered the TALENs via a loop of bacterial DNA called a plasmid. Usually, after the plasmid-encoded TALENs do their snipping, the plasmid's work is done and it doesn't hang around. But in Buri's case, the whole plasmid ended up inserting itself into the bull's genome, right next to the inserted stretch of DNA for hornlessness.

That means that Buri's genome contains the entire DNA sequence of the plasmid. And in addition to all the bacterial-editing machinery from the loop of DNA, Buri's genome includes the antibiotic resistance genes present on the plasmid, too—though they're unlikely to have any effect.

Blind spot

The plasmid insertion is a big cow plop. But the fact that the company didn't find the problem itself is perhaps more embarrassing.

"It was not something expected, and we didn't look for it," Tad Sonstegard, CEO of Acceligen, a subsidiary of Recombinetics that owns the animals, told MIT Technology Review. He added that a more thorough check "should have been done."

The FDA scientists who found the problem agreed. In their report on the case, they noted that their find "highlights a potential blind spot in standard genome-editing screening methods."

However embarrassing, the genetic insertion is unlikely to affect the cows or anyone who might end up eating them. As Sonstegard put it, they're "safe to eat with or without the plasmid."

But the inclusion of bacterial DNA in a cow's genome makes the regulatory aspects of Buri and his offspring far more complicated—practically untenable. They're not just edited, all-cow cows—they are genetically modified organisms with DNA from a completely different branch of life.

Some of the animals have already been incinerated, and regulators in Brazil have rejected plans involving the animals.

Recombinetics, meanwhile, isn't ruminating over the blunder. It has already moved forward with gene-edited, heat-tolerant beef. The company noted that it hasn't found any bacterial genes in those animals.

https://n.pr/32mjHH2

Optimists For The Win: Finding The Bright Side Might Help You Live Longer

Even if optimism doesn't come naturally, it can be taught, researchers say. Therapists can help you practice reframing your expectations, to cultivate a sunnier outlook.

Patti Neighmond

Good news for the cheery: A Boston study published this month suggests people who tend to be optimistic are likelier than others to live to be 85 years old or more.

That finding was independent of other factors thought to influence life's length — such as "socioeconomic status, health conditions, depression, social integration, and health behaviors," the researchers from Boston University School of Medicine and the Harvard T.H. Chan School of Public Health say. Their work appears in a recent issue of the science journal *PNAS*.

"We wanted to consider, in the current issue, benefits of psychological resources like optimism as possible new targets for promoting healthy aging," says Lewina Lee, who headed the study. She's a clinical research psychologist at Boston University. "The more we know about ways to promote healthy aging the better."

Researchers already knew from previous work that optimistic individuals tend to have a reduced risk of depression, heart disease and other chronic diseases. But might optimism also be linked to exceptional longevity? Lee looked at medical records from two long term research studies — one involving female nurses and the other involving men, mostly veterans.

The study included 69,744 women and 1,429 men. Both groups completed survey measures to assess their level of optimism, as well as their overall health and health habits such as diet, smoking and alcohol use. In the survey, study participants were asked if they agreed with statements such as "in uncertain times I usually expect the best" or "I usually expect to succeed in things that I do."

Health outcomes from women in the study were tracked for 10 years, while the men's health was followed for 30 years. Researchers found that the most optimistic men and women demonstrated, on average, an 11-15% longer lifespan, and had far greater odds of reaching 85 years old, compared to the least optimistic group.

Now, researchers say they can't tell from this study *how* optimism might affect longevity. Optimistic people might be more motivated to try to maintain good health — such as maintaining a decent diet, engaging in regular exercise and not smoking.

They may also be better at regulating stress, Lee says.The burden of unrelieved stress is well known to have negative effects on health, including an increase in heart disease, liver disease and gastrointestinal problems.

Clinical health psychologist Natalie Dattilo, with Brigham and Women's Hospital in Boston, says even if it doesn't come naturally, optimism can be taught. In her practice she works mostly with adults who struggle with depression and anxiety — "a lot of folks who worry," she says. Many are pessimistic and "tend to see things through a half empty glass and typically expect negative outcomes."

In treatment, Dattilo works to expand their world view, so their set of assumptions about the world and themselves are more uplifting and empowering.

"We examine their thinking under a psychological microscope," Dattilo says, discussing why they anticipate a particular negative outcome. "If we can look at that together, we can begin to uncover systems of beliefs and assumptions people are making about themselves in their lives and we can begin to change those."

Dattilo challenges patients to pay attention when a negative outlook kicks in, and consciously shift it. "Just try it on, try on a different thought, attitude or mindset and play that out and just see what happens," she advises.

Also, she emphasizes, optimism isn't simply the absence of depression or sadness or stress.

"People who think in optimistic ways are still prone to stress," she says. "They are functioning in our society, meeting demands, prone to burn out. And it's not like negative events won't happen."

But the way they cope with problems makes a difference, she says. Difficulties don't tend to cause them distress for extended periods of time.

"Resilience is our ability to bounce back, to recover," she says. "And what this study shows is that optimism actually plays a very big role in our ability to bounce — even if we experience setbacks."

So, are gloomy curmudgeons doomed to short, brutish lives, even if they are content to be pessimistic? Some people find eternal optimists insufferable.

Lewina Lee says she treats pessimistic patients "all the time." While some seem satisfied with their outlook, others are more open to lightening up, once they know how, in order to achieve goals that are important to them.

"I would try to challenge their negativity and shake it loose," she says, and get rid of some of the patients' more rigidly held beliefs for their own benefit.

Pessimists who try this will likely end up happier, she suggests. And they might even extend their lives.