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Pay Attention to Self-harm: It Is a Precursor to Suicide

Self-harm and Suicide

William T. Basco, Jr., MD, MS

Among teens and young adults aged 15 to 24 years, suicide is the second-leading cause of death. A recent study[1] sought to determine whether self-harm (a nonfatal self-injury or self-poisoning that occurred with or without suicidal intent) predicted future suicide. Other cohort studies have shown that the frequency of suicide in the first year after self-harm was less than 1%. Olfson and colleagues add to what is known by looking at expanded covariates, including gender, age, race, and ethnicity, as well as clinical diagnoses that might alter the risk for suicide after self-harm.

They analyzed 2001-2007 Medicaid data from 45 states, matched to the National Death Index, to identify persons aged 12-24 years who had a diagnosis of deliberate self-harm in the Medicaid data. The first instance of self-harm that appeared for any patient was assessed, and each person's subsequent 365-day history after the self-harm event was evaluated. Those who died at the time of the initial self-harm event were excluded. Most persons with nonfatal initial self-harm were white, female adolescents. Other demographics of the cohort are shown in the table.

Table. Demographic Composition of Cohort.

Race	***Proportion of Cohort***
Non-Hispanic white	*62.3%*
Non-Hispanic black	*27%*
Hispanic	*13.1%*
American Indian/Alaska Native	*5.1%*
Other Characteristics	
Female	*67.6%*
Male	*32.4%*
Depressive disorder	*35.6%*
Anxiety disorder	*15.4%*
Substance-use disorder	*23.3%*
Schizophrenia	*10%*
Attention-deficit/hyperactivity disorder	*8.9%*
Two or more mental health diagnoses	*21%*

Among more than 32,000 self-harm events, the method was classified as violent in 4.5% of the episodes and nonviolent in 83.4% of the episodes (two-thirds of which were poisoning and 18% of which were cutting).

About 17% of the young people who harmed themselves had at least one repeat nonfatal self-harm event during the following year. Several factors were positively associated with repeated self-harm, including female sex, bipolar or anxiety disorder, substance use disorder, personality disorder, and two or more clinical mental health diagnoses.

The overall standardized mortality ratio (SMR) was 26.7 (95% confidence interval [CI], 19.9-305.1) when the children were compared with a matched cohort in the general US population. The SMR of 46 was particularly high for adolescents (aged 12-17 years) compared with 19.2 among young adults (aged 18-24 years).

A self-harm episode that involved a firearm had a much greater hazard ratio (33.45; 95% CI, 13.3-84.1) for suicide after controlling for covariates.

These findings are consistent with previous research, which found that being male, being an American Indian or Alaskan native, or use of a violent method at initial presentation was a risk factor for suicide.

The investigators conclude that risk for suicide in a teen or young adult is increased after nonfatal self-harm. They suggest that knowing the demographic and clinical correlations with self-harm

and later suicide can help prioritize populations for care and follow-up.

Viewpoint

Many of these findings will not surprise practitioners in emergency departments or inpatient or other settings where suicidal patients are seen frequently. Still, it's worth reiterating the results for other frontline providers who may see patients will self-harm at much lower frequencies.

These data point out that any self-harm, including cutting, which has the same hazard ratio as poisoning, is a risk factor. The magnitude of increase in standardized mortality or hazard ratio is also worth emphasizing and not forgetting.

References

1. Olfson M, Wall M, Wang S, et al. Suicide after deliberate self-harm in adolescents and young adults. Pediatrics. 2018;141 pii:e20173517.

http://bit.ly/2Nhwjrt

Using hepatitis C-infected donor kidneys could reduce time on dialysis for transplant patients with HCV

Transplanting HCV patients with organs from HCV-positive donors and then treating the infection more effective than waiting

CINCINNATI--Transplanting hepatitis C (HCV)-infected dialysis patients with organs from HCV-positive donors and then treating the infection after transplantation is more effective, costs less and will shorten wait times for donated organs, according to a computer analysis conducted by physician-researchers at the University of Cincinnati (UC) College of Medicine.

The findings are available online in the *Annals of Internal Medicine*. The study's lead author is Mark Eckman, MD, professor and director of the UC Division of General Internal Medicine.

The model predicts that transplantation with an HCV-infected kidney followed by HCV treatment was more effective and less costly than treating HCV before transplantation, largely because of the longer wait times for HCV-uninfected kidneys, explains Eckman. A typical 57.8 year-old patient receiving hemodialysis would gain an average of six months of additional quality adjusted life years at a lifetime cost savings of $41,591, says Eckman.

A patient receiving a non-infected kidney waits on average more than two years for that organ, while the wait for an HCV-infected kidney is about eight months, says Eckman, a UC Health physician. Also, 15 percent of patients undergoing dialysis for end-stage renal disease are infected with HCV.

"There is a high excess mortality risk for patients receiving hemodialysis and it is associated with a decreased quality of life for some patients," says Eckman. "If you can spend less time on dialysis, you will be better off. The annual cost of hemodialysis is more than $90,000."

In the United States, an estimated 110,000 patients start dialysis each year. Of the approximately 500,000 patients who received dialysis for end stage renal disease in 2016, only 3.8 percent or 19,060 received kidney transplants, says Eckman.

The computerized decision analytic model pulled data from a variety of sources including the United States Renal Data System (USRDS), medical literature and clinical trials. The model looks at several factors such as sex, age, the degree of liver damage from chronic HCV infection, and treatment costs to predict outcomes that may occur over the lifetime of a patient cohort for each of the clinical strategies studied, explains Eckman.

"While people are waiting for a kidney, there is a risk of dying on hemodialysis, with a mortality rate of approximately 7.5 percent per year," says Eckman. "If you wait a shorter time to get a kidney transplant by accepting an HCV-infected kidney, you can avoid a year-and-a-half or more of time on a waiting list.

"Once you have a transplant, the annual mortality rate is roughly 2 percent per year instead of about 7.5 percent per year. The shorter

the period of time waiting for a kidney on dialysis, the better your outcomes will be."

Eckman says the computer model is needed because there are no large clinical trials yet that have addressed this question.

"This isn't something we would have asked or thought about even a year ago," says Eckman. "Now, we have very effective HCV treatments that we didn't have two or three years ago. Some of these new medications can be used in patients on dialysis. The new drugs have much fewer side effects, and the treatment course is a lot shorter. The treatment of HCV has advanced dramatically."

Several clinical trials have shown HCV cure rates as high as 98 percent with the new drugs, says Eckman.

"Secondly, a year ago we didn't have drugs to treat HCV that could be used in patients with end stage renal disease," says Eckman. "While treatment of HCV is very expensive, this cost balances out in our analysis as patients in both strategies are getting treated for HCV."

There are tradeoffs between the two strategies. Patients who get a non-infected HCV kidney have a lower risk of dying from liver disease because HCV is treated earlier, before kidney transplantation, says Eckman. But HCV-infected patients who receive an HCV-infected kidney are able to get off of dialysis sooner and have a lower risk of dying from end stage kidney disease.

"It is better to wait less time for a kidney by getting an HCV-infected kidney followed by treatment after transplantation," says Eckman.

He adds that the supply of HCV-infected kidneys has increased due to the unfortunate deaths of otherwise generally healthy young individuals who suffer opioid overdoses.

"What we hope is that this study will have some impact on policy," says Eckman.

Other authors contributing to the study at are E. Steve Woodle, MD, director of solid organ transplantation for UC Health and William A. Altemeier Professor of Research Surgery in UC College of Medicine; Charuhas Thakar, MD, professor and director of the UC Division of Nephrology Kidney CARE Program; Flavio Paterno, MD, assistant professor in the UC Division of Transplantation; and Kenneth Sherman, MD, PhD, Gould Professor of Medicine and director of the UC Division of Digestive Diseases.

The study was funded by a grant from Merck Sharp & Dohme Corp. It also received support by the National Center for Advancing Translational Sciences (NIH - UL1TR000077-05). Merck Sharp & Dohme was given the opportunity to review the manuscript for intellectual property considerations.

Sherman has grants/contracts (institutional funding) from AbbVie, Bristol-Myers Squibb, Gilead, Innovio, Intercept, MedImmune, and Merck, and serves on advisory boards for Abbott Laboratories, Gilead, MedImmune, Merck, and Shionogi. He also serves on safety monitoring boards for Watermark and MedPace. Thakar is a consultant to Merck and NxStage. He has investigator-initiated funding from Bioporto and Otsuka. Eckman and Woodle have no conflicts of interest with the current study other than grant support from Merck through the Merck Investigator Studies Program.

http://bit.ly/2ultSNm

ANU scientists discover the world's oldest colors

1.1 BYO bright pink pigments extracted from rocks beneath the Sahara desert

Scientists from The Australian National University (ANU) and overseas have discovered the oldest colours in the geological record, 1.1 billion-year-old bright pink pigments extracted from rocks deep beneath the Sahara desert in Africa.

Dr Nur Gueneli from ANU said the pigments taken from marine black shales of the Taoudeni Basin in Mauritania, West Africa, were more than half a billion years older than previous pigment discoveries. Dr Gueneli discovered the molecules as part of her PhD studies.

"The bright pink pigments are the molecular fossils of chlorophyll that were produced by ancient photosynthetic organisms inhabiting an ancient ocean that has long since vanished," said Dr Gueneli from the ANU Research School of Earth Sciences.

The fossils range from blood red to deep purple in their concentrated form, and bright pink when diluted.

ANU led the research with support from Geoscience Australia and researchers in the United States and Japan.

The researchers crushed the billion-year-old rocks to powder, before extracting and analysing molecules of ancient organisms from them.
"The precise analysis of the ancient pigments confirmed that tiny cyanobacteria dominated the base of the food chain in the oceans a billion years ago, which helps to explain why animals did not exist at the time," Dr Gueneli said.
Senior lead researcher Associate Professor Jochen Brocks from ANU said that the emergence of large, active organisms was likely to have been restrained by a limited supply of larger food particles, such as algae.
"Algae, although still microscopic, are a thousand times larger in volume than cyanobacteria, and are a much richer food source," said Dr Brocks from the ANU Research School of Earth Sciences.
"The cyanobacterial oceans started to vanish about 650 million years ago, when algae began to rapidly spread to provide the burst of energy needed for the evolution of complex ecosystems, where large animals, including humans, could thrive on Earth."
The research is published in *PNAS*.

http://bit.ly/2NhZlXV

Leukemia researchers discover way to predict healthy people at risk for developing AML

An international team of leukemia scientists has discovered how to predict healthy individuals at risk of developing acute myeloid leukemia (AML), an aggressive and often deadly blood cancer.

TORONTO - The findings, published today in *Nature*, illuminate the 'black box of leukemia' and answer the question of where, when and how the disease begins, says co-principal investigator Dr. John Dick, Senior Scientist at Princess Margaret Cancer Centre, University Health Network.
"We have been able to identify people in the general population who have traces of mutations in their blood that represent the first steps in how normal blood cells begin on a pathway of becoming increasingly abnormal and puts them at risk of progressing to AML. We can find these traces up to 10 years before AML actually develops," says Dr. Dick. "This long time window gives us the first opportunity to think about how to prevent AML."
Dr. Dick is also a Professor, Department of Molecular Genetics, University of Toronto, holds the Canada Research Chair in Stem Cell Biology, and is Co-Leader of the Acute Leukemia Translational Research Initiative at the Ontario Institute for Cancer Research.
Study author Dr. Sagi Abelson, a post-doctoral fellow in the Dick lab, says: "AML is a devastating disease diagnosed too late, with a 90 per cent mortality rate after the age of 65. Our findings show it is possible to identify individuals in the general population who are at high risk of developing AML through a genetic test on a blood sample.
"The ultimate goal is to identify these individuals and study how we can target the mutated blood cells long before the disease actually begins."
The study builds on Dr. Dick's 2014 discovery that a pre-leukemic stem cell could be found lurking amongst all the leukemia cells that are present in the blood sample taken when a person is first diagnosed with AML. The pre-leukemic stem cell still functions normally but it has taken the first step in generating pathway of cells that became more and more abnormal resulting in AML (*Nature*, February 12, 2014), and continues his quest to trace every step in the evolution of AML, starting with blood cells from healthy people.
"Our 2014 study predicted that people with early mutations in their blood stem cells, long before the disease appears and makes them sick, should be able to be detected within the general population by testing a blood sample for the presence of the mutation." says Dr. Dick.
Co-principal investigator Dr. Liran Shlush, a former fellow in the Dick lab, and now Senior Scientist at the Weizmann Institute in Israel, led the approach to use data from a large European population health

and lifestyle study that tracked 550,000 people over 20 years to determine correlations to cancer.

The leukemia team extracted the data from more than 100 participants who developed AML six to 10 years after joining the study, plus the data from an age-matched cohort of more than 400 who did not develop the disease.

Dr. Dick says: "We wanted to know if there was any difference between these two groups in the genetics of their 'normal' blood samples taken at enrollment. To find out, we developed a gene sequencing tool that captured the most common genes that get altered in AML and sequenced all the 500 blood samples."

The answer was "Yes". The seeds of the blood system started picking up mutations years before an individual was diagnosed with AML, a finding that enabled the team to predict accurately who had been at risk of disease progression.

Furthermore, the team used advanced computational technology to assay the information obtained from routinely collected blood tests taken over 15 years in Israel and housed in a massive database of 3.4 million electronic health records.

The study has deepened our understanding of the distinction between AML and a common feature of aging called ARCH-age-related clonal hematopoiesis-whereby blood stem cells acquire mutations and become a little more proliferative. For the vast majority of people this is just a completely benign feature of aging.

"Every AML patient has ARCH but not everyone with ARCH gets AML," explains Dr. Dick.

The UHN research team was funded by the Leukemia and Lymphoma Society, Ontario Institute for Cancer Research, Canadian Cancer Society, Canadian Institutes for Health Research, International Development Research Centre, Terry Fox Research Institute, Medicine by Design - Canada First Research Excellence Fund, the Benjamin Pearl Fellowship from the McEwen Centre for Regenerative Medicine, the Ontario Ministry of Health and Long-term Care, and The Princess Margaret Cancer Foundation.

Major international collaborators included the Wellcome Sanger Institute and the University of Cambridge in the UK; the Weizmann Institute of Science and the Clalit Research Institute in Israel.

http://bit.ly/2zD2Yp8

Rescued from the Cave, Thai Soccer Team Gets Quarantined: Here's Why

Caves can be petri dishes for bacteria and viruses

By Yasemin Saplakoglu, Staff Writer | July 10, 2018 09:25am ET

The immense rescue operation for the Thai soccer team trapped in a cave finally concluded on Tuesday (July 10): All twelve boys and their coach have been successfully extracted.

But before the rescued boys can finally go home to their families, they need to make a pit stop at the hospital, where they're being briefly quarantined to make sure they didn't pick up any diseases in the caves, according to news reports.

Indeed, caves can be petri dishes for bacteria and viruses.

"The big worry that you get with caves is the presence of bats," said Dr. Amesh Adalja, a senior scholar at the John Hopkins Center for Health Security in Baltimore. "We know that bats can transmit many different infectious diseases, including things like rabies."

It's unclear if the boys were exposed to bats or if this cave even has a large bat population, though most caves do.

But if the doctors suspect any contact with the winged mammals, the boys will most likely get postexposure vaccinations to prevent any possible rabies infections, Adalja told Live Science.

And the bats themselves aren't always the problem — the animals can also "drop" problems all over the place.

"Certain fungi can really thrive in bat droppings," Adalja said, and inhaling these fungal spores can lead to lung infections, including cryptococcosis or histoplasmosis, which is also known as "caver's disease."

But symptoms of some of these fungal diseases might not pop up during the boys' time in quarantine, Adalja said. In some cases, it can take months or years for the fungi to cause a problem in the body; for example, symptoms may not pop up unless a person's immune system is suppressed due to another cause. In other cases, the fungal infections never cause any problems, he said.

Still, it means that later in life, the boys and the coach should be sure to tell any doctors about their time spent in the cave, as it may aid in a later diagnosis, Adalja added.

Another concern is leptospirosis, a bacterial infection that can cause bleeding in the lungs, or can even cause meningitis (inflammation in the lining of the brain and spinal cord), according to Reuters.

That said, some of the health problems the boys could develop in the caves might have less-exotic origins.

"People jump to think about the exotic stuff, but it's important to focus also on the common" stuff, Adalja said.

For example, the kids could have gastrointestinal issues due to the poor sanitation in the caves. In close quarters without sanitation, it wouldn't be surprising if the boys had contact with each other's feces, he added.

Furthermore, by drinking the cave water — even if they licked water dripping from the walls and didn't drink water on the ground — the boys could have contracted lots of bacteria that could also cause gastrointestinal problems.

There could also be small infections on the boys' skin from cuts and scrapes, he said.

Ultimately, however, there are so many unknowns, and it's difficult to predict what pathogens, if any, the boys have been exposed to, Adalja said.

Overall, the reports suggest the rescued teens are in good health and spirit — and they even requested their favorite food dishes, according to MSN.

https://wb.md/2uyFk7E

Prescription Drugs and Iatrogenic Depression

Can physicians be contributing to the prevalence of depression?

Charles P. Vega, MD

Hello. I'm Dr Charles Vega, and I am a clinical professor of family medicine at the University of California at Irvine. Welcome to Medscape Morning Report, our 1-minute news story for primary care.

Depression is one of the most common chronic illnesses affecting adults, but can physicians be contributing to the prevalence of depression? An analysis of prescribing habits suggests that the answer is yes.

A new analysis of data from the National Health and Nutrition Examination Survey concluded that more than one third of US adults used a prescription medication that had depression as a potential adverse effect in the previous 30 days.

Concomitant use of three or more of these drugs occurred in almost 10% of adults. And use of meds causing potential suicidal symptoms also increased, with almost a quarter of adults using one of these agents. Commonly used medications with this adverse effect include beta-blockers, proton pump inhibitors, analgesics, and hormonal contraceptives. The number of medications associated with depression as an adverse event was correlated with a higher prevalence of depression.

This study serves as a reminder that we should all be considering the potential risk for depression when we write routine prescriptions.

http://bit.ly/2zEpAFS

Artificial intelligence helps Stanford researchers predict drug combinations' side effects

Often, doctors have no idea what side effects may arise from adding another drug to a patient's personal pharmacy

Last month alone, 23 percent of Americans took two or more prescription drugs, according to one CDC estimate, and 39 percent

over age 65 take five or more, a number that's increased three-fold in the last several decades. And if that isn't surprising enough, try this one: in many cases, doctors have no idea what side effects might arise from adding another drug to a patient's personal pharmacy.

The problem is that with so many drugs currently on the U.S. pharmaceutical market, "it's practically impossible to test a new drug in combination with all other drugs, because just for one drug that would be five thousand new experiments," said Marinka Zitnik, a postdoctoral fellow in computer science. With some new drug combinations, she said, "truly we don't know what will happen."

But computer science may be able to help. In a paper presented July 10th at the 2018 meeting of the International Society for Computational Biology in Chicago. Zitnik and colleagues Monica Agrawal, a master's student, and Jure Leskovec, an associate professor of computer science, lay out an artificial intelligence system for predicting, not simply tracking, potential side effects from drug combinations. That system, called Decagon, could help doctors make better decisions about which drugs to describe and help researchers find better combinations of drugs to treat complex diseases.

Too many combinations

Once available to doctors in a more user-friendly form, Decagon's predictions would be an improvement over what's available now, which essentially comes down to chance - a patient takes one drug, starts taking another and then develops a headache or worse. There are about 1000 different known side effects and 5,000 drugs on the market, making for nearly 125 billion possible side effects between all possible pairs of drugs. Most of these have never been prescribed together, let alone systematically studied.

But, Zitnik, Agrawal and Leskovec realized they could get around that problem by studying how drugs affect the underlying cellular machinery in our body. They composed a massive network describing how the more than 19,000 proteins in our bodies interact with each other and how different drugs affect these proteins. Using more than 4 million known associations between drugs and side effects, the team then designed a method to identify patterns in how side effects arise based on how drugs target different proteins.

To do that, the team turned to deep learning, a kind of artificial intelligence modeled after the brain. In essence, deep learning looks at complex data and extracts from them abstract, sometimes counterintuitive patterns in the data. In this case, the researchers designed their system to infer patterns about drug interaction side effects and predict previously unseen consequences from taking two drugs together.

Predicting complications

Just because Decagon found a pattern doesn't necessarily make it real, so the group looked to see if its predictions came true, and in many cases, they did. For example, there was no indication in the team's data that the combination of atorvastatin, a cholesterol drug, and amlopidine, a blood pressure medication, could lead to muscle inflammation, yet Decagon predicted that it would, and it was right. Although it did not appear in the original data, a case report from 2017 suggested the drug combination had led to a dangerous kind of muscle inflammation.

That example was born out in other cases as well. When they searched the medical literature for evidence of ten side effects predicted by Decagon but not in their original data, the team found that five out of the ten have recently been confirmed, lending further credence to Decagon's predictions.

"It was surprising that protein interaction networks reveal so much about drug side effects," said Leskovec, who is a member of Stanford Bio-X, Stanford Neurosciences Institute and the Chan Zuckerberg Biohub.

Right now, Decagon only considers side effects associated with pairs of drugs, and in the future the team hopes to extend their results to include more complex regimens, Leskovec said. They also hope to create a more user-friendly tool to give doctors guidance on whether it's a good idea to prescribe a particular drug to a particular patient and to help researchers developing drug regimens for complex diseases with fewer side effects.

"Today, drug side effects are discovered essentially by accident," Leskovec said, "and our approach has the potential to lead to more effective and safer healthcare."

The research was supported by the National Science Foundation, the National Institutes of Health, the Defense Advanced Research Projects Agency, the Stanford Data Science Initiative and the Chan Zuckerberg Biohub.

https://nyti.ms/2uvk6Yq

Dying Organs Restored to Life in Novel Experiments

An unusual transplant may revive tissues thought to be hopelessly damaged, including the heart and brain.

By Gina Kolata

When Georgia Bowen was born by emergency cesarean on May 18, she took a breath, threw her arms in the air, cried twice, and went into cardiac arrest.

The baby had had a heart attack, most likely while she was still in the womb. Her heart was profoundly damaged; a large portion of the muscle was dead, or nearly so, leading to the cardiac arrest.

Doctors kept her alive with a cumbersome machine that did the work of her heart and lungs. The physicians moved her from Massachusetts General Hospital, where she was born, to Boston Children's Hospital and decided to try an experimental procedure that had never before been attempted in a human being following a heart attack.

They would take a billion mitochondria — the energy factories found in every cell in the body — from a small plug of Georgia's healthy muscle and infuse them into the injured muscle of her heart.

Mitochondria are tiny organelles that fuel the operation of the cell, and they are among the first parts of the cell to die when it is deprived of oxygen-rich blood. Once they are lost, the cell itself dies.

But a series of experiments has found that fresh mitochondria can revive flagging cells and enable them to quickly recover.

In animal studies at Boston Children's Hospital and elsewhere, mitochondrial transplants revived heart muscle that was stunned from a heart attack but not yet dead, and revived injured lungs and kidneys. Infusions of mitochondria also prolonged the time organs could be stored before they were used for transplants, and even ameliorated brain damage that occurred soon after a stroke.

In the only human tests, mitochondrial transplants appear to revive and restore heart muscle in infants that was injured in operations to repair congenital heart defects.

For Georgia, though, the transplant was a long shot — a heart attack is different from a temporary loss of blood during an operation, and the prognosis is stark. There is only a short time between the onset of a heart attack and the development of scar tissue where once there were living muscle cells.

The problem was that no one knew when the baby's heart attack had occurred. Still, said Dr. Sitaram Emani, a pediatric heart surgeon who administered the transplant, there was little risk to the infant and a chance, though slim, that some cells affected by her heart attack might still be salvageable. "They gave her a fighting chance," said the infant's mother, Kate Bowen, 36, of Duxbury, Mass.

The idea for mitochondrial transplants was born of serendipity, desperation and the lucky meeting of two researchers at two Harvard teaching hospitals — Dr. Emani at Boston Children's and James McCully at Beth Israel Deaconess Medical Center.

Dr. Emani is a pediatric surgeon. Dr. McCully is a scientist who studies adult hearts. Both were wrestling with the same problem: how to fix hearts that had been deprived of oxygen during surgery or a

heart attack. “If you cut off oxygen for a long time, the heart barely beats,” Dr. McCully said. The cells may survive, but they may never fully recover.

While preparing to give a talk to surgeons, Dr. McCully created electron micrographs of damaged cells. The images turned out to be revelatory: The mitochondria in the damaged heart cells were abnormally small and translucent, instead of a healthy black.

The mitochondria were damaged — and nothing Dr. McCully tried revived them. One day, he decided simply to pull some mitochondria from healthy cells and inject them into the injured cells.

Working with pigs, he took a plug of abdominal muscle the size of a pencil eraser, whirled it in a blender to break the cells apart, added some enzymes to dissolve cell proteins, and spun the mix in a centrifuge to isolate the mitochondria.

He recovered between 10 billion and 30 billion mitochondria, and injected one billion directly into the injured heart cells. To his surprise, the mitochondria moved like magnets to the proper places in the cells and began supplying energy. The pig hearts recovered.

Meanwhile, Dr. Emani was struggling with the same heart injuries in his work with babies. Many of his patients are newborns who need surgery to fix life-threatening heart defects. Sometimes during or after such an operation, a tiny blood vessel gets kinked or blocked.

The heart still functions, but the cells that were deprived of oxygen beat slowly and feebly.

He can hook the baby up to a machine like the one that kept Georgia Bowen alive, an extracorporeal membrane oxygenator, or Ecmo. But that is a stopgap measure that can work for only two weeks. Half of the babies with coronary artery problems who end up on an Ecmo machine die because their hearts cannot recover.

But one day Dr. Emani was told of Dr. McCully’s work, and the two researchers met. “It was almost an ‘aha’ moment,” Dr. Emani said.

Dr. McCully moved to Boston Children’s, and he and Dr. Emani prepared to see if the new technique might help tiny babies who were the sickest of the sick — those surviving on Ecmo.

It was not long before they had their first patient.

Early one Saturday morning in March 2015, the hospital got a call from a hospital in Maine. Doctors there wanted to transfer to Boston Children’s a newborn baby boy whose heart had been deprived of oxygen during surgery to fix a congenital defect.

The baby was on an Ecmo but his heart had not recovered. “We turned the intensive care unit into an operating room,” Dr. Emani said. He snipped a tiny piece of muscle from the baby’s abdomen. Dr. McCully grabbed it and raced down the hall.

Twenty minutes later, he was back with a test tube of the precious mitochondria. Dr. Emani used an echocardiogram to determine where to inject them. “The spot that is weakest is where we want to go,” he said. “It is important to give as much of a boost as you can.” He injected a billion mitochondria, in about a quarter of a teaspoon of fluid.

Within two days, the baby had a normal heart, strong and beating quickly. “It was amazing,” Dr. Emani said.

The scientists have now treated 11 babies with mitochondria, and all but one were able to come off Ecmo, Dr. Emani said. Still, three of them ultimately died, which Dr. Emani attributes to a delay in treatment and other causes. Two died because their hearts were still so damaged, and one died of an infection. All of the more recent patients survived and are doing well.

In comparison, the death rate among a similar group of babies that did not get mitochondrial transplants was 65 percent. And none of the untreated babies recovered any of their heart function — more than a third of the survivors ended up on heart transplant lists.

More recently, Dr. Emani and his colleagues have discovered that they can infuse mitochondria into a blood vessel feeding the heart,

instead of directly into the damaged muscle. Somehow the organelles will gravitate almost magically to the injured cells that need them and take up residence.

He and his colleagues are persuaded that these transplants work, but acknowledge that it would take a randomized trial to prove it.

The main problem is a scarcity of patients. Even if every pediatric center in the United States participated, along with every infant with injured heart muscle, it still would be hard to enroll enough participants in the trial.

But what about adult heart patients? Researchers are hoping that mitochondrial transplants also can repair heart muscle damaged during heart attacks in adults. And finding enough of those patients should not be an issue, said Dr. Peter Smith, chief of cardiothoracic surgery at Duke University.

Already researchers are planning such a trial. The plan is to infuse mitochondria or a placebo solution into the coronary arteries of people having bypass surgery or — an even more dire situation for the heart — having both bypass and valve surgery.

The patients would be those whose hearts are so damaged that it would be difficult to wean them from heart-lung machines after surgery. For these desperate patients, mitochondrial transplants "are a really intriguing option," Dr. Smith said.

"The likelihood is very high" that the study will begin next year, said Annetine Gelijns, a biostatistician at Mount Sinai Medical Center in New York.

For Georgia Bowen, the procedure came too late: The portion of her heart muscle affected by the heart attack had died. Her doctors implanted a device that takes over the heart's pumping, and hope her heart will recover enough for them to remove the device.

But, to be safe, they put her on a list for a heart transplant. She seems to be improving, though — she is breathing on her own and can drink breast milk through a tube. Her heart is showing signs of healing.

"Georgia is a miracle who continues to fight daily and persevere through the obstacles she is dealt," Ms. Bowen said.

"In our hearts, we know she will pull through this and come home."

Correction: *July 10, 2018*

Because of an editing error, a previous version of this article referred incorrectly to the source of the mitochondria infused into Georgia Bowen. They were taken from neck muscle, not abdominal muscle.

Gina Kolata writes about science and medicine. She has twice been a Pulitzer Prize finalist and is the author of six books, including "Mercies in Disguise: A Story of Hope, a Family's Genetic Destiny, and The Science That Saved Them." @ginakolata • Facebook

http://bit.ly/2LiL4cT

Drugs that kill off old cells may limit a body's aging

Mice given a drug combo see a reverse of some problems caused by senescent cells.

John Timmer - 7/11/2018, 12:28 AM

We have a good idea of what makes individual cells old. Things like DNA damage, shortened chromosome ends, and a lack of proliferative ability can all cause cells to basically shut down—they don't die, but they stop dividing and become quiescent. But we don't have a strong sense of what makes an organism old. It could be the cumulative effect of lots of their cells getting old, or there may be additional means of registering an organism's age.

Now, a new study suggests at least part of the answer may be a mix of the two. The study, done using mice, indicates that having a small population of cells that have hit the wall due to aging can induce symptoms of age-related decline in otherwise young mice. And a drug combination that targets these cells can block these problems from taking root. The same drugs, when given to elderly mice, also reduce mortality and limit some of the symptoms of age.

Senescent

Cells pick up damage all the time, either through environmental exposures or simply as a byproduct of their normal metabolism. If the damage is sufficiently critical, the cell will respond by committing an orderly sort of suicide called apoptosis, which keeps

it from causing any further problems. For lesser damage, there's a less drastic alternative called senescence, in which the cell remains active and contributes its normal functions to the organism's health, but it commits to no longer dividing. Over time, as animals age, more and more cells enter senescence, a process that's thought to contribute to aging.

But it has gradually become apparent that senescent cells don't just continue performing their normal function. They also produce a set of senescence-specific signaling molecules that can influence cells elsewhere in the body, including some that can trigger inflammation. The new work is based on the hypothesis that these signaling molecules might contribute to the changes that are associated with aging.

To test this, a large team of researchers did a relatively straightforward experiment: take senescent cells and implant them in an otherwise young and healthy mouse.

The authors chose fat cells, which typically don't trigger an immune response when transplanted to a new animal. To get lots of senescent cells, they induced DNA damage, using either a drug or radiation (both produced similar results). While it would have been more relevant to obtain senescent cells from an older mouse, this allowed them to obtain lots of the cells they needed to do the experiments.

At various times after the transplant, the team measured a series of physical traits that change with age: average walking speed, muscle strength, endurance on a treadmill, time spent active, food intake and body weight. And while some of these didn't change after the senescent cells were transplanted in, the young mice had clearly lost some strength by a month after the transplant: walking speed, endurance, and grip strength were all down significantly.

This change comes despite the fact that only about one in 10,000 cells in the body were senescent, transplanted cells. Obviously, this suggests that the cells are having an effect by talking to all the healthy ones around them. In fact, the researchers found that the transplanted cells' presence seemed to cause some of the young animal's cells to become senescent, amplifying their effect. Other experiments showed that the transplanted cells had stronger effects if the recipient was older or eating a high-fat diet.

For older mice receiving transplanted cells, one of the consequences was an increased chance of death. Risk of mortality was up by 5.2 fold, and there was no single cause of death or pathology that was increased by a similar amount. Instead, the animals just seemed to be less healthy.

Aging delayed

At this point, the researchers shift focus to what they call a "senolytic agent." That bit of jargon refers to a combination of two chemicals that cause senescent cells to die, possibly by shifting them from the senescence response over into the cell death response. The chemicals in question are quercetin, something found in a huge variety of plants (anyone who eats any vegetables undoubtedly ingests some of this every day). The second is called dasatinib, and you're very unlikely to come across this as part of your diet, since it's normally used as chemotherapy.

The combo of the two chemicals did what you'd expect. If they were administered immediately after the senescent cells were transplanted, the chemicals helped limit the cells' impact on strength and endurance. For mice that were simply aging normally, the two chemicals also helped limit the loss of strength and endurance, and increased the animals' daily activity relative to controls. In addition, the chemicals increased the average lifespan by 36 percent.

Could this work in humans? There's a hint that it might. The researchers obtained fat from obese people in for surgery; this normally contains senescent cells. The researchers confirmed that treating the fat with these chemicals reduced the number of senescent cells present.

Obviously, putting everyone on a chemotherapy drug once they hit 60 isn't going to happen—especially one that has a large collection of side effects like dasatinib. But the authors argue that the chemicals seem to work even if they're given for short courses weeks apart. This, they argue, could avoid most of the side effects. And the mice it was tested on were roughly the equivalent of a 75 year old human, so it seemingly can have positive effects even when given after signs of aging are apparent.

The paper would read a bit like an argument for conducting some safety tests in humans, except it indicates that clinical trials are already ongoing. But it's important to recognize that, even if they're successful, the treatment had no significant impact on a variety of symptoms of aging that the researchers also tested for. So, while senescent cells may be part of the picture, they're far from the whole story on aging.

Nature Medicine, *2018. DOI: 10.1038/s41591-018-0092-9 (About DOIs).*

http://bit.ly/2JnODga

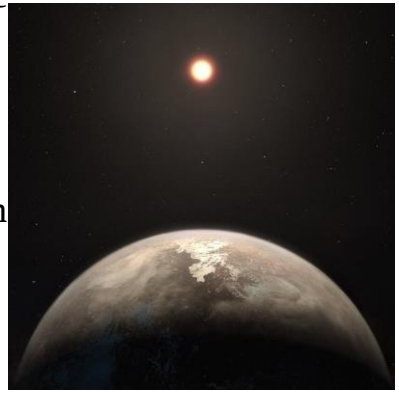
Rocky planet neighbor looks familiar, but is not Earth's twin

Detailed chemical abundances of the Ross 128 help us understand its exoplanet Ross 128 b

Pasadena, CA--Last autumn, the world was excited by the discovery of an exoplanet called Ross 128 b, which is just 11 light years away from Earth. New work from a team led by Diogo Souto of Brazil's Observatório Nacional and including Carnegie's Johanna Teske has for the first time determined detailed chemical abundances of the planet's host star, Ross 128.

Understanding which elements are present in a star in what abundances can help researchers estimate the makeup of the exoplanets that orbit them, which can help predict how similar the planets are to the Earth.

"Until recently, it was difficult to obtain detailed chemical abundances for this kind of star," said lead author Souto, who developed a technique to make these measurements last year.



This artist's impression shows the temperate planet Ross 128 b, with its red dwarf parent star in the background. **It is provided courtesy of ESO/M. Kornmesser.**

Like the exoplanet's host star Ross 128, about 70 percent of all stars in the Milky Way are red dwarfs, which are much cooler and smaller than our Sun. Based on the results from large planet-search surveys, astronomers estimate that many of these red dwarf stars host at least one exoplanet.

Several planetary systems around red dwarfs have been newsmakers in recent years, including Proxima b, a planet which orbits the nearest star to our own Sun, Proxima Centauri, and the seven planets of TRAPPIST-1, which itself is not much larger in size than our Solar System's Jupiter.

Using the Sloan Digital Sky Survey's APOGEE spectroscopic instrument, the team measured the star's near-infrared light to derive abundances of carbon, oxygen, magnesium, aluminum, potassium, calcium, titanium, and iron.

"The ability of APOGEE to measure near-infrared light, where Ross 128 is brightest, was key for this study," Teske said. "It allowed us to address some fundamental questions about Ross 128 b's `Earth-like-ness'," Teske said.

When stars are young, they are surrounded by a disk of rotating gas and dust from which rocky planets accrete. The star's chemistry can influence the contents of the disk, as well as the resulting planet's mineralogy and interior structure. For example, the amount of

magnesium, iron, and silicon in a planet will control the mass ratio of its internal core and mantle layers.

The team determined that Ross 128 has iron levels similar to our Sun. Although they were not able to measure its abundance of silicon, the ratio of iron to magnesium in the star indicates that the core of its planet, Ross 128 b, should be larger than Earth's.

Because they knew Ross 128 b's minimum mass, and stellar abundances, the team was also able to estimate a range for the planet's radius, which is not possible to measure directly due to the way the planet's orbit is oriented around the star.

Knowing a planet's mass and radius is important to understanding what it's made of, because these two measurements can be used to calculate its bulk density. What's more, when quantifying planets in this way, astronomers have realized that planets with radii greater than about 1.7 times Earth's are likely surrounded by a gassy envelope, like Neptune, and those with smaller radii are likely to be more-rocky, as is our own home planet.

The estimated radius of Ross 128 b indicates that it should be rocky. Lastly, by measuring the temperature of Ross 128 and estimating the radius of the planet the team was able to determine how much of the host star's light should be reflecting off the surface of Ross 128 b, revealing that our second-closest rocky neighbor likely has a temperate climate.

"It's exciting what we can learn about another planet by determining what the light from its host star tells us about the system's chemistry," Souto said. "Although Ross 128 b is not Earth's twin, and there is still much we don't know about its potential geologic activity, we were able to strengthen the argument that it's a temperate planet that could potentially have liquid water on its surface."

This work was supported by NASA's Astrophysics Division of the Science Mission Directorate, the Spanish Ministry of Economy and Competitiveness, the U.S. National Science Foundation, CONICYT, the Crafoord Foundation, and Stiftelsen Olle Engkvist Byggmästare.

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The 'Big Bang' of Alzheimer's: Scientists ID genesis of disease

Scientists have discovered a "Big Bang" of Alzheimer's disease - the precise point at which a healthy protein becomes toxic but has not yet formed deadly tangles in the brain.

DALLAS - July 10, 2018 - A study from UT Southwestern's O'Donnell Brain Institute provides novel insight into the shape-shifting nature of a tau molecule just before it begins sticking to itself to form larger aggregates. The revelation offers a new strategy to detect the devastating disease before it takes hold and has spawned an effort to develop treatments that stabilize tau proteins before they shift shape. "We think of this as the Big Bang of tau pathology. This is a way of peering to the very beginning of the disease process."

Dr. Mark Diamond, Director for UT Southwestern's Center for Alzheimer's and Neurodegenerative Diseases "This is perhaps the biggest finding we have made to date, though it will likely be some time before any benefits materialize in the clinic. This changes much of how we think about the problem," said Dr. Marc Diamond, Director for UT Southwestern's Center for Alzheimer's and Neurodegenerative Diseases and a leading dementia expert credited with determining that tau acts like a prion - an infectious protein that can self-replicate.

The study published in *eLife* contradicts the previous belief that an isolated tau protein has no distinct shape and is only harmful after it begins to assemble with other tau proteins to form the distinct tangles seen in the brains of Alzheimer's patients.

Scientists made the discovery after extracting tau proteins from human brains and isolating them as single molecules. They found that the harmful form of tau exposes a part of itself that is normally folded inside. This exposed portion causes it to stick to other tau proteins, enabling the formation of tangles that kill neurons.

"We think of this as the Big Bang of tau pathology," said Dr. Diamond, referring to the prevailing scientific theory about the formation of the universe.

"This is a way of peering to the very beginning of the disease process. It moves us backward to a very discreet point where we see the appearance of the first molecular change that leads to neurodegeneration in Alzheimer's.

This work relied on a close collaboration with my colleague, Dr. Lukasz Joachimiak."

Despite billions of dollars spent on clinical trials through the decades, Alzheimer's disease remains one of the most devastating and baffling diseases in the world, affecting more than 5 million Americans alone.

Dr. Diamond is hopeful the scientific field has turned a corner, noting that identifying the genesis of the disease provides scientists a vital target in diagnosing the condition at its earliest stage, before the symptoms of memory loss and cognitive decline become apparent.

His team's next steps are to develop a simple clinical test that examines a patient's blood or spinal fluid to detect the first biological signs of the abnormal tau protein. But just as important, Dr. Diamond said, efforts are underway to develop a treatment that would make the diagnosis actionable.

He cites a compelling reason for cautious optimism: Tafamidis, a recently approved drug, stabilizes a different shape-shifting protein called transthyretin that causes deadly protein accumulation in the heart, similar to how tau overwhelms the brain.

"The hunt is on to build on this finding and make a treatment that blocks the neurodegeneration process where it begins," Dr. Diamond said. "If it works, the incidence of Alzheimer's disease could be substantially reduced. That would be amazing."

Dr. Diamond's lab, at the forefront of many notable findings relating to tau, previously determined that tau acts like a prion - an infectious protein that can spread like a virus through the brain.

The lab has determined that tau protein in the human brain can form many distinct strains, or self-replicating structures, and developed methods to reproduce them in the laboratory.

He said his newest research indicates that a single pathological form of tau protein may have multiple possible shapes, each associated with a different form of dementia.

Dr. Diamond, who holds the Distinguished Chair in Basic Brain Injury and Repair, is founding Director of the Center for Alzheimer's and Neurodegenerative Diseases, and Professor of Neurology & Neurotherapeutics with the Peter O'Donnell Jr. Brain Institute at UT Southwestern. He collaborated on the study with co-corresponding author Dr. Joachimiak, an Assistant Professor in the Center for Alzheimer's and Neurodegenerative Diseases and an Effie Marie Cain Scholar in Medical Research.

The research was supported with funding from the Rainwater Charitable Foundation, the National Institutes of Health, and the Effie Marie Cain Endowed Scholarship.

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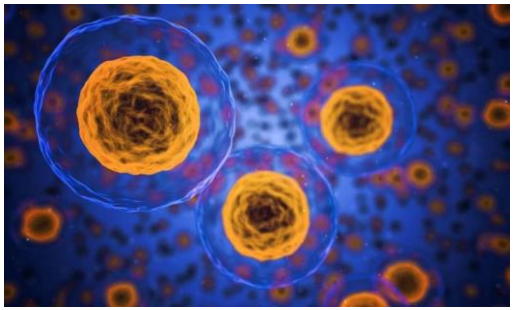
Cellular 'garbage disposal' has another job

Cellular "garbage disposal," known to scientists as proteasomes, but actually work on some of the most important proteins to neuronal development



Credit: CC0 Public Domain

Johns Hopkins researchers have found that the cellular "garbage disposal," known to scientists as proteasomes, may not only be responsible for the removal of cellular waste, but actually work on some of the most important proteins to neuronal development.

Building on a previous discovery, which found that specialized proteasomes in the membrane of brain cells have the potential to play a role in neuronal signaling, Seth Margolis, Ph.D., associate professor of biological chemistry and neuroscience at the Johns Hopkins University School of Medicine, and his research team set

out to find the specific proteins targeted by this specialized proteasome.

In the new study, published July 5 in *Molecular Cell*, the researchers found that this membrane-bound proteasome only accepts specific proteins—a far cry from its original characterization as a catch-all trash disposal system.

In particular, they target a pool of proteins that are still in the process of being made, an important distinction from the full-length proteins that classic proteasomes target for degradation.

Among these are Fos and Npas4, which are critical mediators in the regulation of active neurons.

"From our observations, we are able to draw a connection between protein synthesis and protein degradation that implies that the full-length version of these proteins and the version that is being broken down could have independent roles in the cell," says Kapil Ramachandran, Ph.D., junior fellow at the Harvard Society of Fellows at Harvard Medical School. It is similar to a paper shredder, says Ramachandran.

"As we understood proteasomes, they would find a sheet of paper in the cell and then shred it.

However, in the case of this membrane-bound proteasome, the shredder is working on the paper as it is being made."

The researchers are hopeful that the discovery of the proteins these specialized neuronal proteasomes interact with will open the door to new discoveries in neuronal function, such as cell-to-cell communication or the structural changes that allow us to form memories.

More information: *Kapil V. Ramachandran et al. Activity-Dependent Degradation of the Nascentome by the Neuronal Membrane Proteasome, Molecular Cell (2018). DOI: 10.1016/j.molcel.2018.06.013*

https://bbc.in/2zF5xae

Stopping type 1 diabetes from birth

Experts believe they may have found a way to prevent high risk babies from developing type 1 diabetes.

By Michelle Roberts Health editor, BBC News online

The idea is to train infants' immune systems by giving them powdered insulin to offer life-long protection. Insulin is the hormone that controls blood sugar, which goes awry in diabetes.

Pregnant women visiting maternity clinics in Berkshire, Buckinghamshire, Milton Keynes and Oxfordshire are being asked to sign up to the trial. Parents that take part will be asked to give their children insulin powder daily from the age of about six months until they are three years old. They will have visits from the research team to monitor the child's health.

Half of the study participants will be given the real insulin while half will get a placebo powder containing no drug. Neither the researchers nor participants will know which they received until after the trial so as not to bias the results.

Type 1 diabetes

It is thought about one in every 100 babies has genes that put them at increased risk of developing type 1, insulin-dependent diabetes.

Experts say a heel prick blood test that is routinely done on newborns to spot other conditions could also detect these genes.

The researchers, from Oxford University, want to screen 30,000 babies in this way to find eligible ones for their trial.

It is hoped that spoon-feeding insulin powder can train the immune system to tolerate the body's own insulin to prevent the onset of type 1 diabetes. Currently, there is no way to prevent type 1 diabetes.

Others have been testing whether giving a different drug, called metformin, in childhood might hold off diabetes.

Type 1 diabetes is a lifelong condition where the pancreas does not produce insulin, causing blood glucose levels to become too high.

This can cause serious long-term health problems such as blindness, cardiovascular disease and stroke.

Chief investigator of the Oxford trial Dr Matthew Snape said: "Preventing children and their families from having to live with diabetes and its threat of complications such as blindness, kidney or heart disease would be fantastic."

The work is being funded by the National Institute for Health Research, the type 1 diabetes charity JDRF, Diabetes UK and the Wellcome Trust, as well as the Leona M and Harry B Helmsley Charitable Trust.

Dr Elizabeth Robertson, director of research at Diabetes UK, said: "This is a huge endeavour, so we would encourage women living in the South East who think they might be eligible to find out more - research like this can't happen without the incredible people who take part."

For more information visit www.ingr1d.org.uk

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

Tools from China are oldest hint of human lineage outside Africa

2.1-million-year-old stone tools suggest hominins reached East Asia much earlier than thought.

Colin Barras

Hominins reached Asia at least 2.1 million years ago, researchers assert in an 11 July *Nature* paper[1]. Stone tools they found in central China represent the earliest known evidence of humans or their ancient relatives living outside Africa.

Other scientists are convinced that the tools were made by hominins and are confident that they are as old as claimed. And although the tools' makers are unknown, the discovery could force researchers to reconsider which hominin species first left Africa — and when.

"This is a whole new palaeo ball game," says William Jungers, a palaeoanthropologist at Stony Brook University, New York.

Most researchers say that hominins — the evolutionary line that includes humans — first left their African homeland around 1.85 million years ago.

This is the age of the oldest hominin fossils discovered beyond Africa — from Dmanisi, Georgia, in the Caucasus region of Eurasia. The oldest hominin remains from East Asia, two incisors from southwest China, are around 1.7 million years old (see 'Travelling Hominins').

Archaeological finds made between 2004 and 2017 at a site called Shangchen in central China now challenge that orthodoxy.

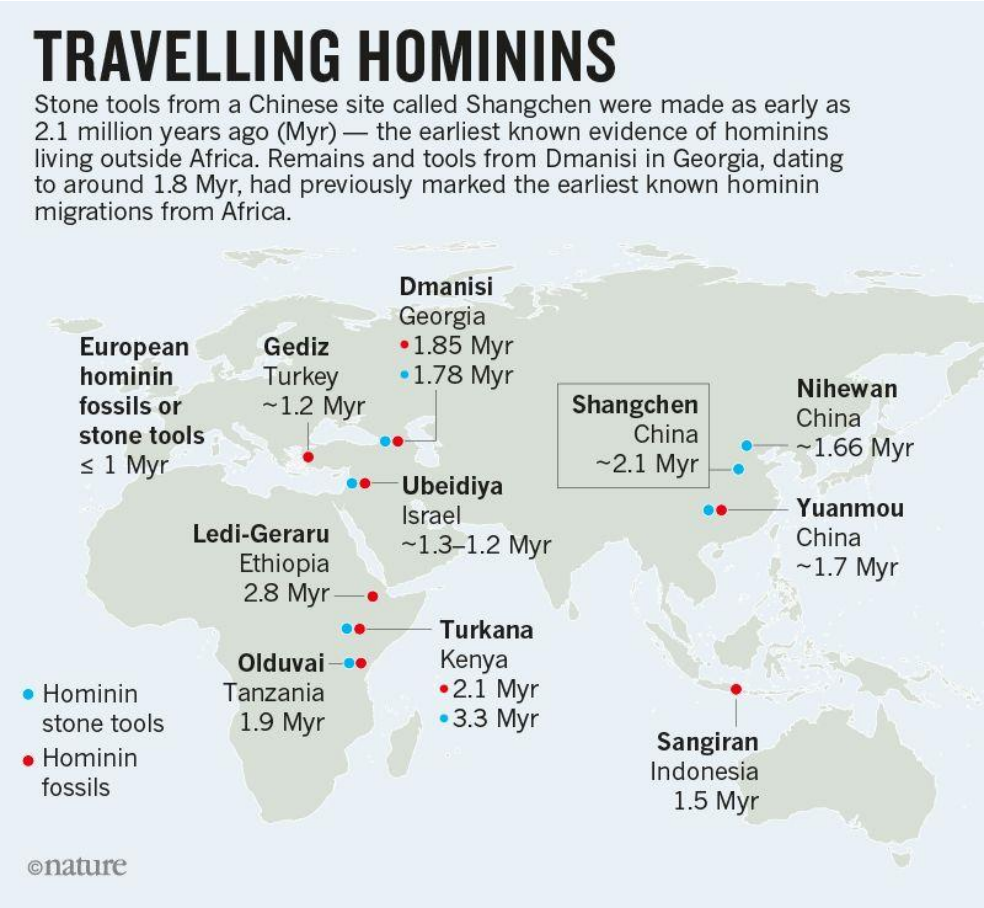
By studying and dating a sequence of ancient soils and deposits of wind-blown dust, a team of Chinese and British geologists and archaeologists led by Zhaoyu Zhu at the Guangzhou Institute of Geochemistry, Chinese Academy of Sciences, has uncovered dozens of relatively simple stone tools. The youngest tools are 1.26 million years old, and the oldest date back to 2.12 million years.

The 2.12-million-year-old geological layers might not even represent the earliest hominin occupation of the region. John Kappelman, an anthropologist and geologist at the University of Texas at Austin and one of the paper's referees, points out that the deepest — and so oldest — layers at the site are currently inaccessible because the region is actively farmed[2]. Investigating them should be a priority, he says.

Polarity pattern

The deposits were dated using a method called palaeomagnetism, which uses well-documented flips in Earth's magnetic field to date rock established between these events.

The pattern of geomagnetic flips that occurred between 1.26 million and 2.12 million years ago is recorded in the magnetic minerals locked in the sediments at Shangchen.



Jan-Pieter Buylaert, a geologist at Aarhus University in Denmark who has worked on the sediments in this region of China, calls the dating “robust”.

Archaeologists are also confident that the tools are genuine. Study co-leader Robin Dennell, an archaeologist at the University of Exeter, UK, says his team has ruled out any natural processes, such as the churning of a river, that can make rocks look like tools. No ancient rivers are known at the Shangchen site, and the proposed tools are the only large stones present.

That absence of alternative explanations for the fractures seen on the stones is enough to persuade Zeljko Rezek, an archaeologist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. “The bottom line: I think these are truly stone tools,” he says.

Michael Petraglia, an archaeologist at the Max Planck Institute for the Science of Human History in Jena, Germany, and another of the paper’s reviewers, agrees that the tools are convincing. They are relatively simple, but this is a common feature of all stone tools from so early in the archaeological record, he says.

Hidden identity

The identity of their makers is, for now, unclear: no hominin bones have been recovered at Shangchen. “We would all love to find a hominin — preferably one with a tool in its hand,” says Dennell. *Homo erectus* is one possibility, because some of the earliest members of this species were found at Dmanisi. But Dennell thinks that the Shangchen toolmakers belonged to an earlier species in the genus *Homo*.

Petraglia and Rezek both say that the age of the tools — not to mention the possibility that hominins arrived in China even earlier than the 2.12-million-year mark — suggests that the toolmaker was a species such as *Homo habilis*. This relatively small-brained hominin is thought to have been confined to Africa between around 2.4 million to 1.4 million years ago.

Jungers holds open the possibility that the Shangchen toolmaker was a species of *Australopithecus*, a group of more ape-like hominins to which the iconic fossil Lucy belongs. So far, all *Australopithecus* fossils have been discovered in Africa.

The new finds imply that hominins covered vast distances before 2 million years ago — Shangchen is 14,000 kilometres from the nearest sites in East Africa where other hominins of this age have been found. It’s possible that the Shangchen toolmakers, hunter-

gatherers, were simply following their foods, says Vivek Venkataraman, an evolutionary ecologist at Harvard University in Cambridge, Massachusetts.

The Shangchen finds are sure to encourage other researchers to hunt for further signs of hominins living in Eurasia before 2 million years ago, says Kappelman.

A few such claims for early Eurasian hominins have previously been made. In 2016, for instance, researchers presented evidence of 2.6-million-year-old stone tools at a site near the India–Pakistan border[3]. Dennell, who has worked in that region, is sympathetic to the idea of an early hominin presence there, but he says the evidence isn't as clear-cut as his team's finds in Shangchen. Proving a hominin presence at any archaeological site, he explains, requires establishing that the tools are real and that their geological context and dating are solid. "It does mean that you have to kiss an awful lot of frogs before you find a princess."

doi: 10.1038/d41586-018-05696-8

http://bit.ly/2JqDHye

Our fractured African roots

Humans did not stem from a single ancestral population in one region of Africa, as is often claimed

A scientific consortium led by Dr. Eleanor Scerri, British Academy Postdoctoral Fellow at the University of Oxford and researcher at the Max Planck Institute for the Science of Human History, has found that human ancestors were scattered across Africa, and largely kept apart by a combination of diverse habitats and shifting environmental boundaries, such as forests and deserts. Millennia of separation gave rise to a staggering diversity of human forms, whose mixing ultimately shaped our species.

While it is widely accepted that our species originated in Africa, less attention has been paid to how we evolved within the continent. Many had assumed that early human ancestors originated as a single, relatively large ancestral population, and exchanged genes and technologies like stone tools in a more or less random fashion.

In a paper published in Trends in Ecology and Evolution this week, this view is challenged, not only by the usual study of bones (anthropology), stones (archaeology) and genes (population genomics), but also by new and more detailed reconstructions of Africa's climates and habitats over the last 300,000 years.

Middle Stone Age cultural artefacts from northern and southern Africa.
Eleanor Scerri/Francesco d'Errico/Christopher Henshilwood

One species, many origins

"Stone tools and other artifacts - usually referred to as material culture - have remarkably clustered distributions in space and through time," said Dr. Eleanor Scerri, researcher at the Max Planck Institute for the Science of Human History and the University of Oxford, and lead author of the study. "While there is a continental-

wide trend towards more sophisticated material culture, this 'modernization' clearly doesn't originate in one region or occur at one time period."

Human fossils tell a similar story. "When we look at the morphology of human bones over the last 300,000 years, we see a complex mix of archaic and modern features in different places and at different times," said Prof. Chris Stringer, researcher at the London Natural History Museum and co-author on the study. "As with the material culture, we do see a continental-wide trend towards the modern human form, but different modern features appear in different places at different times, and some archaic features are present until remarkably recently."

The genes concur. "It is difficult to reconcile the genetic patterns we see in living Africans, and in the DNA extracted from the bones of Africans who lived over the last 10,000 years, with there being one ancestral human population," said Prof. Mark Thomas, geneticist at University College London and co-author on the study. "We see indications of reduced connectivity very deep in the past, some very old genetic lineages, and levels of overall diversity that a single population would struggle to maintain."

An ecological, biological and cultural patchwork

To understand why human populations were so subdivided, and how these divisions changed through time, the researchers looked at the past climates and environments of Africa, which give a picture of shifting and often isolated habitable zones. Many of the most inhospitable regions in Africa today, such as the Sahara, were once wet and green, with interwoven networks of lakes and rivers, and abundant wildlife. Similarly, some tropical regions that are humid and green today were once arid. These shifting environments drove subdivisions within animal communities and numerous sub-Saharan species exhibit similar phylogenetic patterns in their distribution.

The shifting nature of these habitable zones means that human populations would have gone through many cycles of isolation - leading to local adaptation and the development of unique material culture and biological makeup - followed by genetic and cultural mixing.

"Convergent evidence from these different fields stresses the importance of considering population structure in our models of human evolution," says co-author Dr. Lounes Chikhi of the CNRS in Toulouse and Instituto Gulbenkian de Ciência in Lisbon."This complex history of population subdivision should thus lead us to question current models of ancient population size changes, and perhaps re-interpret some of the old bottlenecks as changes in connectivity," he added.

"The evolution of human populations in Africa was multi-regional. Our ancestry was multi-ethnic. And the evolution of our material culture was, well, multi-cultural," said Dr Scerri. "We need to look at all regions of Africa to understand human evolution."

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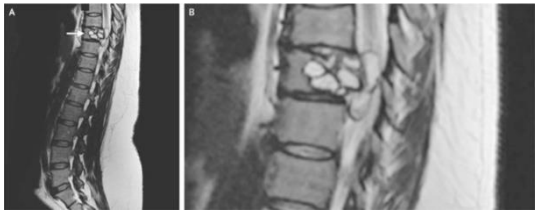
A Woman Had Strange Feelings in Her Legs. Doctors Found Parasites in Her Spine

Unusual symptoms turned out to have a surprising cause: tapeworm larvae lurking in her spine

By Rachael Rettner, Senior Writer | July 11, 2018 05:01pm ET

When the 35-year-old woman arrived at a hospital in France, she told doctors it felt like electric shocks were running down her legs. What's more, she felt weak and had experienced a number of falls recently.



An MRI revealed tapeworm larval cysts in the woman's spine, indicated by the arrow in the image on the left. The image on the right shows a close-up.

The New England Journal of Medicine ©2018

The woman's unusual symptoms turned out to have a surprising cause: Tapeworm larvae lurking in her spine, according to a new report of the case, published today (July 11) in The New England Journal of Medicine.

The woman lived in France and told doctors that she hadn't been out of the country recently. But she said she did ride horses and have contact with cattle. In addition to her other symptoms, the woman said that over the last three months, she'd had difficulty riding her horse, according to the report.

An MRI revealed a lesion on her spine, at her ninth thoracic vertebra, which is located in the middle of the back, the report said.

The woman needed surgery to remove the lesion, and tests revealed that it was caused by an infection with *Echinococcus granulosus*, a small tapeworm that's found in dogs and some farm animals, including sheep, cattle, goats and pigs.

This tapeworm can cause a disease called cystic echinococcosis, also known as hydatidosis, in which the larvae form cysts that grow slowly in a person's body, according to the Centers for Disease Control and Prevention (CDC).

These cysts typically grow in the liver or the lungs, but they can also appear in other parts of the body, including the bones and the central nervous system. However, infections of the bones, including the spinal column, are rare, making up just 0.5 to 4 percent of cases of this disease, according to a 2013 paper on cystic echinococcosis.

The life cycle of *Echinococcus granulosus* is somewhat complex: The "adult" form of the worm lives in the intestines of dogs and can grow to be 6 millimeters (0.2 inches) long, according to the CDC. Tapeworm eggs are passed in the dogs' stool, and other farm animals become infected when they ingest food or water that's contaminated with the tapeworm eggs. Once ingested by farm animals, the eggs develop into larvae, but they cannot develop into adult worms until they are again ingested by dogs (which can happen if dogs are fed slaughtered livestock, according to the CDC.)

Humans become infected with *Echinococcus granulosus* when they ingest the tapeworm eggs, which can happen if people consume food or water that's contaminated with stool from infected dogs, according to the CDC. For example, a person might become infected if they consumed plants or berries gathered from fields where infected dogs have been. Humans are considered "accidental" hosts, because they aren't involved in transmitting the disease back to dogs, according to the World Health Organization. (The worms can't grow into adults in humans.)

Dr. Lionel Piroth, an infectious-disease specialist at the Centre Hospitalier Universitaire de Dijon, who treated the woman, said that cystic echinococcosis "is very rare in France," and it wasn't clear how the woman got the infection. She did not report having any contact with dogs, he said.

One possibility is that the woman could've gotten sick by eating vegetables that were contaminated with the parasite, Piroth told Live Science. (If this were the case, the vegetables would've been contaminated by an "unknown" dog, he noted.) Adding to the mystery, the woman was the only one in her family to be infected.

In addition to surgery, the woman was treated with an anti-parasitic medication. Nine months later, she had no lingering symptoms of her infection or signs that it was coming back, the report said.

Editor's Note: This article was updated on July 12 to add comments from Dr. Piroth.

http://bit.ly/2uoI6gw

Gastrointestinal flora -- the culprit for severe lung damage after blood transfusion

Previously unknown link between the bacteria in the gut and acute lung injury after blood transfusions revealed

Knowledge that the gastrointestinal flora affects both healthy physiological processes and various disease mechanisms has

increased in recent years. A study conducted at Lund University is now published in one of the leading haematology journals, *Blood Advances*, and reveals a previously unknown link between the bacteria in the gut and acute lung injury after blood transfusions.

It is now becoming clear that the gastrointestinal flora affects multiple processes in health and several disease states but exactly how the microbes in our intestines affect lung diseases has been difficult to determine. The gastrointestinal flora is believed to play a role in both asthma and pneumonia but much more knowledge is needed, something stressed by the associate news editor of Nature Medicine, Shraddha Chakradhar, among others.

Researchers at Lund University in Sweden, in an international collaborative project, have now found a direct link between the gastrointestinal flora and lung disease in the setting of blood transfusions.

The gastrointestinal flora drives the disease progression

The researchers made the discovery when studying TRALI (Transfusion Related Acute Lung Injury), a pulmonary complication that can occur after a blood transfusion and the leading cause of transfusion-related fatalities. The TRALI disease process, however, is incompletely understood and more insights into this disorder are needed in order to develop diagnostic and therapeutic approaches.

"We observed that the composition of the gastrointestinal flora drives the pathogenic immune response in the lungs during TRALI", says Rick Kapur, a post-doctoral researcher at Lund University, one of the participants behind the study.

Sterile environments builds resistance to TRALI

The researchers compared two groups of mice where one group was kept in a strictly sterile environment, allowing the gastrointestinal flora to be minimally affected by external factors, whereas the other group was raised in a normal, less sterile environment.

"We saw that the mice kept in a more sterile environment were resistant to TRALI development while the less sterile-raised mice developed severe TRALI, says Professor John W. Semple, the lead investigator of the study at Lund University.

The composition of the gastrointestinal flora was demonstrated to be significantly different between the two groups of mice, as was determined by genetic sequencing of the stool in collaboration with the Centre for Translational Genomics (CTG) of Lund University. In addition, when the researchers wiped out the gastrointestinal flora with several different types of antibiotics, they saw that the mice that suffered from TRALI no longer developed the disease.

Faecal transplant provided protection against TRALI

The researchers then transplanted stool from mice that developed TRALI into mice that were resistant to TRALI. After the stool transplantation, the resistant mice were also able to develop TRALI, which confirmed the link between the composition of the gastrointestinal flora and the onset of TRALI.

Gastrointestinal flora analysis may be used for screening

The researchers still need to clarify which specific gut bacteria are directly involved but the knowledge that intestinal bacteria may affect the lungs is a critical finding which may facilitate diagnostics and the development of potential new drugs. Additionally, the ability to be able to easily assess the risk for TRALI due to analysis of gastrointestinal flora is equally important, argues the researchers.

"Knowing the composition of the gastrointestinal flora of people who will receive blood transfusions, an analysis which can be easily performed today, would allow you to assess who may be at increased risk for developing TRALI", says Rick Kapur.

The studies which were performed on mice, are clinically relevant, since the mouse model mirrors the human condition argue the researchers.

"The TRALI model in mice is very similar to the condition in humans and the next step will be to validate these findings in humans. "It's not often that these types of findings in mice can lead directly to clinical studies in humans but that will be our aim" says John W. Semple.

The study was financed by the Swedish Research Council, the Crafoord Foundation, the Royal Physiographic Society of Lund and Canadian Blood Services.

Link to research article

Gastrointestinal microbiota contributes to the development of murine transfusion-related acute lung injury http://www.bloodadvances.org/content/2/13/1651

Blood Advances *10 July, 2018, doi:* https://doi.org/10.1182/bloodadvances.2018018903

FACTS: TRALI

TRALI (Transfusion Related Acute Lung Injury) is the most serious transfusion-related complication known today. It is the most common cause of death in patients undergoing a blood transfusion and it is estimated to affect 1 in 5 000 people who receive blood but these numbers are still uncertain. In cases of TRALI, a serious inflammatory reaction occurs that affects respiration and damages the lungs but there is little knowledge of how this damage occurs and currently, there are no available treatments for TRALI.

http://bit.ly/2mjVjTr

Traitorous Tumor Cells Kill Their Own Kind

Researchers plan to turn cancer cells into defectors, engineering them to kill the tumors from whence they came, and have tested the approach in mice.

Ruth Williams

Using cancer to fight cancer might seem counterintuitive, but there's method to the apparent madness and, according to proof-of-principle animal experiments reported in *Science Translational Medicine* today (July 11), it works. Tumor cells engineered to secrete anticancer agents yet resist self-destruction can be used to kill tumors in mice and then, in a fate befitting this act of betrayal, off themselves. "This is an interesting study showing that genetically-engineered autologous cancer cells can be exploited as a sort of Trojan horse for delivering TRAIL, a pro-apoptotic agent, to tumors," oncologist Angelo Corti of the Vita-Salute San Raffaele University in Milan, Italy, who was not involved in the study, writes in an email to *The Scientist*. "This novel approach undoubtedly represents an important step ahead in translational cancer research."

TRAIL—or, tumor necrosis factor-related apoptosis-inducing ligand—is an antitumor agent identified in mammals that can induce cell death in a variety of cancer cells and yet leaves healthy cells relatively unscathed. "For TRAIL-sensitive tumors, TRAIL is an excellent therapeutic agent. . . . It's very potent," says cancer researcher Gen Sheng Wu of Wayne State University School of Medicine in Detroit who also did not participate in the research. However, he adds, TRAIL has not translated well clinically because of the protein's short half-life and thus the difficulty of delivering a sufficient and sustained dose to the tumor.

Engineered cells that produce TRAIL on site may be a solution to this problem, and neurologist Khalid Shah of Harvard Medical School and colleagues considered the cancer cells themselves as potential candidates for the job. Using the very cells they aimed to kill "may seem a paradoxical approach," writes Corti, but there's a number of reasons the idea might work.

For one, cancer cells are easy to obtain during surgery to remove the tumor and easy to grow in the laboratory, says Wu. The cells would also be derived from the patient, "so there's no immunorejection." And, of key importance, tumor cells have a natural homing ability, Wu explains. Aside from disseminating around the body during metastasis, cancer cells can also return to and recolonize their tumors of origin—a phenomenon known as tumor self-seeding.

To test out the idea, Shah and colleagues engineered human glioblastoma cells to both secrete TRAIL and to be resistant to the protein, by removing the cells' ability to express the TRAIL surface receptors.

Of course, says Shah, deploying cancer cells for therapy "is a double-edged sword" because they could spawn new tumors themselves. To prevent this possibility, the team also built in a suicide system—an

enzyme that converts a relatively harmless medication into a locally acting, toxic substance, eliminating the therapeutic cells when the mouse is given the drug.

The researchers delivered the engineered cells a small distance from autologous tumors developed in mice and found evidence of cell migration toward the cancer that resulted in diminished tumor size and improved survival of the animals when compared with controls that received equivalent cells unable to secrete TRAIL.

Although autologous cells would be ideal for clinical translation, says Shah, his team also created off-the-shelf, allogenic therapeutic cells using a TRAIL-insensitive gliobastoma cell line, which was also effective at treating tumors in mice. In a clinical setting, such cell lines could be HLA matched to patients to improve the chances of immunocompatibility.

"This is an interesting manuscript that builds upon previous work exploring the biological phenomena of tumor self-seeding enabling self-targeting with genetically engineered tumor cells," Renata Pasqualini of Rutgers Cancer Institute of New Jersey who was not involved in the research writes in an email to *The Scientist.* However, "the translational potential really depends on safety being demonstrated as further studies are performed," she says.

In addition to safety testing, "the use of multiple vectors and of labor-intensive technologies to produce this therapeutic agent may represent another limitation for its clinical development," writes Corti,

"Nevertheless, the results of this study, which provide an important proof-of-principle, may burst further studies to make this process simple and safe and to finally exploit cancer cells as novel vehicles of therapeutic agents."

C. Reinshagen et al., "CRISPR-enhanced engineering of therapy-sensitive cancer cells for self-targeting of primary and metastatic tumors," Science Translational Medicine, 10:eaao3240, 2018.

https://bbc.in/2JpKAzK

Emerging sex disease MG 'could become next superbug'

A little known sexually transmitted infection could become the next superbug unless people become more vigilant, experts are warning.

By Michelle Roberts Health editor, BBC News online

Mycoplasma genitalium (MG) often has no symptoms but can cause pelvic inflammatory disease, which can leave some women infertile. MG can be missed - and if it is not treated correctly, it can develop resistance to antibiotics. The British Association of Sexual Health and HIV is launching new advice. Its draft guidelines detail how best to spot and treat MG.

What is MG?

Mycoplasma genitalium is a bacterium that can cause inflammation of the urethra in men, causing discharge from the penis and making it painful to urinate. In women, it can cause inflammation of the reproductive organs (womb and fallopian tubes) too, causing pain and possibly a fever and some bleeding.

You can get it by having unprotected sex with someone who has it. Condoms can prevent this spread. It was first identified in the UK in the 1980s and is thought to affect 1-2% of the general population.

MG does not always cause symptoms and will not always need treatment, but it can be missed or mistaken for a different sexually transmitted infection, such as Chlamydia. The BASHH says this is concerning.

Tests for MG have recently been developed but are not available in all clinics yet although doctors can send samples to Public Health England's laboratory to get a diagnostic result. It can be treated with antibiotics - but the infection is developing resistance to some of these drugs.

'I tested positive for MG'

John - not his real name - contacted the BBC to tell of his experience of having the infection. "I was diagnosed with MG last year after meeting my new partner. "We both sensibly got tested and declared clean at the start of the relationship but GUM [genitourinary medicine] clinics don't test for MG, unless you have symptoms.

"So about a month into the relationship I developed the male symptoms - a sharp burning pain while urinating and a pus-like dishcharge from my urethra - but I had no idea what was wrong.

"After a few weeks I tested positive, while my partner was negative, which didn't make sense. She then got tested again and was positive.

"We were put on antibiotics for two weeks but had no sexual contact for five, to make sure we were clean. After further tests we both tested negative but I still had some small amount of leakage which I was told would go away. It eventually cleared. "Then out of the blue I got a UTI and symptoms were exactly like MG.

"I am now certain it has returned and I am awaiting further test results.

"The GUM clinic refused to retest my partner as she hasn't shown any symptoms. "I think clinics should test for MG as part of their sexual health screening process, as this would have been picked up at the start for me."

'Pack condoms'

Eradication rates of MG following treatment with one family of antibiotics, called macrolides, are decreasing globally. Macrolide resistance in the UK is estimated at about 40%, say the guidelines.

One particular macrolide antibiotic, azithromycin, still works in most cases however.

Dr Peter Greenhouse, a sexual consultant in Bristol and BASHH member, urged people to take precautions. "It's about time the public learned about *Mycoplasma genitalium*," he said. "It's yet another good reason to pack the condoms for the summer holidays - and actually use them."

'Out of control'

Paddy Horner, who co-wrote the guidelines, said: "These new guidelines have been developed, because we can't afford to continue with the approach we have followed for the past 15 years as this will undoubtedly lead to a public health emergency with the emergence of MG as a superbug.

"Our guidelines recommend that patients with symptoms are correctly diagnosed using an accurate MG test, treated correctly then followed up to make sure they are cured.

"Resources are urgently needed to ensure that diagnostic and antimicrobial resistance testing is available for women with the condition who are at high risk of infertility.

- ***MG - what to look out for***

"We are asking the government directly to make this funding available to prevent a public health emergency waiting to happen and which is already spiralling out of control."

Public Health England says testing is available to diagnose MG and any signs of drug resistance, if necessary.

Dr Helen Fifer, consultant microbiologist at Public Health England, welcomed the guidelines, adding: "If you have symptoms of an STI, we recommend you get tested at your local sexual health clinic.

"Everyone can protect themselves from STIs by consistently and correctly using condoms with new and casual partners."

http://bit.ly/2zEZ5A5

Smell receptors in the body could help sniff out disease

Olfactory cells found throughout the body may help or harm depending on location

Rockville, Md. - A review of more than 200 studies reveals that olfactory receptors--proteins that bind to odors that aid the sense of smell--perform a wide range of mostly unknown functions outside the nose. The function of extra-nasal olfactory receptors has the potential to be used in the diagnosis and treatment of health conditions such as

cancer. The article is published in the July issue of *Physiological Reviews*.

Olfactory, or smell, receptors were originally thought to be only in the sensory nerve cells (neurons) of nasal cavity tissues. However, more recent and extensive study suggests that the receptors "occur in nearly the entire human body, [and] they appear to be substantially more functionally important than previously suggested," researchers from Ruhr-University Bochum in Germany wrote. In addition to the receptors playing a major role in the sense of smell, "several essential physiological and pathophysiological processes have been described as targeted by human [olfactory receptors], including path finding, cell growth, [cell death], migration and secretion."

The research team summarized the location and purpose of certain types of olfactory receptors, including those that may be beneficial to general health:

- ***Receptors present in heart muscle cells may be a metabolic regulator of heart function.***
- ***Receptors activated in the immune system have been seen to promote the death of certain types of leukemia cells.***
- ***Smell receptors in the liver reduce the spread of liver cancer cells.***
- ***Receptors in the skin increase the regeneration of skin cells and help speed wound healing.***

The review also reveals ways in which olfactory receptors may affect the development of disease, including:

- ***Receptors concentrated in the prostate tissue, especially in men with prostate cancer, contribute to the reduction or progression of the disease.***
- ***Receptors in the colon may reduce the growth of colon cancer cells.***
- ***Receptors in the digestive tract may cause chronic diarrhea or constipation but may also contribute to better digestion.***

The existence of olfactory receptors outside the nose--either positive or negative--plays an important role in disease progression and physiological function but is not yet fully understood. Their role as a possible biomarker for disease requires more research, the authors said. Study "must be expanded to develop promising clinical strategies in the future," the researchers wrote.

Read the full article, "Human olfactory receptors: novel cellular functions outside of the nose," published in Physiological Reviews.

http://bit.ly/2NPRstI

Why internal scars won't stop growing

Rogue molecules provoke out-of-control scar tissue, strangle organs

- ***New compound discovered that halts some fibrotic diseases***
- ***Fibrosis accounts for up to 40 percent of all global deaths***
- ***Human fibrotic cells reveal immune abnormality***

CHICAGO --- Normal scar tissue forms to heal an internal wound and quietly retreats when the job is done. But in many common diseases - kidney, liver and lung fibrosis -- the scar tissue goes rogue and strangles vital organs. These diseases are largely untreatable and ultimately fatal.

A new Northwestern Medicine study has newly identified a trigger of some fibrotic diseases and an experimental compound to treat it.

Fibrosis - a progressive scarring and hardening of internal organs - is estimated to cause 35 to 40 percent of deaths in the world. Fibrotic diseases include diabetic kidney fibrosis, alcoholic liver cirrhosis, hepatitis C, pulmonary fibrosis and nonalcoholic fatty liver disease, which may lead to fibrosis of the liver, the leading cause of liver transplant.

In one subset of human fibrosis cells, scientists discovered a delinquent gang of molecules that continually shouted at an immune receptor - the antennae on the cell -- to produce scar tissue instead of quieting down and allowing the scar tissue to go back to sleep.

Scientists collaborated with a University of Colorado researcher who used crystallography and computer modeling to predict a molecule that could block the receptor that leads to the uncontrolled scarring.

When they tested the molecule, T53, in three different mouse models of fibrosis, the abnormality was significantly reversed.

"Our study opens a new door into fibrosis by looking at it as an aberrant innate immune response and suggesting a novel approach to treat it," said senior author Dr. John Varga, director of the Northwestern Scleroderma Program and the John and Nancy Hughes Distinguished Professor of Rheumatology at Northwestern University Feinberg School of Medicine. The paper will be published July 12 in the *Journal of Clinical Investigation Insight*.

"The leading cause of liver failure in western world is obesity and that's because of liver fibrosis," Varga said. "In the U.S., many of these diseases are lifestyle or age dependent. As we get fatter or older, they get worse."

Most fibrotic disease likely begins as normal repair of an injury, scientists said. "But if the immune system produces too much of an initial scar, it can't go back to normal," Varga said. "You have an unhealed scar that keeps growing and can wipe out the entire organ."

Not everyone's fibrosis is caused by the same abnormality, Varga said. If the compound, T53, is eventually developed into an approved drug, it would be targeted to patients with the specific genetic signature identified in the study.

"There is an emerging direction for treating fibrosis with precision medicine," said first author Swati Bhattacharyya, research associate professor of medicine in rheumatology and scientific director of the Scleroderma Research Laboratory at Feinberg. "Some people live with fibrotic disease for 30 years while others die in two years. We need to identify the rapid progressors from the slow progressors. That's where precision medicine becomes really critical."

"The results of this study are encouraging," Varga said. "We are not saying this compound is ready to be a drug. It's an initial compound that would need to be developed and tweaked. It would need significant funding to go to the next step."

Varga has spent more than a decade researching the cause and treatment of scleroderma, a type of fibrosis that simultaneously affects multiple organs. He directs the Northwestern Scleroderma Program, a clinical and research effort that follows 1,500 patients with scleroderma.

This work was supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR42309), National Institute of General Medicine (GM101279), of the National Institutes of Health, and the Scleroderma Foundation.

http://bit.ly/2uCSUXF

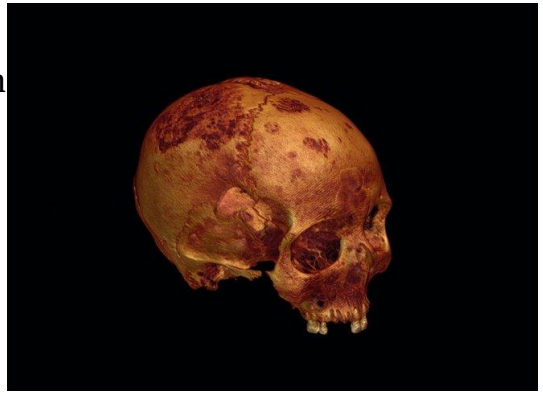
This Holey Skull May Have Watched Over Dead People in the Afterlife Some 2,500 Years Ago

Around 2,500 years ago, the skull of a woman who died of cancer was buried facing into an artificial cave dug out of the rock, as if staring at the remains of at least 50 people hidden inside, archaeologists have discovered.

By Owen Jarus, Live Science Contributor | July 12, 2018 01:05pm ET

The "extremely peculiar position" of the buried skull, which was discovered near the town of Baucina, in Sicily, Italy, has scientists puzzled, they said.

The skull belonged to a woman who died when she was between 35 and 50 years old. She seems to have had a cancer that had spread to her skull, leaving 14 holes in it. Scientists believe the cancer may have started in her breasts, eventually spreading into her skeleton.



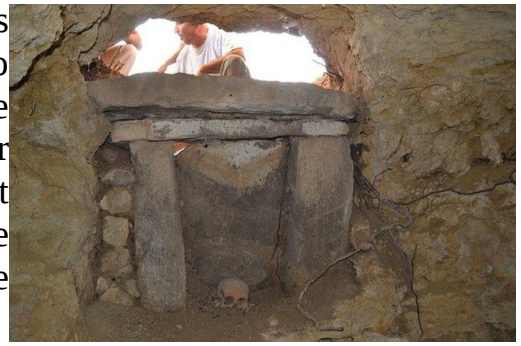
A rendering of the ancient skull created from CT scans. **Courtesy Roberto Miccichè, Giuseppe Carotenuto & Luca Sìneo**

Unfortunately, the tomb had been robbed at some point in time, the skeletons in the cave became jumbled up and any grave goods that they were buried with were stolen, the team of scientists wrote in a

paper published in June in a special "cancer issue" of the International Journal of Paleopathology.

It's uncertain where the rest of her body is buried; nevertheless, archaeologists believe her skull was not disturbed by tomb robbers.

"We can assume that it [the skull] was found undisturbed in its original position, as grave robbers have used another way to get into the cave immediately above the entrance," study researcher Roberto Miccichè, an adjunct anthropology professor at the University of Palermo, told Live Science.

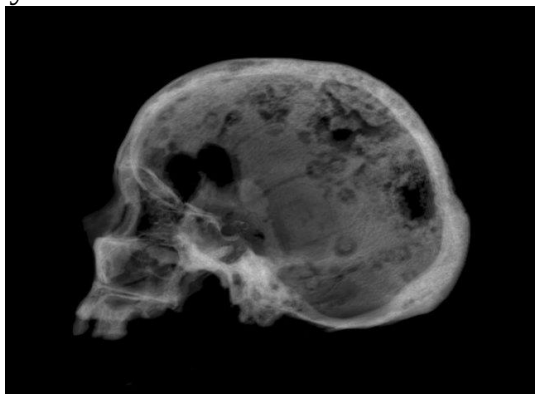


The 2,500-year-old skull of a woman with cancer was found facing into an artificial cave that holds at least 50 burials. **Courtesy Roberto Miccichè, Giuseppe Carotenuto & Luca Sìneo**

Miccichè and others from the university's archaeology department discovered the skull in 2014 during excavations in the artificial cave.

Possible answers

The cancer itself may explain why she was buried with her skull facing into the cave. The holes the cancer left on her skull and other symptoms of her disease may have appeared unusual to the people in her community and may have left a strong enough impression that they chose to have her skull buried facing 50 other dead people.



A digitally reconstructed radiograph of the ancient skull reveals the holes caused by cancer. **Courtesy Roberto Miccichè, Giuseppe Carotenuto & Luca Sìneo**

"Personally, I agree with this interpretation, as the clinical appearance of metastases on the skull [with its scattered holes] may have impressed the afterlife perception of people who lived beside the individual," Miccichè told Live Science.

"Another possibility could be connected to a particular role occupied in life within the ancient community by the person to whom the skull belonged," Miccichè said, noting that "both of these interpretations are very hard to prove, as we do not have many similar cases that we can use for comparison purposes."

Research continues and "we are starting with a new research project with the aim to explore the perception of death and illness among ancient cultures in Sicily and maybe we will be able to provide further information on this case under a broader social and sacred perspective," Miccichè said.

http://bit.ly/2KWN12u

NASA Discovered Evidence of Life on Mars 40 Years Ago, Then Set It On Fire

In the late 1970s, two Viking robots sailed to Mars, pillaged the soil and burnt any traces of life they found.

By Brandon Specktor, Senior Writer | July 12, 2018 04:40pm ET

That was never the plan, of course. When NASA first landed the twin spacecraft named Viking 1 and Viking 2 on the surface of Mars 40 years ago, scientists were ecstatic to finally start studying Martian soil for signs of organic (carbon-based) molecules that could prove the Red Planet was hospitable for life. It should've been a slam-dunk mission. The pockmarked face of Mars was constantly being pelted with tiny, carbon-rich meteorites, after all — detecting signs of that carbon was thought to have been a sure thing.

But it wasn't. After half a decade of studying the planet, neither of the Viking landers could find any evidence of organic matter. Why not? NASA's Curiosity rover confirmed the presence of organic molecules on Mars earlier this year, so what was Viking missing?

A new paper, published June 20 in the Journal of Geophysical Research: Planets, provides an explanation. The carbon was there all along, the researchers wrote; unfortunately, the Viking landers set it all on fire.

"A total of four [soil] samples were analyzed, each multiple times, by rapidly heating the sample to one of four temperature steps," researchers from NASA's Ames Research Center in California and the Atmosphere, Media, Spatial Observations Laboratory (LATMOS) in France, wrote in the new study.

The Vikings heated up their soil samples to a maximum temperature of 932 degrees Fahrenheit (500 degrees Celsius) to try and release any volatile organic compounds trapped within those samples. If there had been any carbon there, the traces should have been detectable in the soil's vapor. So, why wasn't it? According to the authors of the new study, there may have been something else in the soil that NASA didn't bargain for — a hyperflammable fuel that accidentally burned the carbon to bits.

Fire and ice

In 2008, a Mars rover named Phoenix was scooping up soil near the Martian north pole when it found evidence of an unusual salt called perchlorate. This was an exciting find at the time; scientists knew that ancient microorganisms on Earth used perchlorate as a source of energy. Perhaps, they thought, this Martian cache of salt served a similar purpose?

The authors of the new study were excited by the salty discovery for a different reason: Perchlorate is flammable — so flammable it's used on Earth today mainly to make rocket fuel and fireworks burn faster. If perchlorate is abundant in Martian soil, the researchers told NewScientist, then Viking's attempts to heat that soil may have caused the perchlorate to catch fire and instantly obliterate any organic molecules that may have been there.

The silver lining to this scenario is, if Martian perchlorate did indeed incinerate any carbon-based molecules in Viking's oven, then there would be evidence in the ashes. When carbon burns with perchlorate, it produces a molecule called chlorobenzene — a mix of carbon, hydrogen and chlorine that can last in soil for months. As luck would have it, NASA's Curiosity rover detected traces of chlorobenzene in Martian soil during a 2013 expedition. For further evidence, the researchers decided to go back to Viking itself.

"We searched the Viking data for a possible reaction product between the salt and organics in the Viking oven," the researchers wrote. The team reanalyzed the original data sets taken during the Viking mission, this time looking specifically for traces of chlorobenzene.

According to their new paper, the researchers found what they were looking for. The team saw trace amounts of chlorobenzene in samples taken by Viking 2, concluding that the lander may well have held organic matter in the palm of its robotic hand before inadvertently setting the whole lot ablaze.

Study author Melissa Guzman, a doctoral student at the LATMOS research center in France, told NewScientist that, while this new evidence is compelling, it's not definitive proof of Martian organics. It's possible, for example, that the carbon compounds burned along with the Martian perchlorate in Viking's oven actually originated from Earth and accidentally contaminated the samples.

Other scientists are ready to believe. Daniel Glavin, a researcher at NASA’s Goddard Space Flight Center in Maryland, who was not involved in the study, told NewScientist that this paper "seals the deal" on Martian organics. Indeed, the study suggests that organic molecules might exist at many sites all over the Red Planet.

Whether that means there's microbial life there — and whether humans can confirm that life before setting it ablaze — remains to be seen.

http://bit.ly/2uyhwkg

Cinnamon oil could be key in preventing superbugs

As antibiotics become less effective against superbugs, a Swinburne researcher has been focusing on traditional agents to modify the behaviour of bacteria rather than killing bacteria.

As part of her Ph.D. studies, Dr. Sanjida Halim Topa investigated cinnamaldehyde, a major component of cinnamon essential oil. She found it inhibited the development of biofilm, a sticky film of bacteria – like the plaque that forms on teeth – that can cause persistent infections, which resist even the most potent antibiotics.

Dr. Topa's research has been published in *Microbiology*.

There is an urgent need to develop alternatives to antibiotics to treat chronic biofilm-mediated infections, such as may occur with urinary catheters and artificial joints.

"Though many previous studies have reported antimicrobial activity of cinnamon essential oil, it is not widely used in the pharmaceutical industry," Dr. Topa says.

"We aimed to search for the molecular activity of this oil, focusing on its major component, cinnamaldehyde. This is the compound that gives cinnamon its flavour."

Developing ways to disrupt biofilms

Rather than killing the bacteria, Dr. Topa was looking to modify the behaviour of bacteria by disrupting bacterial communication to prevent biofilm formation.

"We hypothesised that using natural antimicrobials, such as essential oils, might interfere in biofilm formation. Thus, we focused on the impact of different concentrations of cinnamaldehyde in different biofilm development stages.

Dr. Topa tested the effect of different concentrations of cinnamaldehyde on biofilms formed from the pathogenic Pseudomonas aeruginosa strain of bacteria. She found that a sub-lethal concentration of cinnamaldehyde controlled the dispersion of Pseudomonas aeruginosa and the development of biofilm.

"Humans have a long history of using natural products to treat infections, and there is a renewed focus on such antimicrobial compounds. Natural products may offer a promising solution to this problem," Dr. Topa says.

This research was undertaken with colleagues at Nanyang Technological University in Singapore.

Dr. Topa is now investigating embedding cinnamaldehyde in nanofibres in wound dressings.

More information: *Sanjida Halim Topa et al. Cinnamaldehyde disrupts biofilm formation and swarming motility of Pseudomonas aeruginosa, Microbiology (2018). DOI: 10.1099/mic.0.000692*

http://bit.ly/2Lk2BkU

Novel therapy delays muscle atrophy in Lou Gehrig's disease model

Mouse study could provide foundation for future human therapeutics

Supplementing a single protein found in the spinal cord could help prevent symptoms of Lou Gehrig's disease, according to a new study out of Case Western Reserve University School of Medicine. Researchers found high levels of the protein--called mitofusion 2 or Mfn2--prevented nerve degeneration, muscle atrophy, and paralysis in a mouse model of the disease. Since Mfn2 is often depleted during Lou Gehrig's, the new study suggests supplementing it could be a novel therapeutic approach for the disease.

Lou Gehrig's disease, or amyloid lateral sclerosis (ALS), is a progressive disorder that devastates motor nerve cells. People with ALS slowly lose the ability to control muscle movement, and are ultimately unable to speak, eat, move, or breathe. The cellular mechanisms behind ALS are also found in certain types of dementia.

For the estimated 15,000 Americans living with ALS, the findings offer new hope for ways to delay symptoms.

"We found a way to alleviate age and ALS-related muscular atrophy in our mouse models," said Xinglong Wang, PhD, associate professor of pathology at Case Western Reserve University School of Medicine. "Amazingly, we could delay ALS symptom onset by 67 days."

Wang led the study, published today in *Cell Metabolism*, in which researchers successfully staved off muscle atrophy and paralysis simply by increasing Mfn2 levels in mouse spinal cords.

Wang and colleagues tested the most widely used ALS mouse model. They genetically engineered the diseased mice to have increased Mfn2 levels--but only in nerve cells that extend from the spinal cord and connect to muscle fibers.

In late stages of the disease, mice with high Mfn2 levels in these nerves were a healthy weight, and did not have any of the muscle atrophy, gait abnormalities, or reduced grip strength that mice in control groups developed. Even mice who underwent heavy sciatic nerve damage benefited from elevated Mfn2 levels.

Said Wang, "Upregulation of Mfn2 specifically in nerve cells is sufficient to abolish skeletal muscle loss in ALS and aged mice, despite ALS-causing protein being found in all organs and tissues."

By studying nerve cells collected from the mice, Wang's team uncovered how Mfn2 offers its protective effects.

The researchers found Mfn2 coexists with nutrients in cell structures called mitochondria. Their experiments showed mitochondria travel along nerve cell extensions--axons--and deliver the nutrients to the point where nerve cells and muscle fibers meet. This preserves sensitive connections--synapses--between nerve and muscle cells and prevents muscle atrophy.

"We found mitochondria function as miniature 'trucks' to transport protein along axons to prevent synaptic degeneration," explained Wang.

Cellular transport is not typically in the job description for mitochondria. The ancient cellular structures are well-known to be "powerhouses of the cell"--producing energy that keeps cells running. According to Wang, "this is a novel, previously unrecognized role for mitochondria."

Specifically, Wang's team found mitochondria use Mfn2 on their surfaces to carry a nutrient called calpstatin. Calpstatin inhibits harmful enzymes that break down nerves and muscle fibers.

With the help of Mfn2, mitochondria carry calpstatin along nerve cells axons to meet muscle cells. There, calpstatin prevents enzymes from destroying delicate synapse connections. But without Mfn2, mitochondria can't carry the nutrient.

According to Wang, the findings have broad implications. "Mfn2 deficiency or mutations are commonly observed in patients with ALS, peripheral neuropathy, Alzheimer's disease, and other neurodegenerative diseases in which synaptic loss has long been recognized as a prominent early feature," he says.

"Supplementing Mfn2 may be a common and effective therapeutic approach to treat a wide range of diseases including but not limited muscular disorders, patients with nerve injury and various major neurodegenerative diseases associated with synaptic loss."

Wang, L., et. al. "Mitofusin 2 regulates axonal transport of calpastatin to prevent neuromuscular synaptic elimination in skeletal muscles." Cell Metabolism*. DOI: 10.1016/j.cmet.2018.06.011*

This research was supported by grants from the National Institutes of Health (1R01NS097679 and 1R01NS089604), Alzheimer's Association (AARG-17-499682), and the Association for Frontotemporal Degeneration and Alzheimer's Drug Discovery Foundation (20161206). H.L. was supported by awards from the National Institutes of Health (R01CA196631 and R01CA208517) and Glenn Foundation for Medical Research.

http://bit.ly/2uCca7p

New study highlights Alzheimer's herpes link, experts say

A new commentary by scientists at the Universities of Manchester and Edinburgh on a study by Taiwanese epidemiologists supports the viability of a potential way to reduce the risk of Alzheimer's disease.

When the Taiwanese authors looked at subjects who suffered severe herpes infection and who were treated aggressively with antiviral drugs, the relative risk of dementia was reduced by a factor of 10.

Manchester's Professor Ruth Itzhaki and Edinburgh's Professor Richard Lathe say the paper, by Tzeng et al. and published in Neurotherapeutics in February 2018, also shows that herpes simplex virus type 1 (HSV1) leads to an increased risk of developing the disease.

"This article and two others by different research groups in Taiwan provide the first population evidence for a causal link between herpes virus infection and Alzheimer's disease, a hugely important finding," said Professor Itzhaki.

They publish a commentary in the *Journal of Alzheimer's Disease* on the three articles, arguing that they provide the strongest evidence yet for a causal link between herpes infection and Alzheimer's disease, backing 30 years of research by Professor Itzhaki.

Professor Itzhaki said: "I believe we are the first to realise the implications of these striking data on this devastating condition which principally affects the elderly. No effective treatments are yet available. "Almost 30 million people worldwide suffer from it and sadly, this figure will rise as longevity increases.

"But we believe that these safe and easily available antivirals may have a strong part to play in combating the disease in these patients. "It also raises the future possibility of preventing the disease by vaccination against the virus in infancy.

"Successful treatment by a specific drug, or successful vaccination against the putative microbe, are the only ways to prove that a microbe is the cause of a non- infectious human disease."

Most Alzheimer's disease researchers investigate its main characteristics - amyloid plaques and neurofibrillary tangles; however, despite the vast amount of research, the causes of their formation are unknown.

HSV1 infects most humans in youth or later and remains lifelong in the body in dormant form within the peripheral nervous system.

From time to time the virus becomes activated and in some people it then causes visible damage in the form of cold sores.

The Taiwanese study identified 8,362 subjects aged 50 or more during the period January to December 2000 who were newly diagnosed with severe HSV infection.

The study group was compared to a control group of 25,086 people with no evidence of HSV infection. The authors then monitored the development of dementia in these individuals over a follow-up period of 10 years between 2001 and 2010.

The risk of developing dementia in the HSV group was increased by a factor of 2.542. But, when the authors compared those among the HSV cohort who were treated with antiviral therapy versus those who did not receive it, there was a dramatic tenfold reduction in the later incidence of dementia over 10 years.

Professor Richard Lathe added: "Not only is the magnitude of the antiviral effect remarkable, but also the fact that--despite the relatively brief duration and the timing of treatment--in most patients severely affected by HSV1 it appeared to prevent the long-term damage in brain that results in Alzheimer's.

Professor Itzhaki said: "It was as long ago as 1991 when we discovered that, in many elderly people infected with HSV1, the virus is present also in the brain, and then in 1997 that it confers a strong risk of Alzheimer's disease in the brain of people who have a

specific genetic factor. "In 2009, we went on to show that HSV DNA is inside amyloid plaques in Alzheimer's patients' brains.

"We suggested that the virus in brain is reactivated by certain events such as stress, immunosuppression, and infection/inflammation elsewhere. "So we believe the cycle of HSV1 reactivation in the brain eventually causes Alzheimer's in at least some patients."

The study by Tzeng et al. investigated only people with severe HSV and cannot be generalised to healthy populations.

NOTES FOR EDITORS

The paper: 'Herpes Viruses and Senile Dementia: First Population Evidence for a Causal Link' is available

http://bit.ly/2unsvxQ

Turbulence allows clinical-scale platelet production for transfusions

Turbulence is critical for promoting large-scale production of functional platelets from human induced pluripotent stem cells

Turbulence is a critical physical factor that promotes the large-scale production of functional platelets from human induced pluripotent stem cells (hiPSCs), researchers in Japan report July 12 in the journal *Cell*. Exposure to turbulent energy in a bioreactor stimulated hiPSC-derived bone marrow cells called megakaryocytes to produce 100 billion platelets—blood cell fragments that help wounds heal and prevent bleeding by forming blood clots. Moreover, transfusion of these platelets in two animal models promoted blood clotting and prevented bleeding just as well as human donor platelets.

"The discovery of turbulent energy provides a new physical mechanism and ex vivo production strategy for the generation of platelets that should impact clinical-scale cell therapies for regenerative medicine," says senior study author Koji Eto, part of the Center for iPS Cell Research and Application at Kyoto University.

Blood transfusion is one the most common forms of cell therapy, with nearly five million Americans undergoing this procedure each year. In the near future, donor blood supplies are not expected to meet patient demand in several countries. One factor that contributes to this problem is the short shelf-life of some blood components.

In particular, human donor platelets have a shelf life of only 5 days in the United States because they gradually lose their aggregation capacity and are susceptible to bacterial contamination. Platelet transfusions are sometimes needed to treat a condition called thrombocytopenia, in which platelet deficiency increases the risk of life-threatening blood loss. The expected shortage of platelets has stimulated researchers to look for alternative sources that don't rely on blood donations.

hiPSCs offer a renewable approach for producing sufficient numbers of platelets for transfusion. This technique involves epigenetically reprogramming blood or skin cells taken from human donors to an embryonic-stem-cell-like state and then converting these immature cells into specialized cell types found in different parts of the body. However, previous attempts to generate platelets from hiPSC-derived megakaryocytes have failed to achieve a scale suitable for clinical manufacturing.

While searching for a solution to this problem, Eto and his collaborators noticed that hiPSC-derived megakaryocytes produced more platelets when being rotated in a flask than under static conditions in a petri dish. This observation suggested that that physical stress from horizontal shaking under liquid conditions enhances platelet generation. Following up on this discovery, the researchers tested a rocking-bag-based bioreactor followed by a new microfluidic system with a flow chamber and multiple pillars, but these devices generated fewer than 20 platelets per hiPSC-derived megakaryocyte.

To examine the ideal physical conditions for generating platelets, Eto and his team next conducted live-imaging studies of mouse bone marrow—the tissue that produces blood components. These experiments revealed that megakaryocytes release platelets only

when they are exposed to turbulent blood flow. In support of this idea, simulations confirmed that the bioreactor and microfluidic system they previously tested lacked sufficient turbulent energy.

"The discovery of the crucial role of turbulence in platelet production significantly extends past research showing that shear stress from blood flow is also a key physical factor in this process," Eto says. "Our findings also show that iPS cells are not the end-all be-all for producing platelets. Understanding fluid dynamics in addition to iPS cell technology was necessary for our discovery."

After thoroughly testing various devices, the researchers discovered that large-scale production of high-quality platelets was possible using a bioreactor called VerMES. This system consists of two oval-shaped, horizontally oriented mixing blades that generate relatively high levels of turbulence by moving up and down in a cylinder. With the optimal level of turbulent energy and shear stress created by the blade motion, the hiPSC-derived megakaryocytes generated 100 billion platelets—enough to satisfy clinical requirements.

Transfusion experiments in two animal models with thrombocytopenia showed that these platelets perform similarly to human donor platelets. Specifically, both types of platelets promoted blood clotting and reduced bleeding times to a comparable extent after ear vein incisions in rabbits and tail artery punctures in mice.

Currently, Eto and his team are improving their approach by designing automated protocols, lowering manufacturing costs, and optimizing platelet yields. They are also developing universal platelets lacking cell-surface proteins called human leukocyte antigens in order to reduce the risk of immune-mediated transfusion reactions.

"We expect clinical trials to begin within a year or two," Eto says. "We believe these findings will be a last scientific step to receiving permission for clinical trials using our platelets."

More information: *Cell, Ito and Nakamura et al.: "Turbulence activates platelet biogenesis to enable clinical scale ex vivo production" https://www.cell.com/cell/fulltext/S0092-8674(18)30736-0 , DOI: 10.1016/j.cell.2018.06.011*

http://bit.ly/2uCFVoK

Southeast Asians Derive Ancestry from Four Ancient Populations

Modern-day Southeast Asian populations are the result of mixing among four ancient populations, including multiple waves of genetic material from more northern East Asian populations, according to researchers who sequenced and analyzed 26 ancient genomes from Southeast Asia and Japan.

McColl* et al *sequenced 26 ancient genomes from Southeast Asia and Japan spanning from the late Neolithic to the Iron Age.

Southeast Asia is one of the most genetically diverse regions in the world, but for more than a century scientists have disagreed about which theory of the origins of this region's population was correct.

One theory believed the indigenous Hoabinhian hunter-gatherers who populated Southeast Asia from 44,000 years ago adopted agricultural practices independently, without the input from early farmers from East Asia.

Another theory, referred to as the 'two-layer model' favors the view that migrating rice farmers from what is now China replaced Hoabinhian hunter-gatherers.

Professor Eske Willerslev from St John's College, the University of Cambridge, and the University of Copenhagen and colleagues found that neither theory is completely accurate.

They discovered that present-day Southeast Asian populations derive ancestry from at least four ancient populations.

In the study, the team extracted DNA from 8,000-year-old skeletal remains from Malaysia, Thailand, the Philippines, Vietnam, Indonesia, Laos and Japan. Scientists had previously only been successful in sequencing 4,000-year-old samples from the region.

The new samples also included DNA from Hoabinhian hunter-gatherers and a Jomon from Japan — a scientific first, revealing a long suspected genetic link between the two populations.

In total, 26 ancient human genome sequences were studied by the researchers and they were compared with modern DNA samples from people living in Southeast Asia today.

"This study tackles a major question in the origins of the diversity of Southeast Asian people, as well as on the ancient relationships between distant populations, such as Jomon and Hoabinhian foragers, before farming," said co-author Professor Marta Mirazón Lahr, Director of the Duckworth Laboratory at the University of Cambridge.

"We put a huge amount of effort into retrieving ancient DNA from tropical Southeast Asia that could shed new light on this area of rich human genetics," Professor Willerslev said. "The fact that we were able to obtain 26 human genomes and shed light on the incredible genetic richness of the groups in the region today is astonishing."

"The human occupation history of Southeast Asia remains heavily debated," said co-author Dr. Fernando Racimo, from the Centre for GeoGenetics at the Natural History Museum, the University of Copenhagen. "Our research spanned from the Hoabinhian to the Iron Age and found that present-day Southeast Asian populations derive ancestry from at least four ancient populations. This is a far more complex model than previously thought."

"By sequencing 26 ancient human genomes, we have shown that neither interpretation fits the complexity of Southeast Asian history," said first author Hugh McColl, a Ph.D. student at the Centre for GeoGenetics in the Natural History Museum of Denmark at the University of Copenhagen.

"Both Hoabonhian hunter-gatherers and East Asian farmers contributed to current Southeast Asian diversity, with further migrations affecting islands in South East Asia and Vietnam."

"Our results help resolve one of the long-standing controversies in Southeast Asian prehistory."

The study is published in the journal *Science*.

http://bit.ly/2ulQddJ

Parental chromosomes kept apart during embryo's first division

Separate spindles for each set of parental chromosomes means genetic information from parents is kept apart during the first division

It was long thought that during an embryo's first cell division, one spindle is responsible for segregating the embryo's chromosomes into two cells. EMBL scientists now show that there are actually two spindles, one for each set of parental chromosomes, meaning that the genetic information from each parent is kept apart throughout the first division.

Science publishes the results—bound to change biology textbooks—on 12 July 2018.

This dual spindle formation might explain the high error rate in the early developmental stages of mammals, spanning the first few cell divisions. "The aim of this project was to find out why so many mistakes happen in those first divisions," says Jan Ellenberg, the group leader at EMBL who led the project. "We already knew about dual spindle formation in simpler organisms like insects, but we never thought this would be the case in mammals like mice. This finding was a big surprise, showing that you should always be prepared for the unexpected."

Solving a 20-year-old mystery

Scientists have always seen parental chromosomes occupying two half-moon-shaped parts in the nucleus of two-cell embryos, but it wasn't clear how this could be explained. "First, we were looking at the motion of parental chromosomes only, and we couldn't make sense of the cause of the separation," says Judith Reichmann, scientist in EMBL's Ellenberg group and first author of the paper. "Only when focusing on the microtubules—the dynamic structures that spindles are made of—could we see the dual spindles for the first time. This allowed us to provide an explanation for this 20-year-old mystery."

What is mitosis?

Mitosis is the process of cell division, when one cell splits into two daughter cells. It occurs throughout the lifespan of multi-cellular organisms but is particularly important when the organism grows and develops. The key step of mitosis is to pass an identical copy of the genome to the next cell generation.

For this to happen, DNA is duplicated and organised into dense thread-like structures known as chromosomes. The chromosomes are then attached to long protein fibres—organised into a spindle—which pulls the chromosomes apart and triggers the formation of two new cells.

What is the spindle?

The spindle is made of thin, tube-like protein assemblies known as microtubules. During mitosis of animal cells, groups of such tubes grow dynamically and self-organise into a bi-polar spindle that surrounds the chromosomes. The microtubule fibres grow towards the chromosomes and connect with them, in preparation for chromosome separation to the daughter cells. Normally there is only one bi-polar spindle per cell, however, this research suggests that during the first cell division there are two: one each for the maternal and paternal chromosomes.

New molecular targets

"The dual spindles provide a previously unknown mechanism—and thus a possible explanation—for the common mistakes we see in the first divisions of mammalian embryos," Ellenberg explains. Such mistakes can result in cells with multiple nuclei, terminating development. "Now, we have a new mechanism to go after and identify new molecular targets. It will be important to find out if it works the same in humans, because that could provide valuable information for research on how to improve human infertility treatment, for example."

The beginning of life

Furthermore, the knowledge from this paper might impact legislation. In some countries, the law states that human life begins—and is thus protected—when the maternal and paternal nuclei fuse after fertilisation. If it turns out that the dual spindle process works the same in humans, this definition is not fully accurate, as the union in one nucleus happens slightly later, after the first cell division.

Impossible until now

This discovery would have been impossible without the light-sheet microscopy technology developed in Ellenberg's and Lars Hufnagel's group at EMBL, which is now available through the EMBL spin-off company Luxendo. This allows for real-time and 3-D imaging of the early stages of development, when embryos are very sensitive to light and would be damaged by conventional light microscopy methods. The high speed and spatial precision of light-sheet microscopy drastically reduce the amount of light that the embryo is exposed to, making a detailed analysis of these formerly hidden processes possible.

More information: *"Dual-spindle formation in zygotes keeps parental genomes apart in early mammalian embryos" Science (2018). science.sciencemag.org/cgi/doi … 1126/science.aar7462*

http://bit.ly/2unyvXa

Products of omega-3 fatty acid metabolism may have anticancer effects, study shows

Endocannabinoids from metabolism of omega-3 fatty acids could inhibit cancer's growth and spread

CHAMPAIGN, Ill. -- A class of molecules formed when the body metabolizes omega-3 fatty acids could inhibit cancer's growth and spread, University of Illinois researchers report in a new study in mice. The molecules, called endocannabinoids, are made naturally by the body and have similar properties to cannabinoids found in marijuana - but without the psychotropic effects.

In mice with tumors of osteosarcoma - a bone cancer that is notoriously painful and difficult to treat - endocannabinoids slowed the growth of tumors and blood vessels, inhibited the cancer cells from migrating and caused cancer cell death. The results were published in the *Journal of Medicinal Chemistry*.

"We have a built-in endocannabinoid system which is anti-inflammatory and pain-reducing. Now we see it is also anti-cancer, stopping the cells from proliferating or migrating," said study leader Aditi Das, a professor of comparative biosciences and an affiliate of biochemistry at Illinois. "These molecules could address multiple problems: cancer, inflammation and pain."

In 2017, the Illinois team identified a new group of omega-3 fatty-acid metabolites called endocannabinoid epoxides, or EDP-EAs. They found that these molecules had anti-inflammatory properties and targeted the same receptor in the body that cannabis does.

Since cannabis has been shown to have some anti-cancer properties, in the new study the researchers investigated whether EDP-EAs also affect cancer cells. They found that in mice with osteosarcoma tumors that metastasized to their lungs, there was an 80 percent increase in naturally occurring EDP-EAs in cancerous lung tissues over the lungs of healthy mice.

"The dramatic increase indicated that these molecules were doing something to the cancer - but we didn't know if it was harmful or good," Das said. "We asked, are they trying to stop the cancer, or facilitating it? So we studied the individual properties and saw that they are working against the cancer in several ways."

The researchers found that in higher concentrations, EDP-EAs did kill cancer cells, but not as effectively as other chemotherapeutic drugs on the market. However, the compounds also combated the osteosarcoma in other ways: They slowed tumor growth by inhibiting new blood vessels from forming to supply the tumor with nutrients, they prevented interactions between the cells, and most significantly, they appeared to stop cancerous cells from migrating.

"The major cause of death from cancer is driven by the spread of tumor cells, which requires migration of cells," said study coauthor Timothy Fan, a professor of veterinary clinical medicine and veterinary oncology. "As such, therapies that have the potential to impede cell migration also could be useful for slowing down or inhibiting metastases."

The researchers isolated the most potent of the molecules and are working to develop derivatives that bind better to the cannabinoid receptor, which is plentiful on the surface on cancer cells.

"Dietary consumption of omega-3 fatty acids can lead to the formation of these substances in the body and may have some beneficial effects. However, if you have cancer, you want something concentrated and fast acting," Das said. "That's where the endocannabinoid epoxide derivatives come into play - you could make a concentrated dose of the exact compound that's most effective against the cancer. You could also mix this with other drugs such as chemotherapies."

Next, the researchers plan to perform preclinical studies in dogs, since dogs develop osteosarcoma spontaneously, similarly to humans.

They also plan to study the effects of EDP-EAs derived from omega-3 fatty acids in other cancer types.

"Particular cancers that might be most interesting to study would be solid tumors or carcinomas, which tend to spread and cause pain within the skeleton. Some of the most common tumors that behave this way are breast, prostate, and lung carcinomas, and we can certainly explore these tumors in the future," said Fan, who is also a member of the Carle Illinois College of Medicine, the Cancer Center at Illinois and the Carl R. Woese Institute for Genomic Biology.

The National Institutes of Health and the American Heart Association supported this work.

The paper "Antitumorigenic properties of omega-3 endocannabinoid epoxides" is available online or from the News Bureau.

https://nyti.ms/2NibdsI

Drug to Treat Smallpox Approved by F.D.A., a Move Against Bioterrorism

First drug approved to treat smallpox; a move that could halt a lethal pandemic if the virus were released

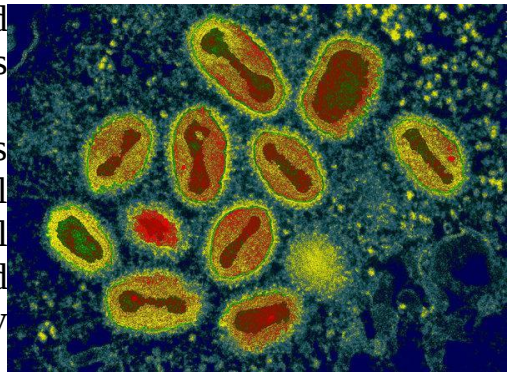
By Donald G. McNeil Jr.

The Food and Drug Administration on Friday approved the first drug intended to treat smallpox — a move that could halt a lethal pandemic if the virus were to be released as a terrorist bioweapon or through a laboratory accident.

The antiviral pill, tecovirimat, also known as Tpoxx, has never been tested in humans with smallpox because the disease was declared eradicated in 1980, three years after the last known case.

But it was very effective at protecting animals deliberately infected with monkeypox and rabbitpox, two related diseases that can be lethal. It also caused no severe side effects when safety-tested in 359 healthy human volunteers, the F.D.A. said.

"This new treatment affords us an additional option should smallpox ever be used as a bioweapon," said Dr. Scott Gottlieb, the F.D.A.'s commissioner.



Smallpox was eliminated in 1980, but experts have feared the virus, above, may return via laboratory accident or terrorist attack. **Eye of Science/Science Source**

Having a drug that usually cures smallpox is an important medical breakthrough, according to several medical experts not associated with the F.D.A. or the company making the drug.

F.D.A. approval is "definitely a good thing," said Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases.

Research on tecovirimat — originally designated ST-246 — began at the institute after the 9/11 terrorist attack on the World Trade Center, Dr. Fauci said. The research accompanied efforts to stretch the national stockpile of smallpox vaccine by safely diluting it.

"It all started back then, but developing a licensed product took until today," he added.

The F.D.A. approval of the drug went to Siga Technologies of Corvallis, Ore., a private company that developed the medicine under a federal biomedical defense contract.

Although circulating smallpox has been eradicated, two known stores of the virus exist in laboratory freezers — one in Russia and one at the Centers for Disease Control and Prevention in Atlanta.

Bioterrorism experts fear that other stocks may exist; for example, in 2014 several forgotten vials containing smallpox were found at the National Institutes of Health.

More worrisome, experts say, is the possibility that a terrorist lab or even a sophisticated amateur could use modern gene-editing techniques to rebuild the virus and then unleash it, deliberately or accidentally, on an unprepared world.

Because routine smallpox vaccination stopped after 1980, almost everyone under the age of 40 is unprotected. The disease kills almost a third of people who get it, and is even more lethal to babies.

Finding a medicine was vital because — unlike, for example, measles or whooping cough vaccine — smallpox vaccine is too dangerous to give everyone, said Dr. Peter J. Hotez, former president of the Sabin Vaccine Institute and dean of the National School of Tropical Medicine at Baylor College of Medicine.

The vaccine is now routinely given only to some members of the military, lab workers and others likely to come in contact with the virus in a bioterrorism event. It cannot be given to pregnant women, or to anyone with H.I.V., under cancer treatment or with any other immunosuppressive condition; nor can the vaccine be given to anyone with eczema or several other skin diseases, Dr. Hotez said.

So a medicine like tecovirimat would be useful for treating anyone infected in the first wave of any release of the virus, as well as the millions of Americans who cannot be vaccinated.

Dr. William Schaffner, a professor of preventive medicine at Vanderbilt University Medical School, noted tecovirimat also could be useful for treating monkeypox, which infects humans and has been increasing rapidly in Africa since smallpox vaccination ended.

Monkeypox sometimes travels internationally; in 2003, there was an outbreak of 47 confirmed and suspected cases in the United States. According to the C.D.C., the virus arrived in a shipment of 800 small mammals from Ghana, including African giant pouched rats and rope squirrels intended for the pet trade. They infected prairie dogs at an Illinois pet warehouse; the prairie dogs in turn infected children who bought them as pets.

Despite its fearsome reputation, smallpox actually spreads slowly compared with more common diseases like measles or chickenpox, Dr. Schaffner said.

Symptoms like fever, exhaustion and headache typically begin 10 to 14 days after infection. These are followed by a rash of small bumps that become pus-filled sores, which can cause permanent scarring.

In severe cases, the infection causes loss of large areas of skin and bleeding. The virus can also reach the brain, leading to encephalitis, and can cause blindness by blistering the eyeballs.

When tecovirimat was tested in humans, the most common side effects it caused were headache, nausea and abdominal pain, the F.D.A. said.

Results of testing by Siga Technologies were published in the New England Journal of Medicine on July 5.

The F.D.A. gave Siga several valuable incentives toward its application for approval, including fast-track and priority review designations.

http://bit.ly/2uFfwXE

Why Do Some People Hate the Taste of Beer?

If the thought of sipping a beer is gag-inducing, you're not alone. But even if you're in good company, it begs the question: Why do some people hate the taste of beer?

By Joanna Fantozzi, Live Science Contributor | July 14, 2018 08:12am ET

The answer comes down to genetics, which influences how our brains process bitter-tasting and cold beverages.

What's more, it turns out that beer's bitter taste triggers evolutionary wiring designed to keep us away from potentially dangerous food and drink, and this trigger is stronger in some people than it is in others.

But first, let's start with beer's bitter taste. As you may remember from science class, there are five types of taste cells within our taste buds that help us perceive salty, sweet, sour, umami (savory) and

bitter flavors. Once the taste buds identify specific flavors, taste receptors send this data via nerves to the brain stem.

"If you think of a receptor as a lock, then whatever it binds to is a specific key," Dr. Virginia Utermohlen Lovelace, an associate professor emeritus of nutritional sciences at Cornell University in Ithaca, New York, told Live Science. "The cell to which that receptor is attached sends a message to the brain to say, 'Oooh this is bitter!'"

There are a whopping 25 different types of taste receptors for bitterness in the human body. In comparison, there are only two different kinds of salt receptors. Meanwhile, beer's bitterness largely comes from hops. The alpha and beta acids found in hops, as well as the low concentrations of ethanol in beer, bind to three of these 25 bitter receptors, signaling a strong bitter taste to the brain when you take a sip of lager, Lovelace said.

But what makes bitter flavors hard to swallow? The next time your friends delight in introducing you to a new craft IPA, you can tell them that their singular tastes are in direct opposition to evolutionary instinct. Humans actually evolved bitter taste receptors for our own safety — to identify poisonous foods that could be harmful.

"Bitter taste is considered a warning system for poisoning," researchers in a 2009 study published in the journal Chemosensory Perception concluded. "Many toxic compounds appear to taste bitter; yet, toxicity seems not to be directly correlated with the taste threshold concentrations of bitter compounds," the researchers said.

In other words, just because something tastes bitter and makes you wince, that doesn't automatically mean that beer (or any other bitter food or beverage) is out to kill you.

This brings us to the science behind genetic functional polymorphisms, also known as genetic variations. Since there are so many taste receptors for bitterness, it's safe to say that bitter flavors — how we perceive them and how much we can tolerate them — have a plethora of inheritable genetic possibilities.

According to a 2017 study published in the journal Scientific Reports, TAS2R16 alone (which is one of the 25 bitter receptors in the human body) has 17 polymorphisms, including a variant that is associated with alcohol dependence.

Lovelace explained that one of the easiest indicators of bitter sensitivity is the number of taste buds you have in your mouth. The more taste buds you have, the more likely you are to detest hoppy beers.

Bitter receptors, however, are not the only variants at play. The carbonation in beer turns on our "cold" receptors (the same temperature receptors that make minty gum taste cold and cinnamon taste hot). Cold receptors have genetic variations too, so while you may not be sensitive to the bitterness of beer, the receptors that signal coldness might also make beer seem unappealing, Lovelace said.

If you're sensitive to the bitterness in beer or other alcohol, there are countermeasures to help "drown out" the strength of the bitter receptors, she noted.

"Sweet and salty foods can help turn off the effects of the bitter receptors, which is why we have beer nuts and why we drink tequila with salt!" Lovelace said. "When you cut away the bitter, you're more likely to receive the specifics of the flavors underneath."