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'Phubbing' can threaten our basic human needs, research shows

Ignoring someone you're with in a social setting to concentrate on your mobile phone 'phubbing' can have a negative effect on relationships

New research has shown that ignoring someone you're with in a social setting to concentrate on your mobile phone - called 'phubbing' - can have a negative effect on relationships by threatening our basic human need to belong.

Psychologists from the University of Kent studied the effect on individuals of being phubbed in a one-to-one social situation.

They found that increased phubbing significantly and negatively affected the way the person being phubbed felt about their interaction with the other person.

Researchers Varoth Chotpitayasunondh and Professor Karen Douglas, of Kent's School of Psychology, considered phubbing a specific form of social exclusion that threatens people's fundamental human needs: belonging, self-esteem, meaningful existence and control. Their study involved 153 participants who were asked to view an animation of two people having a conversation and imagine themselves as one of them. Each participant was assigned to one of three different situations: no phubbing, partial phubbing or extensive phubbing.

The results showed that, as the level of phubbing increased, people experienced greater threats to their fundamental needs. They also perceived the communication quality to be poorer, and the relationship to be less satisfying. The results also showed that phubbing affected the need to belong in particular, which explained the overall negative effects on social interaction.

Unlike other, more well-studied forms of social exclusion, phubbing can take place anywhere and at any time as someone reaches for their phone and ignores their conversation partner, the researchers point out.

The study, entitled The effects of 'phubbing' on social interaction (Varoth Chotpitayasunondh & Karen M. Douglas) is published in the Journal of Applied Social Psychology. See: https://onlinelibrary.wiley.com/doi/full/10.1111/jasp.12506

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Children with autism and their younger siblings less likely to be fully vaccinated

Children with autism and their younger siblings are less likely to be fully vaccinated than the general population

Children with autism and their younger siblings are significantly less likely to be fully vaccinated than the general population, according to new Kaiser Permanente research published today in JAMA Pediatrics.

"In this large and comprehensive study, we found that after children received an autism diagnosis, the rates of vaccination were significantly lower when compared with children of the same age who did not have an autism diagnosis," said lead author Ousseny Zerbo, PhD, postdoctoral fellow with the Kaiser Permanente Northern California Division of Research.

The retrospective matched cohort study, "Vaccination Patterns in Children After Autism Spectrum Disorder Diagnosis and in Their Younger Siblings," included more than 3,700 children with autism spectrum disorders diagnosed by 5 years of age, and nearly 500,000 children without ASD born between Jan. 1, 1995 and Sept. 30, 2010; and their respective younger siblings, born between Jan. 1, 1997 and Sept. 30, 2014.

The researchers reviewed whether the children received vaccines recommended by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices. The data were drawn from six sites participating in the CDC's Vaccine Safety Datalink: Kaiser Permanente locations in California, Colorado, Oregon and Washington, and Marshfield Clinic in Wisconsin.

"There were large disparities in vaccination rates between children with and without autism spectrum disorders, as well as between their siblings, across all age groups and after adjusting for important confounding

factors," said senior author Nicola Klein, MD, PhD, director of the Kaiser Permanente Vaccine Study Center.

For example, among children aged 7 years or older, 94 percent of those without an ASD received all vaccines recommended between 4 and 6 years of age, compared with 82 percent of those with an ASD; and for the measles, mumps, rubella (or MMR) vaccine, 96 percent of those without an ASD were vaccinated, compared with 84 percent of those with an ASD.

In addition, the proportion of children who were fully vaccinated with the recommended vaccines was also lower among younger siblings of children with ASD compared with younger siblings of children without ASD. For example, for vaccines recommended between one and 11 months, 73 percent of younger siblings of children with ASD were fully vaccinated compared to 85 percent of younger siblings of children without ASD.

"Numerous scientific studies have reported no association between childhood vaccination and the incidence of autism spectrum disorders," said co-author Frank DeStefano, MD, MPH, Immunization Safety Office, Centers for Disease Control and Prevention. "Nonetheless, this new study suggests that many children with autism and their younger siblings are not being fully vaccinated.

"We need to better understand how to improve vaccination levels in children with autism spectrum disorder and their siblings, so they can be fully protected against vaccine-preventable diseases."

This study was funded by the Centers for Disease Control and Prevention.

In addition to Dr. Klein, Zerbo and Dr. DeStefano, co-authors were Sharareh Modaressi, MD, MPH, Kristin Goddard, MPH, Edwin Lewis, MPH, Bruce H. Fireman, MA, of the Kaiser Permanente Vaccine Study Center, Oakland, California; Matthew F. Daley, MD, Kaiser Permanente Institute for Health Research, Denver; Stephanie A. Irving, MHS, Kaiser Permanente Center for Health Research, Portland, Oregon; Lisa A. Jackson, MD, MPH, Kaiser Permanente Washington Health Research Institute, Seattle; James G. Donohue, DVM, PhD, Marshfield Clinic Research Institute, Wisconsin; Lei Qian PhD, Darios Getahun, MD, PhD, Kaiser Permanente Department of Research and Evaluation, Pasadena, California; and Michael M. McNeil, MD, MPH, Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta.

https://wb.md/2GyvSsV

A Conspiracy of Silence on Physician Suicide

A Call for a Physician Safety Movement

George D. Lundberg, MD

Hello and welcome. I'm Dr George Lundberg, and this is At Large at Medscape.

We talk a lot about patient safety, albeit perhaps not enough. But who talks about physician safety? Another young resident physician recently jumped off a 33-story building in New York City to her death.[1] Her body goes to the medical examiner's office, whose job is to officially determine the cause of death (presumably blunt force trauma) and the manner of death (homicide, suicide, accidental, undetermined). But who performs the psychological autopsy, the institutional autopsy, the sociologic autopsy, the supervisorial autopsy, the autopsy of the failed support network? Who performs the root-cause analysis of this suicide? Who apologizes to the corpse and the survivors and those people, institutions, and other supporters who have invested so much time, effort, and resources into this accomplished physician who is suddenly gone, forevermore unproductive? Where is the early warning system to prevent such catastrophes from being repeated? Where is the study of "near misses"—unsuccessful suicide attempts or serious suicidal ideation by physicians? And where are the interventions when they really matter? I propose a physician safety movement. It can begin as an initiative, just as the patient safety movement started more than 25 years ago.

Physician burnout is rampant. Physicians seeking early retirement seem epidemic. Psychiatric drug use by medical students and young physicians is rife.[2] Enough American physicians to fill the graduating classes of two medium-sized medical schools are lost annually to suicide.[3]

Where should the physician safety movement be nested? The obvious answer is: in all branches of organized medicine. Perhaps an added function within impaired physician programs could include 24/7

troubled physician hotlines to seek help. Hospital medical staffs, student health offices, residency programs, and employee assistance programs all should have a role.

It is time to change the culture of "let's blame and shame the physician" to a culture of valuing and nurturing, prevention, intervention, and treatment as needed.

That's my opinion. I am Dr George Lundberg, at large at Medscape.

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http://bit.ly/2Gjmi9Q

Portable device detects severe stroke in seconds with 92 percent accuracy

A new device worn like a visor can help emergency medical personnel detect stroke requiring comprehensive care within seconds and with greater than 90 percent accuracy.

A new device worn like a visor can detect emergent large-vessel occlusion in patients with suspected stroke with 92 percent accuracy, report clinical investigators at the Medical University of South Carolina (MUSC), Mount Sinai, the University of Tennessee Health Sciences Center and elsewhere in an article published online on March 6, 2018, in the *Journal of Neurointerventional Surgery*. Patients with large-vessel occlusions can then be routed to a Comprehensive Stroke Center with endovascular capabilities. In contrast, a standard physical examination achieved only 40 to 89 percent accuracy in identifying patients with large-vessel occlusion who could benefit from endovascular therapy.

The volumetric impedance phase shift spectroscopy (VIPS) device (Cerebrotech VisorTM, Cerebrotech Medical Systems, Pleasanton, CA) works by sending low-energy radio waves through the brain that change frequency when passing through fluids. Such waves are reflected back through the brain and then detected by the device. When a patient is having a severe stroke, the brain's fluids will change, producing an asymmetry in the radio waves detected by the VIPS device. The greater the asymmetry, the more severe the stroke.

Endovascular therapy within 24 hours is the standard of care for emergent large-vessel occlusion, but the chance of achieving a good outcome decreases by approximately 20 percent for each hour that passes before treatment.

The researchers hope that the device will save valuable time -- especially important in stroke where time is brain -- when it is deployed with emergency medical personnel in the field. This is because the accuracy of the device simplifies the decision made by emergency personnel about where to take patients first, according to Raymond D. Turner, M.D., professor of neurosurgery and chief of the Neuroscience Integrated Center of Clinical Excellence at MUSC. Turner served as principal investigator for MUSC in the VIPS for the Non-Invasive Detection of Hemispheric Bioimpedance Asymmetry in Severe Brain Pathology (VITAL) study reported in the article.

"Transfer between hospitals takes a lot of time," said Turner. "If we can give the information to emergency personnel out in the field that this is a large-vessel occlusion, that should change their thought process in triage as to which hospital they go to."

In the study, the VIPS device was deployed with emergency medical personnel in regions served by five Comprehensive Stroke Centers equipped with the endovascular capabilities to treat large-vessel occlusions that underlie severe stroke. Their goal was to use the device to accurately identify severe stroke and then compare the results to established physical examination methods practiced by emergency personnel such as the Prehospital Acute Stroke Severity Scale.

Both healthy participants and patients with suspected stroke were evaluated by emergency personnel using the VIPS device. Three readings were taken and averaged -- a process that takes about 30

seconds. Patients were also later evaluated by neurologists who provided definitive diagnoses using neuroimaging.

Compared to the neurologists' diagnoses, the device displayed 92 percent specificity -- the ability to detect the difference between patients with severe stroke and those with other conditions such as mild stroke or healthy participants with no brain pathology. This places the VIPS device above standard physical examination tools used by emergency personnel that display specificity scores between 40 and 89 percent.

The VIPS device is made by Cerebrotech Medical Systems, which paid consultants to analyze the neuroimaging data independently. The neuroimaging data was needed to teach the VIPS device which radio waves were indicative of stroke. Yet the consultants did not have access to the VIPS radio wave data during their review of the images, thereby eliminating the potential of the consultants to choose data that might artificially inflate the device's accuracy. It is also not clear how the device would work for patients with cranial implants, as metal interferes with the device's operating radio frequencies.

The device's success may be found in its ability to give emergency personnel a clear answer as to whether a patient is experiencing a severe stroke. The VIPS device requires very little training to operate compared to that required to learn standard emergency examination skills, thereby reducing the possibility of human error during emergency diagnosis.

In their next steps, the researchers are undertaking the VITAL 2.0 study to determine if the VIPS device can use complex machine learning algorithms to teach itself how to discriminate between minor and severe stroke without the help of neurologists. If so, the VIPS device could have widespread clinical implications, helping emergency personnel decide whether to take a patient to a comprehensive stroke center or a primary stroke center for treatment.

Turner likens the use of the VIPS device in detecting severe stroke to the use of electrocardiography (ECG) to definitively detect acute myocardial infarction. He predicts that the device has the potential to be used widely by emergency personnel but also to appear in other public spaces. "This could potentially be something like a defibrillator," said Turner. "You can find out if a patient is having a stroke, just like you can put a defibrillator on a patient to see if they're having a heart attack."

This study was funded by Cerebrotech Medical Systems.

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Canadian neuroscientists say daily ibuprofen can prevent Alzheimer's disease

Dr. Patrick McGeer, has successfully carried out studies suggesting that, if started early enough, a daily regimen of the non-prescription NSAID ibuprofen can prevent the onset of Alzheimer's disease

VANCOUVER, BC: A Vancouver-based research team led by Canada's most cited neuroscientist, Dr. Patrick McGeer, has successfully carried out studies suggesting that, if started early enough, a daily regimen of the non-prescription NSAID (nonsteroidal anti-inflammatory drug) ibuprofen can prevent the onset of Alzheimer's disease. This means that by taking an over-the-counter medication, people can ward off a disease that, according to Alzheimer's Disease International's World Alzheimer Report 2016, affects an estimated 47 million people worldwide, costs health care systems worldwide more than US$818 billion (1) per year and is the fifth leading cause of death in those aged 65 or older.

The Alzheimer's Association estimates that there are more than 5 million cases in the United States alone, with a new case being identified every 66 seconds. The annual cost to the country in 2017 is estimated have been $259 billion, with that figure predicted to potentially rise to $1.1 trillion by 2050. (2)

Dr. McGeer, who is President and CEO of Vancouver-based Aurin Biotech, and his wife, Dr. Edith McGeer, are among the most cited neuroscientists in the world. Their laboratory is world-renowned for their 30 years of work in neuroinflammation and neurodegenerative diseases, particularly Alzheimer's disease. A paper detailing Dr. McGeer's most recent discoveries were published Friday in the

prestigious *Journal of Alzheimer's Disease*. (*Journal of Alzheimer's Disease 62* (pp. 1219-1222).

In 2016, Dr. McGeer and his team announced that they had developed a simple saliva test that can diagnose Alzheimer's disease, as well as predict its future onset. The test is based on measuring the concentration of the peptide amyloid beta protein 42 (Abeta42) secreted in saliva. In most individuals, the rate of Abeta 42 production is almost exactly the same regardless of sex or age. However, if that rate of production is two to three times higher, those individuals are destined to develop Alzheimer's disease. That is because Abeta42 is a relatively insoluble material, and although it is made everywhere in the body, deposits of it occur only in the brain, causing neuroinflammation, which destroys neurons in the brains of people with Alzheimer's disease.

Contrary to the widely held belief that Abeta 42 is made only in the brain, Dr. McGeer's team demonstrated that the peptide is made in all organs of the body and is secreted in saliva from the submandibular gland. As a result, with as little as one teaspoon of saliva, it is possible to predict whether an individual is destined to develop Alzheimer's disease. This gives them an opportunity to begin taking early preventive measures such as consuming non-prescription non-steroidal drugs (NSAIDs) such as ibuprofen.

"What we've learned through our research is that people who are at risk of developing Alzheimer's exhibit the same elevated Abeta 42 levels as people who already have it; moreover, they exhibit those elevated levels throughout their lifetime so, theoretically, they could get tested anytime," says Dr. McGeer. "Knowing that the prevalence of clinical Alzheimer's Disease commences at age 65, we recommend that people get tested ten years before, at age 55, when the onset of Alzheimer's would typically begin. If they exhibit elevated Abeta 42 levels then, that is the time to begin taking daily ibuprofen to ward off the disease.

"Unfortunately, most clinical trials to date have focused on patients whose cognitive deficits are already mild to severe, and when the therapeutic opportunities in this late stage of the disease are minimal. Consequently, every therapeutic trial has failed to arrest the disease's progression. Our discovery is a game changer. We now have a simple test that can indicate if a person is fated to develop Alzheimer's disease long before it begins to develop. Individuals can prevent that from happening through a simple solution that requires no prescription or visit to a doctor. This is a true breakthrough since it points in a direction where AD can eventually be eliminated."

***About Aurin Biotech**:*

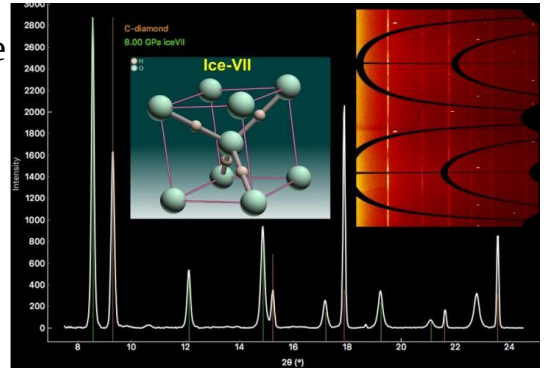
Aurin Biotech is a private, early stage Vancouver company which develops agents for the treatment of Alzheimer's disease and other chronic degenerative diseases. The company was founded in 2012 to advance the discoveries made by the McGeer and Associates Laboratory at the University of British Columbia (UBC). For more information, visit http://www.aurinbiotech.com

http://bit.ly/2IbrtJD

Argonne's powerful X-rays key to confirming water source deep below Earth's surface

Researchers identify a form of water which was trapped within diamonds that crystallized deep in the Earth's mantle

A study published in *Science* last week relies on extremely bright X-ray beams from the U.S. Department of Energy's (DOE) Advanced Photon Source (APS) at Argonne National Laboratory to confirm the presence of naturally occurring water at least 410 kilometers below the Earth's surface. This exciting discovery could change our understanding of how water circulates deep in the Earth's mantle and how heat escapes from the lower regions of our planet.



***Using Argonne's Advanced Photon Source, researchers identified a form of water known as Ice-VII, which was trapped within diamonds that crystallized deep in the Earth's mantle.* Image courtesy of the University of Chicago.**

Through use of the APS, a DOE Office of Science User Facility, the researchers identified a form of water known as Ice-VII, which was

trapped within diamonds that crystallized deep in the Earth's mantle. This is the first time Ice-VII has been discovered in a natural sample, making the compound a new mineral accepted by the International Mineralogical Association.

"[T]hanks to the amazing technical capabilities of the APS, this team of researchers was able to pinpoint and study the exact area on the diamonds that trapped the water." -- Stephen Streiffer, Argonne Associate Laboratory Director for Photon Sciences and Director of the APS

This study is just the latest in a long line of research projects at the APS that have shed light on the composition and makeup of the deep Earth, regions that humans cannot explore directly. Instead, scientists used high-powered X-ray beams to analyze inclusions in diamonds, which were formed in the deep Earth, so as to come to conclusions about what happened in those regions.

In other geological studies at the APS, researchers have used high-pressure chambers and lasers to put materials under extreme pressure and temperatures for study, literally recreating the conditions deep below the Earth's surface to understand what happens there.

"In this study, thanks to the amazing technical capabilities of the APS, this team of researchers was able to pinpoint and study the exact area on the diamonds that trapped the water," said Stephen Streiffer, Argonne Associate Laboratory Director for Photon Sciences and Director of the APS. "That area was just a few microns wide. To put that in context, a human hair is about 75 microns wide.

"This research, enabled by partners from the University of Chicago and the University of Nevada, Las Vegas, among other institutions, is just the latest example of how the APS is a vital tool for researchers across scientific disciplines," he said.

In this case, researchers analyzed rough, uncut diamonds mined from regions in China and Africa. Using an optical microscope, mineralogists first identified inclusions, or impurities, which must have formed when the diamond crystallized. Most diamonds have inclusions caused by a sample of other elements or compounds that were trapped as the carbon fused into a diamond.

"We are interested in those inclusions because they tell us about the chemical composition and conditions in the deep Earth when the diamond was formed," said Antonio Lanzirotti, a University of Chicago Research Associate Professor and a co-author on the study.

After many millions of years, diamonds are pushed up from the Earth's mantle to the surface, where many are mined for jewelry and industrial purposes.

To positively identify the composition of the inclusions, mineralogists needed a stronger instrument. That's where University of Chicago's GeoSoilEnviroCARS's (GSECARS) beamlines at the APS came in. GSECARS operates a suite of instruments at the APS dedicated to frontier research in the Earth sciences.

Oliver Tschauner, the lead author on the study and a mineralogist at University of Nevada in Las Vegas, worked with the GSECARS group to probe more than a dozen diamonds that he had identified with this inclusion.

Because of the pressure required for diamonds to form, the scientists know that these specimens formed between 410 and 660 kilometers below the Earth's surface.

Thanks to the very high brightness of the APS X-rays, which are a billion times more intense than conventional X-ray sources, scientists can determine the molecular or atomic makeup the specimens that are only micrometers across.

When the focused beam of X-rays hits the molecules of the specimen, they scatter. Pictures or images taken of this scattering pattern are then analyzed, as each compound or molecule shows a unique pattern.

What the team identified in this study was surprising: water, in the form of ice.

The composition of the water is the same as the water that we drink and use every day, but in a cubic crystalline form, the result of the extremely high pressure of the diamond.

This form of water, Ice-VII, was created in the lab decades ago, but this study was the first to confirm that it also forms naturally.

"This wasn't easy to find," said Vitali Prakapenka, a University of Chicago Research Professor and a co-author of the study, who said that the team used high-resolution diffraction techniques to get the right scans, or images, of the Ice-VII. "People have been searching for this kind of inclusion for a long time."

The researchers said the significance of the study is profound because it shows that flowing water is present much deeper below the Earth's surface than originally thought. Going forward, the results raise a number of important questions about how water is recycled in the Earth and how heat is circulated.

Tschauner has said the discovery can help scientists create new, more accurate models of what's going on inside the Earth, specifically how and where heat is generated under the Earth's crust. This may help scientists better understand one of the driving mechanisms for plate tectonics.

For now, the GSECARS team is wondering whether the mineral Ice-VII will be renamed, now that it is officially a mineral. This is not the first mineral to be identified thanks to research done at the APS beamlines managed by GSECARS: Bridgmanite, the Earth's most abundant mineral and a high-density form of magnesium iron silicate, was researched extensively at the APS before it was named. Tschauner was a lead author on that study, too.

Other GSECARS team members who are co-authors of the Science *journal article, "Ice-VII inclusions in diamonds: Evidence for aqueous fluid in Earth's deep mantle," are Eran Greenberg, Dongzhou Zhang and Matt Newville.*

In addition to the University of Chicago and the University of Nevada, Las Vegas, other institutions cited in the study include the California Institute of Technology, China University of Geosciences, the University of Hawaii at Manoa and the Royal Ontario Museum, Toronto.

Data was also collected at Carnegie Institute of Washington's High Pressure Collaborative Access Team at the APS and the Advanced Light Source, a DOE Office of Science User Facility.

The research was funded, in part, by the U.S. Department of Energy's Office of Science (Office of Basic Energy Sciences) and the National Science Foundation.

http://bit.ly/2pMyYPI

This Medieval Mother Had a Gruesome 'Coffin Birth' After Medieval Brain Surgery

In a cramped stone grave beneath the medieval town of Imola, Italy, a 1,300-year-old woman lies dead with a hole in her skull and a fetus between her legs.

By Brandon Specktor, Senior Writer | March 26, 2018 04:50pm ET

A mysterious, medieval skeleton discovered in Italy shows signs of a "coffin birth" and primitive brain surgery. **Pasini et al./World Neurosurgery/Elsevier**

The fetus, now just a collection of tiny bones trailing below the mother's skeletal pelvis, was likely delivered in the grave through a phenomenon called "coffin birth" — essentially, when an unborn child is forced out of its mother's womb by posthumous gases after both mother and child have died.

It's a rare sight in archaeology — but rarer still might be the peculiar circular wound bored into the mother's skull.

Archaeologists from the University of Ferrara and University of Bologna attempted to unwind the mystery of this mother's and child's deaths in a new study published in the May 2018 issue of the journal *World Neurosurgery*. According to the researchers, these remarkable skeletal remains may present a rare Middle Ages example of a primitive brain-surgery technique called trepanation. This procedure involved drilling or scraping a hole into the patient's skull to relieve pressure and (theoretically) a whole host of medical ailments. In this case, sadly, that relief may not have been enough.

"Our hypothesis is that the pregnant woman incurred preeclampsia or eclampsia [two pregnancy conditions involving high blood pressure] and she was treated with a frontal trepanation to relieve the intracranial pressure," the researchers wrote in the new paper.

"Despite the intervention, she did not survive, and died with the fetus in her womb."

Reading human remains

The grave in question was discovered in 2010, during an excavation of the town of Imola in northern Italy, near the city of Bologna.

The skeletal remains of the mother were found among several other burials that researchers dated to the Lombard period (lasting from the 7th to 8th century A.D.). Because the woman's remains were found face-up and surrounded by cut stones, the researchers concluded that she was intentionally buried and likely hadn't been moved or altered (before now).

A closeup of the skeleton's pelvis reveals the bones of a partially-delivered fetus. This "coffin birth" likely occurred after posthumous gasses built up inside the dead mother's body, eventually pushing the unborn baby partway out. **Pasini et al./World Neurosurgery/Elsevier**

The woman was likely in her mid-20s to 30s and appeared to be nearing the end of her pregnancy when she was buried. Although the baby's sex was impossible to determine, leg measurements suggested that it was near the 38th week of gestation.

At the top of the woman's skull, researchers detected a small, circular hole measuring 4.6 millimeters (0.2 inches) in diameter — a little smaller than the diameter of a pencil. The puncture was precise and round, suggesting that it didn't result from violence or a single, extreme blow, the researchers wrote. Rather, the wound appeared consistent with repetitive drilling directly into the bone — a hallmark of some trepanation surgeries, the study said.

Because the skull showed early signs of healing near the wound, it was likely that the hole was inflicted at least one week before the woman's death, not posthumously, the scientists said. The researchers also found a linear cut mark a few centimeters above the hole, measuring less than 3 mm (0.12 inches) in length. This, they said, could indicate an area where the scalp was cut or peeled away to prepare the skull for surgery.

A rare cut

The researchers concluded that there was suitable evidence to suggest the wound in the woman's head was caused by a medical procedure similar to trepanation.

Why drill into a pregnant woman's head weeks before she's due?

One possible reason was to reduce symptoms related to pregnancy, such as high blood pressure, the researchers said.

The mother's skull showed a small, circular wound, likely caused during primitive brain surgery called trepanation. A linear cut mark (bottom left) may show where her scalp was peeled back pre-surgery. **Pasini et al./World Neurosurgery/Elsevier**

"Because trepanation was once often used in the treatment of hypertension to reduce blood pressure in the skull, we theorized that this lesion could be associated with the treatment of a hypertensive pregnancy disorder, such as preeclampsia," the researchers wrote.

"This finding is one of the few documented cases of trepanation in the European early Middle Ages, and the only one featuring a pregnant woman in association with a postmortem fetal-extrusion phenomenon."

While trepanation wounds have been documented in more than 1,500 skulls dating to the Neolithic period, this possible example from Middle Ages Italy remains a unique mystery.

Further study is required to help answer how and why the surgery was conducted, and why similar examples are so hard to find.

https://nyti.ms/2GlXLkM

For Many Strokes, There's an Effective Treatment. Why Aren't Some Doctors Offering It?

Principal investigator of a clinical trial that found an effective treatment for stroke still finds himself explaining the data to doubters in the medical community two decades later.

By GINA KOLATA MARCH 26, 2018

It was one of those findings that would change medicine, Dr. Christopher Lewandowski thought.

For years, doctors had tried — and failed — to find a treatment that would preserve the brains of stroke patients. The task was beginning to seem hopeless: Once a clot blocked a blood vessel supplying the brain, its cells quickly began to die. Patients and their families could only pray that the damage would not be too extensive.

But then a large federal clinical trial proved that a so-called clot-buster drug, tissue plasminogen activator (T.P.A.), could prevent brain injury after a stroke by opening up the blocked vessel. Dr. Lewandowski, an emergency medicine physician at Henry Ford Health System in Detroit and the trial's principal investigator, was ecstatic.

"We felt the data was so strong we didn't have to explain it" in the published report, he said.

He was wrong. That groundbreaking clinical trial concluded 22 years ago, yet Dr. Lewandowski and others are still trying to explain the data to a powerful contingent of doubters.

The skeptics teach medical students that T.P.A.is dangerous, causing brain hemorrhages, and that the studies that found a benefit were deeply flawed. Better to just let a stroke run its course, they say.

It's a perspective with real-world consequences. Close to 700,000 patients have strokes caused by blood clots each year and could be helped by T.P.A. Yet up to 30 percent of stroke victims who arrive at hospitals on time and are perfect candidates for the clot-buster do not receive it.

The result: paralysis and muscle weakness; impaired cognition, speech or vision; emotional and behavioral dysfunction; and many other permanent neurological injuries.

Stroke treatment guidelines issued by the American Heart Association and the American Stroke Association strongly endorse T.P.A. for patients after they've been properly evaluated. But treatment must start within three hours (in some cases, four-and-a-half hours) of the stroke's onset, and the sooner, the better.

A number of medical societies also endorse the treatment as highly effective in reducing disability. The drug can cause or exacerbate cerebral hemorrhage, or bleeding in the brain — a real risk. But in most stroke patients it prevents brain injury, and in any event, rates of cerebral hemorrhage have declined as doctors have gained experience over the years.

Without treatment, "many patients end up permanently disabled," said Dr. Gregg C. Fonarow, a cardiologist at the University of California, Los Angeles. "The stroke neurologists who are involved in chronic care see the devastating consequences." "For some reason, the emergency medicine doctors are not factoring this in," he added.

While the vocal disbelievers are a minority, it is increasingly easy for them to spread their message on social media, said Dr. Edward C. Jauch, a professor of neurosciences at the Medical University of South Carolina.

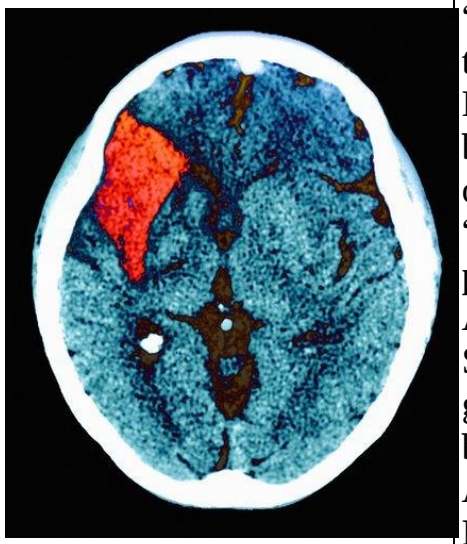
"The way information and opinion is now communicated to the younger generation of physicians is much more through web and social media and less through peer review journals, journal clubs or live debates," Dr. Jauch said.

Dr. Charles R. Wira III, a professor of emergency medicine at Yale, said that when he talked to residents about T.P.A., they often start citing blogs and podcasts "as the divine word for why T.P.A. is harmful," he said. "They have not read the articles or practice guidelines."

Skepticism has spread around the world, Dr. Jauch said, and he has come to expect naysayers wherever he goes. In Saudi Arabia, where he

was lecturing at a conference, a Saudi doctor said over dinner that he simply did not believe in T.P.A.

A leader of the skeptical contingent, Dr. Jerome Hoffman, an emergency medicine specialist and emeritus professor at U.C.L.A., believes that while the initial trial and a second one were positive, both were flawed. He reviewed the raw data from the federal study and concluded that more patients who got T.P.A. had the least severe type of stroke and fewer had the most severe type. The treatment and control groups were dissimilar — that is, those getting T.P.A. were less badly affected from the start. Experts disagree with this analysis.



A CT scan of a stroke patient. The brain tissue that died from reduced blood flow is in red. **Zephyr/Science Source**

And 11 other studies did not show a benefit, Dr. Hoffman claims. But supporters note that those studies were meant to investigate whether T.P.A. might help patients with more severe strokes or those outside the recommended window of time.

The failure of those efforts, they say, does not mean T.P.A. cannot help patients like those in the original clinical trials.

A charismatic, riveting speaker, Dr. Hoffman has given educational courses across the country and sold informational tapes expounding his theory. And his influence has spread.

At U.C.L.A., he said in an interview, he has spoken to stroke patients and their families even as their medical teams headed into the emergency room. He has told the patients that although the stroke team would strongly recommend T.P.A., there actually was debate over whether the treatment benefits patients in the long term.

In addition, no study suggested that a clot-buster was lifesaving, he told them, and it may cause bleeding in the brain in a small number of patients.

"In my experience, almost no one — after hearing a neutral version and then a positive version — chose T.P.A.," Dr. Hoffman said.

Dr. Hoffman said he has debated renowned neurologists about the benefits of T.P.A. at several meetings. Afterward, audiences voted overwhelmingly against the drug.

"This is not a testament to any debating skill of mine, but reflects how people react when they are shown the actual evidence," he said.

At Sierra Vista Regional Medical Center in San Luis Obispo, Calif., Dr. Scott Bisheff, an emergency medical physician, tells patients there is great uncertainty about whether T.P.A. helps or harms. If it caused bleeding in a patient's brain, the consequences could be catastrophic.

About half of his stroke patients decline the treatment, Dr. Bisheff said.

For neurologists, the worst scenario by far is the patient who is never even asked if he or she wants the clot-buster. At Yale, Dr. Wira said, patients sometimes are transferred from community hospitals where they have not received T.P.A. Usually, it's far too late to try.

Dr. Wira and other staff do not tell the family about the missed opportunity. "We try not to raise issues that may lead to litigation," he said.

But sometimes family members cannot help knowing what went on. It happened to Dr. Lewandowski.

About a decade ago, Dr. Lewandowski was at work when he got a call that his father had had a stroke — his right side was paralyzed. But his father had gotten to the hospital within 45 minutes, well inside the window to receive T.P.A.

Dr. Lewandowski told his mother to make the family's wishes very clear. They wanted the emergency room doctor to give the clot-buster to his dad. The doctor refused.

"He told my mom that he doesn't believe in the drug and he is not giving it. He doesn't care who I am," Dr. Lewandowski said.

"I got in my car and drove 400 miles to the hospital," he recalled. But by the time he got there, it was too late. The treatment window had closed.

His father had a facial droop and slurred speech. His right arm and right leg flopped about uselessly. His stroke scale was 7, moderately disabling, but he survived for a few more years.

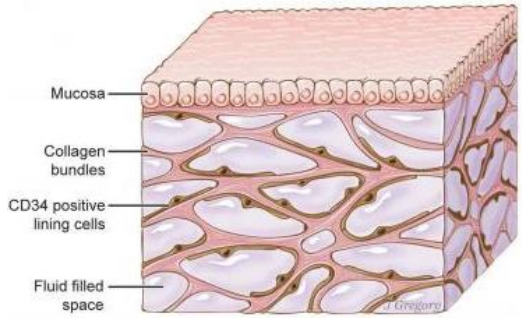
"It was very difficult for me personally," Dr. Lewandowski recalled. "I had spent so much of my professional life working on this treatment. It actually worked." "I felt like I had let my dad down."

http://bit.ly/2GfXqbL

Newfound 'organ' had been missed by standard method for visualizing anatomy

Researchers have identified a previously unknown feature of human anatomy with implications for the function of all organs, most tissues and the mechanisms of most major diseases.

Published March 27 in Scientific Reports, a new study co-led by an NYU School of Medicine pathologist reveals that layers of the body long thought to be dense, connective tissues - below the skin's surface, lining the digestive tract, lungs and urinary systems, and surrounding arteries, veins, and the fascia between muscles - are instead interconnected, fluid-filled compartments.



A newfound organ, the interstitium, is seen here beneath the top layer of skin, but is also in tissue layers lining the gut, lungs, blood vessels, and muscles. The organ is a body-wide network of interconnected, fluid-filled compartments supported by a meshwork of strong, flexible proteins. Illustration by Jill Gregory. **Printed with permission from Mount Sinai Health System, licensed under CC-BY-ND.**

This series of spaces, supported by a meshwork of strong (collagen) and flexible (elastin) connective tissue proteins, may act like shock absorbers that keep tissues from tearing as organs, muscles, and vessels squeeze, pump, and pulse as part of daily function.

Importantly, the finding that this layer is a highway of moving fluid may explain why cancer that invades it becomes much more likely to spread. Draining into the lymphatic system, the newfound network is the source of lymph, the fluid vital to the functioning of immune cells that generate inflammation. Furthermore, the cells that reside in the space, and collagen bundles they line, change with age, and may contribute to the wrinkling of skin, the stiffening of limbs, and the progression of fibrotic, sclerotic and inflammatory diseases.

The field has long known that more than half the fluid in the body resides within cells, and about a seventh inside the heart, blood vessels, lymph nodes, and lymph vessels. The remaining fluid is "interstitial," and the current study is the first to define the interstitium as an organ in its own right, and as one of the largest of the body, say the authors.

The researchers say that no one saw these spaces before because of the medical field's dependence on the examination of fixed tissue on microscope slides, believed to offer the most accurate view of biological reality. Scientists prepare tissue this examination by treating it with chemicals, slicing it thinly, and dying it to highlight key features. The "fixing" process makes vivid details of cells and structures, but drains away any fluid. The current research team found that the removal of fluid as slides are made causes the connective protein meshwork surrounding once fluid-filled compartments to pancake, like the floors of a collapsed building.

"This fixation artifact of collapse has made a fluid-filled tissue type throughout the body appear solid in biopsy slides for decades, and our results correct for this to expand the anatomy of most tissues," says co-senior author Neil Theise, MD, professor in the Department of Pathology at NYU Langone Health. "This finding has potential to drive dramatic advances in medicine, including the possibility that the direct sampling of interstitial fluid may become a powerful diagnostic tool."

The study findings are based on newer technology called probe-based confocal laser endomicroscopy, which combines the slender camera-toting probe traditionally snaked down the throat to view the insides of organs (an endoscope) with a laser that lights up tissues, and sensors that analyze the reflected fluorescent patterns. It offers a microscopic view of living tissues instead of fixed ones.

Using this technology in the fall of 2015 at Beth Israel Medical Center, endoscopists and study co-authors David Carr-Locke, MD, and Petros Benias, MD, saw something strange while probing a patient's bile duct for cancer spread. It was a series of interconnected cavities in this submucosal tissue level that not match any known anatomy.

Faced with a mystery, the endoscopists walked the images into the office of their partnering pathologist in Theise. Strangely, when Theise made biopsy slides out of the same tissue, the reticular pattern found by endomicroscopy disappeared. The team would later confirm that very thin spaces seen in biopsy slides, traditionally dismissed as tears in the tissue, were instead the remnants of collapsed, previously fluid-filled compartments.

A New Bodily Space

For the current study, the team collected tissue specimens of bile ducts during twelve cancer surgeries that were removing the pancreas and the bile duct. Minutes prior to clamping off blood flow to the target tissue, patients underwent confocal microscopy for live tissue imaging.

Once the team recognized this new space in images of bile ducts, they quickly recognized it throughout the body, wherever tissues moved or were compressed by force. The cells lining the space are also unusual, perhaps responsible for creating the supporting collagen bundles around them, say the authors. The cells may also be mesenchymal stem cells, says Theise, which are known to be capable of contributing to the formation of scar tissue seen in inflammatory diseases. Lastly, the protein bundles seen in the space are likely to generate electrical current as they bend with the movements of organs and muscles, and may play a role in techniques like acupuncture, he says.

The other first study author was Rebecca Wells of the Perelman School of Medicine at the University of Pennsylvania, who determined that the mesh in the newfound sinus was comprised of collagen and elastin bundles. Also study authors were Jason Reidy of the Electron Microscopy Lab within the Department of Pathology at NYU School of Medicine; Heather Klavan, Markus Miranda, Darren Buonocore, Susan Kornacki, and Michael Wayne of Mount Sinai Beth Israel Medical Center; and Bridget Sackey-Aboagye from the University of Pennsylvania. Carr-Locke is currently clinical director for the Center for Advanced Digestive Care at Weill Cornell Medicine. Benias is an assistant professor at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health.

This work was funded in part by a grant from the National Institutes of Health (DK081523).

http://bit.ly/2GoXahW

Antibiotics Increase Mouse Susceptibility to Dengue, West Nile, and Zika

The drugs' disruption of the microbiome makes a subsequent flavivirus infection more severe.

By Shawna Williams | March 27, 2018

It's a truism that antibiotics won't help treat a viral infection. And it now appears they could even hurt, making viral infections more severe. In a study out today (March 27) in *Cell Reports*, researchers found that when mice were treated with antibiotics and then infected with pathogens in the flavivirus family (which includes Zika, West Nile, and dengue), they fared far worse than their untreated counterparts. The authors suggest the antibiotics may have compromised the animals' immunity by altering their microbiomes.

"The clinical phenotype of the animals when they got antibiotics, compared to those that didn't, was pretty dramatic. They got a lot sicker and then they died, ultimately, of West Nile encephalitis," says Michael Diamond, an immunobiology researcher at Washington University School of Medicine in St. Louis who led the study. "And this was true

not just for West Nile virus, but also for two related viruses in the family, Zika virus and also dengue virus."

While the idea that antibiotics can modulate antiviral immunity is not new, an interesting aspect of this study is that it suggests a mechanism for that effect, says Paulo Verardi, a virologist at the University of Connecticut who was not involved in the study—namely, that changes in gut microbes affect the abundance and activity of immune cells present in the body. "What they were able to show is that they do have an impairment of this T-cell immunity, particularly the [CD8+] T-cell immunity," he tells *The Scientist*.

The question motivating the study, Diamond says, was to find out why some people get extremely sick from West Nile infections, while others come away unscathed. Genetics, age, and immune-system strength are all known to influence the severity of West Nile infection in humans, he explains, but they collectively only explain a small portion of the wide variability in symptoms. While many people who are infected experience no symptoms at all, a few become gravely ill or even die.

Previous studies by other groups had found that mice could ward off some viral infections after oral antibiotic treatments, presumably through the drugs' effects on the microbiome. But for other viruses, the medication made infections worse. To test the effect of antibiotic treatment on flavivirus infection, Diamond and his colleagues treated mice with vancomycin, neomycin, ampicillin, and metronidizole—an oral cocktail shown to deplete microbiota—for 14 days before and 14 days after injecting the animals with West Nile virus. While 80 percent of untreated mice survived for at least 21 days after infection, just one of the antibiotic-treated mice made it that long. Survival similarly plummeted even if the antibiotics were stopped either seven or three days prior to infection, and if the virus used was dengue or Zika. Treating the mice with just ampicillin, or amoxicillin plus metronidizole, also decreased survival, though not by as much as the full cocktail.

The researchers also found that the cocktail-treated mice that had not been exposed to a virus had fewer of the cells in bone marrow that give rise to immune cells. And even before infection, the treated mice had different levels of various immune cells in some of their tissues from their untreated counterparts, while other tissues were the same between the two groups. To further tease apart the effects of one class of immune cells, CD8+ T cells, which recognize and kill infected host cells and had been shown in previous studies to be key to clearing West Nile from the central nervous system, the investigators treated the cocktail-dosed mice with West Nile virus–specific effector CD8+ T cells from other animals. They found that the immune cells increased survival after West Nile infection, though not to the levels seen in mice not treated with antibiotics. This suggests that altering CD8+ T cell activity is one important way in which the microbiome affects immunity.

Nichole Broderick, who studies host-microbe interactions in *Drosophila* at the University of Connecticut and was not involved in the new work, says the tissue-specific effects the researchers saw point to considerable complexity in the factors that determine susceptibility to disease. She notes that the antibiotics could have affected antiviral immunity independently of their impact on the microbiome—a possibility the study could not rule out. Broderick suggests doing the experiment in germ-free mice could help clarify whether that's the case. "They saw that some organs had impaired [immune] response whereas others didn't," says Akiko Iwasaki, an immunologist at Yale University who has collaborated with Diamond in the past but was not involved in this study. This raises the question for future research to explore how changes in the microbiome affect particular immune-related organs. It will also be important to tease out "which bacteria is doing what," she adds, as that understanding could help in devising therapies, such as probiotics, to restore immune responses.

L. Thackray et al., "Oral antibiotic treatment of mice exacerbates the disease severity of multiple flavivirus infections," Cell Reports, doi:10.1016/j.celrep.2018.03.001, 2018.

http://bit.ly/2GoSxoe

Liver cancer caused by alcohol consumption may have worse prognosis than other forms

Study indicates patients with alcohol-related liver cancer often do not live as long as those with liver cancer not associated with alcohol consumption

A new study indicates that patients with alcohol-related liver cancer often do not live as long as patients with liver cancer that is not associated with alcohol consumption, mainly due to diagnoses at later stages. Published early online in *CANCER*, a peer-reviewed journal of the American Cancer Society, the findings indicate that efforts should be made to improve both screening for early signs of liver cancer and the management of alcohol abuse.

Liver cancer is the second leading cause of cancer-related deaths worldwide, with hepatitis B and C infections being the main causes. Alcohol abuse and non-alcoholic fatty liver disease are other dominant risk factors. Due to improvements in the treatment of hepatitis infections and increased alcohol consumption in some regions, it is likely that alcohol will become a leading cause of liver cancer in the near future. Indeed, alcohol is already the first cause of liver cancer in France and involved in 25 percent to 30 percent of diagnoses in the United States. The real US figure is likely higher as alcohol consumption is often underreported when another risk factor is present.

To compare aspects of alcohol-related and non-alcohol-related liver cancer, Charlotte Costentin, MD, of Hôpital Henri-Mondor in France, and her colleagues examined 894 patients with newly diagnosed liver cancer who were followed for 5 years; 582 patients (65 percent) had a history of chronic alcohol abuse and 312 (35 percent) did not. Investigators also recorded whether patients with alcohol-related liver cancer were abstinent or not at the time of cancer diagnosis.

A total of 601 patients had died by the time of the investigators' final analyses. Alcohol-related liver cancers were more likely to be diffuse and were detected in patients with worse liver function. Median overall survival was 9.7 versus 5.7 months in the non-alcohol-related and alcohol-related groups respectively. When investigators looked at each stage of cancer individually, however, survival was similar in patients with non-alcohol-related and alcohol-related cancer. The findings suggest that patients with alcohol-related liver cancer have a reduced overall survival mainly due to worse liver function and tumor characteristics at diagnosis.

The analysis also examined whether patients were participating in cirrhosis follow-up programs before their cancers were diagnosed. (Most people who develop liver cancer show signs of scarring, or cirrhosis, in the liver, and international guidelines recommend ultrasound every six months to detect early liver cancer in patients with cirrhosis.) Patients whose liver cancer was detected during a cirrhosis follow-up program had improved survival compared with patients whose cancer was diagnosed incidentally. This was especially pronounced in patients with non-alcohol-related liver disease or those with alcohol-related liver disease who are no longer drinking alcohol compared with non-abstinent patients. Also, non-abstinent alcoholic patients had the lowest survival in the study, even when restricting the analysis to patients involved in cirrhosis follow-up programs.

"To improve prognosis of liver cancer in the alcoholic population, efforts should be made to implement effective screening programs for both cirrhosis and liver cancer, and to improve access to alcoholism treatment services," said Dr. Costentin. "A smaller tumor burden and a better liver function at diagnosis should translate into higher rates of patients with alcohol-related liver cancer amenable to curative treatment such as tumor resection or ablation and liver transplantation."

Additional Information

Full Citation: "Hepatocellular carcinoma is diagnosed at a later stage in alcoholic patients: results of a prospective nationwide study." Charlotte E. Costentin, Abbas Mourad, Pierre Lahmek, Xavier Causse, Alexandre Pariente, Hervé Hagège, Anca Stela Dobrin, Claire Becker, Bérangère Marks, Robert Bader, Bertrand Condat, Frédéric Héluwaert, Jean François Seitz, Bruno Lesgourgues, Jacques Denis, Sylvie Deuffic-Burban, Isabelle Rosa, and Thomas Decaens on behalf of CHANGH study group. CANCER; Published Online: March 28, 2018 (DOI: 10.1002/31215). URL Upon Publication: http://doi.wiley.com/10.1002/31215

http://bit.ly/2GWmrRO

A runaway star in the Small Magellanic Cloud

Runaway" star is speeding across its galaxy at 300,000 miles per hour

Astronomers have discovered a rare "runaway" star that is speeding across its galaxy at 300,000 miles per hour (at that speed it would take about half a minute to travel from Los Angeles to New York). The runaway star (designated J01020100-7122208) is located in the Small Magellanic Cloud, a close neighbor of the Milky Way Galaxy, and is believed to have once been a member of a binary star system.

When the companion star exploded as a supernova, the tremendous release of energy flung J01020100-7122208 into space at its high speed. The star is the first runaway yellow supergiant star ever discovered, and only the second evolved runaway star to be found in another galaxy.

Observations of the yellow supergiant runaway were conducted using the large 6.5-meter Magellan telescope at Las Campanas Observatory. The Large Magellanic Cloud (companion galaxy to the Small Magellanic Cloud, not shown) is visible right above the telescope enclosure. The bright band of light from lower left to upper riht is the southern Milky Way. **Kathryn Neugent**

After ten million years of traveling through space, the star evolved into a yellow supergiant, the object that we see today. Its journey took it 1.6 degrees across the sky, about three times the diameter of the full moon. The star will continue speeding through space until it too blows up as a supernova, likely in another three million years or so. When that happens, heavier elements will be created, and the resulting supernova remnant may form new stars or even planets on the outer edge of the Small Magellanic Cloud.

The star was discovered and studied by an international group of astronomers led by Kathryn Neugent, a Lowell Observatory researcher who is also a graduate student at the University of Washington in Seattle. The team included Lowell staff members Phil Massey and Brian Skiff, Las Campanas (Chile) staff astronomer Nidia Morrell, and Geneva University (Switzerland) theorist Cyril Georgy. Their findings have been accepted for publication in the *Astronomical Journal*. The discovery was made using the National Optical Astronomy Observatory's 4-meter Blanco telescope, and the Carnegie Observatory's 6.5-meter Magellan telescope, both located northern Chile. Their work was funded by the National Science Foundation.

The north-pole star, Polaris, is a yellow supergiant, as is Canopus, one of the brightest stars visible from the southern hemisphere. Yellow supergiants are very rare objects because the yellow supergiant phase is so short. A massive star may live for as much as ten million years but the yellow supergiant phase itself lasts only ten to a hundred thousand years, an eye-blink in the life of a star. After this short time, yellow supergiants expand into giant red supergiants, like Betelgeuse, with sizes as large as the orbits of Mars or Jupiter. These stars eventually die in spectacular supernova explosions.

More information: *A Runaway Yellow Supergiant Star in the Small Magellanic Cloud. arXiv:1803.02859 [astro-ph.SR]* arxiv.org/abs/1803.02859

Read more at: https://phys.org/news/2018-03-runaway-star-small-magellanic-cloud.html#jCp

https://bbc.in/2pTcfl1

Australia's indigenous languages have one source, study says

Researchers in Australia say they have traced the country's indigenous languages back to a single, common tongue.

The languages are all derived from a mother tongue, known as Proto-Australian, that was spoken about 10,000 years ago, according to a new study. Linguists have long debated the subject in Australia. More than 200 languages were spoken at the time of British settlement in 1788.

The research, published in the Diachronica linguistics journal, is the first to prove that all of those languages came from the same family, said linguists at the University of Newcastle, Australia and Western Sydney University.

"Until now, it was speculated that Australia was significantly more linguistically diverse than somewhere like Europe, because it had not been proven that all Australian languages actually stemmed from the same lineage," said Associate Prof Mark Harvey from the University of Newcastle, Australia. Although an estimated 120 indigenous languages still exist, only about 20 are actively spoken today, he said.

Geographical distance

Researchers said they found "recurrent" and "systematic" traits in the sounds of words among the languages.

"[We were] essentially looking for consistent similarities, like how there's a link between 'good' and 'gut' in English and German," Associate Prof Harvey told the BBC.

He said such similarities were found in the basic vocabulary of languages "that might be 100km (60 miles) apart" in terms of where they were being spoken. "[It] makes it very unlikely that they are the result of chance or [subsequent] language contact," said Associate Prof Robert Mailhammer from Western Sydney University.

Diversity in the north

Researchers said the language family had spread and diversified from a small area in northern Australia. "Where you have the greatest diversity is where the original forms [of language] were, so your standard starting point would be the Kimberleys [in Western Australia] and the Top End [upper Northern Territory]," he said.

However, he said the findings did not fit well with existing understandings of how populations had moved across the continent.

People movements are usually regarded as key factors in spreading languages, Associate Prof Harvey said. "So there are still lots of questions about how we understand the pre-history of Australia," he said.

Last year, scientists found evidence to suggest that indigenous Australians have lived on the continent for at least 65,000 years.

Aboriginal Australians are believed to be the world's oldest continuous civilisation.

http://bit.ly/2pWOGYC

Taking a standard prostate cancer drug with food boosts impact, lowers cost

Savings per patient could reach as high as $300,000

By taking a high-cost drug with a low-fat meal--instead of on an empty stomach, as prescribed--prostate cancer patients could decrease their daily dose, prevent digestive issues and cut costs by 75 percent, according to a new study in the March 28, 2018, issue of the *Journal of Clinical Oncology (JCO)*.

Abiraterone acetate, marketed as Zytiga®, is the standard medicine used to treat metastatic castration-resistant prostate cancer. Patients taking Zytiga are told to take four of the 250 milligram pills first thing in the morning. Then, having gone without food overnight, they must wait at least one more hour before eating breakfast.

"This schedule is not only inconvenient for patients, it's also wasteful, in several ways," said the study's lead author, Russell Szmulewitz, MD, associate professor of medicine at the University of Chicago and a prostate cancer specialist.

A one-month supply of the recommended dose of abiraterone costs $8,000 to $11,000 when purchased wholesale. That adds up to a little more than $100,000 each year. Many patients take the drug for two to three years.

So Szmulewitz and colleague Mark Ratain, MD, the Leon O. Jacobson professor of medicine and director of the Center for Personalized Therapeutics at the University of Chicago Medicine, designed a randomized clinical trial to see if the drug could be used more efficiently and at less expense.

Abiraterone, approved in 2011 for the treatment of metastatic prostate cancer, has a "food effect" that is greater than any other marketed drug. The amount of abiraterone that gets absorbed and enters the blood stream can be multiplied four or five times if the drug is swallowed with a low-fat meal (7 percent fat, about 300 calories). That can increase to 10 times with a high-fat meal (57 percent fat, 825 calories).

Working with colleagues at the University of Chicago as well as researchers at the National Cancer Institute, Emory University, Illinois Cancer Care in Peoria, Illinois, and the National University Cancer Institute, Singapore, the team designed a clinical trial that could compare the cost, risks and benefits of taking this drug with or without breakfast.

The study launched in 2012. The team enrolled 72 patients with advanced prostate cancer. Half of those patients agreed to take the recommended dose of 1,000 milligrams: four pills each morning with water on an empty stomach. They had to wait an hour afterwards before they could eat breakfast. The other half were told to take one-fourth of the standard dose, a single 250-milligram pill, with a low-fat breakfast such as cereal with skim milk. Patients were advised to avoid high-fat items such as bacon or sausage.

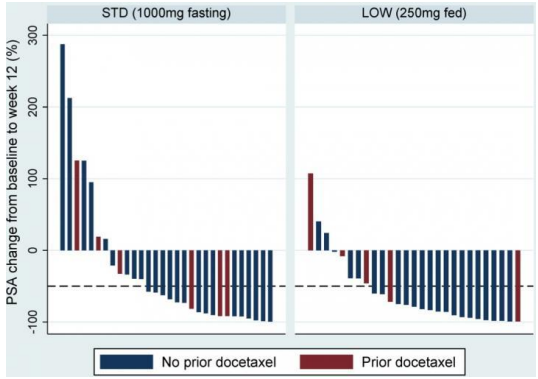
Four patients, two from each group, dropped out before the study began. The researchers found that the lower dose with breakfast kept the disease under control as well as the recommended dose. Abiraterone's ability to lower levels of prostate-specific antigen, a surrogate marker for prostate cancer, was slightly greater for patients in the low-dose with food group when measured at 12 weeks.

Progression-free survival for patients in both the low- and high-dose groups was identical, about 8.6 months. Despite the small size of the study, the authors were confident that the low-dose arm was comparable to the standard dose. It was also slightly more convenient and much less expensive, cutting costs by as much as $300,000 per patient.

"The patient gets a simplified schedule, slightly more control over his daily life, the convenience of eating whenever he chooses and the opportunity to share the cost-savings with his insurance company," Szmulewitz said. "Taking this medicine while fasting is wasteful."

"Although it should be validated with a larger trial with more robust clinical endpoints," he added, "given the pharmacoeconomic implications, these data warrant consideration by prescribers, payers and patients."

"If this study were enlarged and repeated successfully, the resulting cost saving would be in the billions of dollars," according to Allen Lichter, MD, author of a related commentary in the JCO, former CEO of the American Society of Clinical Oncology and board chair of the Value in Cancer Care Consortium (Vi3C).



This is the standard dose (1000mg, without food) compared to low dose (250mg with a meal). **Russell Szmulewitz , MD**

Abiraterone, taken with prednisone to prevent side effects, "represents a new standard of care for metastatic disease," according to a recent review article in the New England Journal of Medicine. The authors were concerned, however, that the "duration and cost of treatment may influence clinical decision making."

At a per-patient cost of about $10,000 a month, "this is a textbook example of what we now call 'financial toxicity'," Ratain said, referring to the economic burden placed on patients by the high cost of care. "At least three-quarters of this expensive drug is wasted," he added. "It's excreted and flushed away."

Additional authors of the study were Abiola Ibraheem, Elia Martinez, Mark Kozloff, Chadi Nabhan, Theodore Karrison and Walter Stadler from the University of Chicago; Cody Peer and William Figg from the National Cancer Institute; Bradley Carthon and Donald Harvey from Emory University; Paul Fishkin from Illinois Cancer Care, in Peoria; and Wei Peng Yong and Edmund Chiong from the National University Cancer Institute, Singapore.

http://bit.ly/2pXmzZW

Decades-long trends, not flawed vaccine, explain resurgent whooping cough

Resurgence of pertussis is the result of factors that began in the middle of the last century, before the latest vaccines were introduced

ANN ARBOR--Researchers and public health officials have struggled to explain the resurgence of whooping cough in the United States since the late 1970s, and the suspected shortcomings of the current generation of vaccines are often blamed.

But a new University of Michigan-led study concludes that the resurgence of the highly contagious respiratory disease is the result of factors--including a phenomenon known as the honeymoon period--that began in the middle of the last century, long before the latest vaccines were introduced in the late 1990s.

"Conventional wisdom is that the current vaccine is the problem, but that's not consistent with what we see," said Aaron King, a U-M infectious disease ecologist and applied mathematician.

King and colleagues from the Institut Pasteur, the University of Georgia and Queens University concluded that natural population turnover, incomplete vaccination coverage, and slowly waning protection from a highly effective yet imperfect vaccine best explain the resurgence of whooping cough. The disease can be fatal to infants and is also known as pertussis.

"This resurgence is the predictable consequence of rolling out a vaccine that isn't quite perfect and not hitting everybody in the population with that vaccine," said King, a professor in the U-M Department of Ecology and Evolutionary Biology and in the mathematics department.

The team's findings are scheduled for publication March 28 in Science Translational Medicine. The first author of the paper is Matthieu Domenech de Cellès, formerly a U-M postdoctoral researcher under King, now at the Institut Pasteur in Paris.

"Our results are important because they show that recent trends in pertussis are not necessarily caused by recent changes in epidemiology or biology," said Domenech de Cellès.

"Rather, the contemporary epidemiology of pertussis may be interpreted as a legacy of longstanding immunization practices. It's an important shift of perspective, which makes pertussis a complex but exciting system to study."

The researchers used disease-transmission models and 16 years of age-stratified pertussis incidence data from Massachusetts, along with statistical methods for extracting information from the data. The authors say their results apply to the rest of the United States and to Western Europe.

According to the study, the introduction of the first pertussis vaccine in the late 1940s led to a honeymoon period, a time of very low disease incidence following the start of a vaccination program. The return of pertussis in recent decades signals the end of that honeymoon period, according to the researchers.

In the pre-vaccine era, whooping cough was a very common childhood disease in the United States. Most kids were exposed to Bordetella pertussis, the bacterium that causes it, and their immune systems mounted a strong response that provided long-lasting immunity. As a result of those naturally acquired infections, most adult Americans were immune to pertussis.

Routine vaccination with a whole-cell pertussis vaccine quickly led to a 100-fold reduction in incidence. Actually, two factors accounted for that sharp drop-off: children protected by the new vaccine and adults with natural immunity acquired in the pre-vaccine era.

But as the decades passed, the number of American adults with naturally acquired pertussis immunity gradually declined as that older group died out.

Concurrently, the number of pertussis-susceptible U.S. adults was on the rise, setting the stage for the resurgence. The susceptible adults included people who were not vaccinated as children and who also avoided naturally acquired pertussis infections.

The mathematical model that best fit the 1990-2005 Massachusetts incidence data was one that explains the current resurgence "as a legacy of incomplete vaccination with effective, but imperfect, vaccines against a background of slow demographic turnover, i.e., as an end-of-honeymoon effect," the authors wrote.

The modeling study also supports the idea that protection from the pertussis vaccine gradually wanes over time--though it lasts a lot longer than many experts believed.

Some critics of the current acellular pertussis vaccine say it wears off after five to seven years. But the new study "suggests that current pertussis vaccines provide lifelong protection to 55 percent of people and protect 90 percent of people for more than a decade," said study co-author Pejman Rohani, a population ecologist at the University of Georgia's Odum School of Ecology. "Furthermore, our models explain that patterns of pertussis incidence previously attributed to rapid vaccine waning are actually consistent with higher contact rates once children enter school."

Though the current vaccine is effective at reducing levels of the pertussis pathogen circulating in the population, routine vaccination alone will never be sufficient to eradicate the bacterium, the researchers conclude.

In infants, pertussis causes violent, gasping coughing spells and can lead to life-threatening complications. People with whooping cough usually spread the disease by coughing or sneezing while in close contact with others. Parents, older siblings or other caregivers can give whooping cough to babies without even knowing they have the disease.

The modeling study identified primary school children and teenagers as the "core transmission group" mainly responsible for spreading the disease. In one simulation, a booster vaccination effort focused on children ages 5 to 10 or 10 to 20 led to a drop in infant cases of about 25 percent.

"The overwhelming amount of transmission is happening in those age groups," King said. "So, we have to make sure that kids are getting vaccinated before they go to school. That's going to have the biggest impact."

The U.S. Centers for Disease Control and Prevention recommends a series of five pertussis shots for children under 7. Additional shots are recommended for older children and for some adults.

Pertussis is responsible for 195,000 infant deaths each year worldwide, mostly in the developing world. There were 17,972 reported pertussis cases in the United States in 2016, including six infant deaths, according to the CDC.

The other author of the Science Translational Medicine *paper, in addition to Domenech de Cellès, King and Rohani, is Felicia M.G. Magpantay, formerly a U-M postdoctoral researcher and now at Queen's University in Kingston, Ontario.*

The new study is the latest result of efforts funded by a $1.7 million, five-year National Institutes of Health grant to King and Rohani aimed at understanding the causes of pertussis resurgence.

http://bit.ly/2uF52KY

A Man's 'Beer Belly' Was Actually a Massive Tumor

A New Jersey man's "beer belly" turned out to be a 30-lb. (13.6 kilograms) tumor.

By Sara G. Miller, Health Editor

The man, Kevin Daly, realized something was wrong when he lost more than 30 lbs. in 2015, but his belly fat didn't budge, the New York Daily News reported earlier this month.

A surgeon holds Daly's 30-lb. tumor. **Courtesy of Lenox Hill Hospital**

A CT scan revealed that the man's belly bulge was in fact a rare type of tumor called a liposarcoma, according to Fox News.

Liposarcomas are tumors that grow in fat tissue, according to the Genetic and Rare Disease Information Center (GARD). Because these tumors can spread to surrounding tissues or organs in the body, they are considered malignant.

Liposarcomas most often develop in fat tissue found in the thigh, behind the knee or in the abdomen, GARD says. (Indeed, Daly's tumor arose from fat tissue in his abdomen.)

The tumors are rare; according to the American Cancer Society (ACS), about 13,000 sarcomas will be diagnosed in 2018. Liposarcomas are

just one type of sarcoma, which refers to a cancer that forms in certain tissues in the body, including bone, muscle and fat.

The first approach to treating a liposarcoma is often surgery, according to GARD, though surgery can be difficult when the tumor is in the abdomen and growing near vital organs.

In Daly's case, the tumor was wrapped around one of his kidneys, and took 4 hours to completely remove, the Daily News reported.

Daly before (left) and after (right) his surgery. **Courtesy of Kevin Daly and Lenox Hill Hospital**

Daly's surgeon, Dr. Julio Teixeira of Lenox Hill Hospital in New York, told the Daily News it was the largest tumor he had ever removed.

http://bit.ly/2uEirTp

Poisoned by Bitter Squash, Two Women Lose Their Hair

There wasn't anything particularly unusual about the squash — just a slightly bitter taste. But that all changed when two women in France started losing their hair.

By Cari Nierenberg, Live Science Contributor

The women didn't know each other, nor did they get their squash from the same seller. Still, they both developed what's known as cucurbit poisoning, or "toxic squash syndrome," according to a new report of the two cases, published today (March 28) in the journal JAMA Dermatology.

In one of the cases, a woman and her family developed symptoms of food poisoning — nausea, vomiting and diarrhea — hours after eating a bitter-tasting pumpkin soup. About a week later, the woman experienced substantial hair loss that affected a large part of her scalp, but none of her family members lost their hair.

In the second case, another woman had severe vomiting about an hour after eating a bitter-tasting squash, but no one else who ate the vegetable got sick. Roughly three weeks later, she lost a massive amount of hair from her head, as well as from her underarms and pubic area.

Bitter squash

As it turns out, some members of the Cucurbitaceae family — which includes pumpkins, squash, melons and cucumbers — can produce a group of chemicals known as cucurbitacins. Not only do these chemicals taste bitter, but they can also have toxic effects on human cells.

Normally, farmers cultivate these plants to produce little to no cucurbitacins, because people don't like the bitter taste. But in some situations, such as when there's accidental cross-pollination of crops or when plants grow in the wild, some varieties may contain high levels of the chemicals. This creates a potentially toxic, bitter-tasting, inedible food.

The problem, however, is that the bitter-tasting vegetable looks no different from a normal one, and a person can't tell the difference until they take a bite.

Toxic squash syndrome

Although it's rare, other cases of cucurbit poisoning have been described in the medical literature; in those cases, people developed food poisoning after eating bitter-tasting squash, zucchini and other gourds, according to the new report. But these are the first two reported cases linking the consumption of bitter-tasting gourds with hair loss, according to the case report author, Dr. Philippe Assouly, a dermatologist at Saint-Louis Hospital in Paris.

Assouly wrote that he suspects that toxic compounds in the plant have a similar effect on hair follicles as do some chemotherapy drugs, which can lead to temporary hair loss.

But because hair loss is a completely new observation that is potentially associated with exposure to cucurbitacins, it's not clear why it occurred in these cases, said Dr. Zane Horowitz, a toxicologist and medical director of the Oregon Poison Center in Portland, who was not involved

in the case. Cucurbit poisoning is a very rare syndrome, and the toxin involved has not been well-studied, Horowitz noted.

In 2012, emergency room physicians at Oregon Health & Science University saw two patients with toxic squash syndrome, both of whom had eaten squash from a home garden. The physicians then reviewed the records from the Oregon and Washington state poison centers and identified about 17 other cases of cucurbit poisoning that had occurred over a 12-year period.

In a more recent review, published in January 2018 in the Journal of Clinical Toxicology, a French poison center reported more than 350 cases of food poisoning linked with bitter-tasting squash that took place between 2012 and 2016. About 56 percent of those cases involved squash purchased at a store, and in 26 percent of the cases, the vegetable came from a home garden, according to the findings.

Squash lovers need to be aware that if they eat one of these popular vegetables and it tastes bitter, they should stop eating it immediately, Horowitz told Live Science. What's clear in all these case reports is that high levels of the toxin make vegetables taste bitter, and those high levels of toxin can put a person at highest risk for symptoms, he said.

As for the two French women who lost their hair, the hair on the head of the woman who ate the pumpkin soup had regrown less than 1 inch (2 centimeters) two months after the incident. The second woman had regrown short hair, of more than 2 inches (6 cm), on most areas of her scalp six months later.

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Dietary supplement shows promise for reversing cardiovascular aging

'NR' shown to mimic caloric restriction, boost arterial health

Scientists have long known that restricting calories can fend off physiological signs of aging, with studies in fruit flies, roundworms, rodents and even people showing that chronically slashing intake by about a third can reap myriad health benefits and, in some cases, extend lifespan.

From a public health perspective, that advice would be impractical for many and dangerous for some.

But a new University of Colorado Boulder study published today indicates that when people consume a natural dietary supplement called nicotinomide riboside (NR) daily, it mimics caloric restriction, aka "CR," kick-starting the same key chemical pathways responsible for its health benefits.

Supplementation also tends to improve blood pressure and arterial health, particularly in those with mild hypertension, the study found.

"This was the first ever study to give this novel compound to humans over a period of time," said senior author Doug Seals, a professor and researcher in the Department of Integrative Physiology. "We found that it is well tolerated and appears to activate some of the same key biological pathways that calorie restriction does."

For the study, published in the journal *Nature Communications*, Seals and lead author Chris Martens, then a postdoctoral fellow at CU Boulder, included 24 lean and healthy men and women ages 55 to 79 from the Boulder area.

Half were given a placebo for six weeks, then took a 500 mg twice-daily dose of nicotinamide riboside (NR) chloride (NIAGEN). The other half took NR for the first six weeks, followed by placebo.

The researchers took blood samples and other physiological measurements at the end of each treatment period.

Participants reported no serious adverse effects.

The researchers found that 1,000 mg daily of NR boosted levels of another compound called nicotinamide adenine dinucleotide (NAD+) by 60 percent. NAD+ is required for activation of enzymes called sirtuins, which are largely credited with the beneficial effects of calorie restriction. It's involved in a host of metabolic actions throughout the body, but it tends to decline with age.

Research suggests that as an evolutionary survival mechanism, the body conserves NAD+ when subjected to calorie restriction. But only

recently have scientists begun to explore the idea of supplementing with so-called "NAD+-precursors" like NR to promote healthy aging.

"The idea is that by supplementing older adults with NR, we are not only restoring something that is lost with aging (NAD+), but we could potentially be ramping up the activity of enzymes responsible for helping protect our bodies from stress," Martens said.

The new study also found that in 13 participants with elevated blood pressure or stage 1 hypertension (120-139/80-89 mmHg), systolic blood pressure was about 10 points lower after supplementation. A drop of that magnitude could translate to a 25 percent reduction in heart attack risk.

"If this magnitude of systolic blood pressure reduction with NR supplementation is confirmed in a larger clinical trial, such an effect could have broad biomedical implications," the authors note.

Ultimately, the authors say, such CR-mimicking compounds could provide an additional option--alongside the dietary changes and exercise currently recommended--for people whose blood pressure is not yet high enough to warrant medication but who are still at risk for a heart attack.

They stress that the study was small and "pilot in nature."

"We are not able to make any definitive claims that this compound is safe or going to be effective for specific segments of the population," said Martens, now an assistant professor at the University of Delaware. "What this paper provides us with is a really good stepping stone for future work."

Martens and Seals have applied for a grant to conduct a larger clinical trial looking specifically at the impact of NR supplementation on blood pressure and arterial health. Martens is also launching a separate trial looking at the impact NR has on older adults with mild cognitive impairment, a precursor to Alzheimer's disease.

The study was partially funded by grants from the National Institutes of Health and the American Federation for Aging Research. ChromaDex, the maker of NIAGEN provided supplements and some financial support.

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Poor grades tied to class times that don't match our biological clocks

Schedules of night owls, morning larks and daytime finches may predict their educational outcomes.

It may be time to tailor students' class schedules to their natural biological rhythms, according to a new study from UC Berkeley and Northeastern Illinois University.

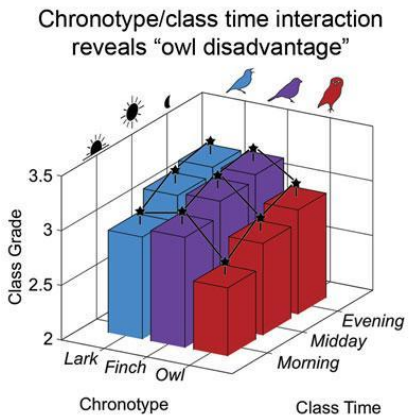
Researchers tracked the personal daily online activity profiles of nearly 15,000 college students as they logged into campus servers.

After sorting the students into "night owls," "daytime finches" and "morning larks" -- based on their activities on days they were not in class -- researchers compared their class times to their academic outcomes.

Their findings, published today in the journal *Scientific Reports*, show that students whose circadian rhythms were out of sync with their class schedules - say, night owls taking early morning courses - received lower grades due to "social jet lag," a condition in which peak alertness times are at odds with work, school or other demands.

"We found that the majority of students were being jet-lagged by their class times, which correlated very strongly with decreased academic performance," said study co-lead author Benjamin Smarr, a postdoctoral fellow who studies circadian rhythm disruptions in the lab of UC Berkeley psychology professor Lance Kriegsfeld.

In addition to learning deficits, social jet lag has been tied to obesity and excessive alcohol and tobacco use.



Owls performed worst of all the groups due to chronic social jet lag. **Benjamin Smarr**

On a positive note: "Our research indicates that if a student can structure a consistent schedule in which class days resemble non-class days, they are more likely to achieve academic success," said study co-lead author Aaron Schirmer, an associate professor of biology at Northeastern Illinois University.

While students of all categories suffered from class-induced jet lag, the study found that night owls were especially vulnerable, many appearing so chronically jet-lagged that they were unable to perform optimally at any time of day. But it's not as simple as students just staying up too late, Smarr said

"Because owls are later and classes tend to be earlier, this mismatch hits owls the hardest, but we see larks and finches taking later classes and also suffering from the mismatch," said Smarr. "Different people really do have biologically diverse timing, so there isn't a one-time-fits-all solution for education."

In what is thought to be the largest-ever survey of social jet lag using real-world data, Smarr and Schirmer analyzed the online activity of 14,894 Northeastern Illinois University students as they logged in and out of the campus's learning management system over two years.

To separate the owls from the larks from the finches, and gain a more accurate alertness profile, the researchers tracked students' activity levels on days that they did not attend a class.

Next, they looked at how larks, finches and owls had scheduled their classes during four semesters from 2014 to 2016 and found that about 40 percent were mostly biologically in sync with their class times. As a result, they performed better in class and enjoyed higher GPAs.

However, 50 percent of the students were taking classes before they were fully alert, and another 10 percent had already peaked by the time their classes started.

Previous studies have found that older people tend to be active earlier while young adults shift to a later sleep-wake cycle during puberty. Overall, men stay up later than women, and circadian rhythms shift with the seasons based on natural light.

Finding these patterns reflected in students' login data spurred researchers to investigate whether digital records might also reflect the biological rhythms underlying people's behavior.

The results suggest that "rather than admonish late students to go to bed earlier, in conflict with their biological rhythms, we should work to individualize education so that learning and classes are structured to take advantage of knowing what time of day a given student will be most capable of learning," Smarr said.

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Scientists find mini gastrointestinal tract growing inside tumor

Lung tumors have been found to morph into developmentally related neighboring organs, namely the gut.

By *Meghana Keshavan*

Embedded in a lung cancer tumor, scientists have found a gastrointestinal tract in miniature. Duke University researchers have observed rudimentary, but functional, stomachs, small intestines, and duodenums growing inside cancerous lungs — illustrating how varied and plastic these metastatic cells can be.

Cancerous cells, after all, use the very same developmental mechanisms as healthy cells do to adapt and survive. So scientists are observing an example of some cells mutating into their developmental cousins.

“During development, the lung and the esophagus all come from the same endodermal progenitor cells,” said Purushothama Rao Tata, lead author of a study about the research and an assistant professor of cell biology at Duke University. “What we think is that these cancer cells in the lung slide into the nearest developmental neighborhood.”

The work was published this week in the journal Developmental Cell.

Tata’s group found that a large proportion of human lung cancer cells lack a developmental gene called NKX2-1, which helps stem cells morph into lung cells. So these cancer cells defaulted to another developmental pathway — instead of taking advantage of the coding that turns stem cells into gut. Indeed, Tata found that many lung cancer

cells expressed genes associated with gastrointestinal organs. “We’ve been most interested in how cells maintain their identity, and what goes wrong in tumor cells so they change their behavior,” Tata said.

This mechanism likely contributes to drug resistance, Tata said. Cancer cells, after all, will do just about anything to survive — and in this instance, lung cells will pick up the characteristics of gut cells to help evade treatment.

Tata was able to reproduce his findings in animal models: When he knocked out the NKX2-1 gene in the lung tissue of mice, he found that tissues that typically only appear in the gut began growing in their lungs. These structures actually excreted digestive enzymes.

The work, while interesting, is “not entirely surprising,” said Deborah Caswell, a researcher at the Francis Crick Institute who studies tumor heterogeneity, particularly in lung cancer. What she finds particularly intriguing, however, is that distinct regions within a single tumor can differentiate in unique ways.

“This finding should improve our ability to model and predict how individual tumor cells will evolve as tumors progress,” Caswell said. It helps illustrate how tumor plasticity and heterogeneity work, she said — and could help scientists develop better therapies to combat drug resistance.

Tata’s group now plans to test new drug combinations in miniaturized tumor models. “We haven’t tested it yet, but based on our findings here, we’re hypothesizing that colon cancer drugs might help treat some lung cancers,” Tata said.

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Pediatric cancer drug shows 93 percent response rate

First-of-its-kind drug targeting fused gene found in many types of cancer effective in 93% of pediatric patients tested

DALLAS - A first-of-its-kind drug targeting a fused gene found in many types of cancer was effective in 93 percent of pediatric patients tested, researchers at UT Southwestern's Simmons Cancer Center announced.

Most cancer drugs are targeted to specific organs or locations in the body. Larotrectinib is the first cancer drug to receive FDA breakthrough therapy designation for patients with a specific fusion of two genes in the cancer cell, no matter what cancer type. The research appears in *The Lancet Oncology*.

"In some cancers, a part of the *TRK* gene has become attached to another gene, which is called a fusion. When this occurs, it leads to the *TRK* gene being turned on when it's not supposed to be and that causes the cells to grow uncontrollably. What's unique about the drug is it is very selective; it only blocks TRK receptors," said lead author Dr. Ted Laetsch, Assistant Professor of Pediatrics and with the Harold C. Simmons Comprehensive Cancer Center.

Larotrectinib, targets *TRK* fusions, which can occur in many types of cancer. While the *TRK* fusions occur in only a small percentage of common adult cancers, they occur frequently in some rare pediatric cancers, such as infantile fibrosarcoma, cellular congenital mesoblastic nephroma, and papillary thyroid cancer, said Dr. Laetsch, who leads the Experimental Therapeutics Program (ETP) in the Pauline Allen Gill Center for Cancer and Blood Disorders at Children's Health in Dallas.

"Every patient with a *TRK* fusion-positive solid tumor treated on this study had their tumor shrink. The nearly universal response rate seen with larotrectinib is unprecedented," Dr. Laetsch said.

Among them was 13-year-old Briana Ayala of El Paso, who aspires to a career in fashion design. In 2016, Briana was found to have a rare tumor in her abdomen wrapped around her aorta, the largest artery in the body.

Surgeons in her hometown said it would be too dangerous to operate, so her family brought Briana to Children's Health in Dallas, where UT Southwestern Professor of Surgery Dr. Stephen Megison had to remove portions of her aorta while removing most of the tumor. But the cancer started to grow again and no further treatments were available.

Dr. Laetsch sent her tumor for genetic testing and found that Briana's cancer had the *TRK* fusion, meaning the new drug might help.

Briana enrolled in the phase 1 clinical trial of larotrectinib and began taking the drug twice a day. Within weeks her pain and the swelling in her abdomen diminished, and scans showed her tumors had shrunk significantly.

Nearly two years later, Briana is back in school and playing with her dog, Goofy, and the family's seven parakeets. She's also been able to pick up her sketch pad and her dreams of a New York City fashion career. "These are the kind of amazing responses we've seen with larotrectinib," said Dr. Laetsch, "and this is why I'm so excited about it." The results of the larotrectinib trial in adult patients - a 75 percent response rate - were published last month in the New England Journal of Medicine.

The *TRK*-fusion mutation can be present in many types of cancers, including lung, colon, thyroid, and breast cancer, as well as certain pediatric tumors. *TRK*, short for tropomyosin receptor kinase, is a gene that plays a key role in brain and nervous system development and has a limited role in nervous system functions such as regulating pain in later life.

Larotrectinib belongs to a class of molecules known as kinase inhibitors, which work by cutting back on the enzymatic activity of a key cellular reaction. The selectivity of the drug means it does not cause the severe side effects associated with many traditional cancer treatments, and none of the patients with *TRK* fusions had to quit the study because of a drug-induced side effect.

Equally important, the response was long-lasting for most patients. "For some of the targeted drugs in the past, many patients responded initially, but then resistance developed quickly. To date, the response to this drug seems to be durable in most patients," said Dr. Laetsch, who investigates the use of tumor molecular profiling to guide therapy in UT Southwestern's Pediatric Hematology and Oncology Division.

A next step in the research is a clinical trial involving a similar drug for those patients who developed resistance. Dr. Laetsch will be the national leader for that clinical trial in children.

The larotrectinib research was supported by Loxo Oncology Inc., the National Institutes of Health, the Cancer Prevention and Research Institute of Texas, the National Center for Advancing Translational Sciences, and Alex's Lemonade Stand Foundation. Dr. Laetsch is a paid consultant for Loxo Oncology Inc.

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Which Patients With Atrial Fibrillation Should Receive Anticoagulation?

Atrial Fibrillation in the General Population

Thomas A. Zelniker, MD; Robert P. Giugliano, MD, FACC

Atrial Fibrillation in the General Population

Atrial fibrillation (AF) is the most prevalent cardiac rhythm disorder in the elderly population and is the leading cause of stroke and systemic embolic events. Although AF is classified clinically according to its duration as paroxysmal, persistent, or permanent,[1] the risk for thromboembolism appears to be consistent among these categories.

AF usually originates in the left atrium at the pulmonary veins and can be easily detected and diagnosed on the basis of an irregular pattern with varying RR intervals on ECG. Because patients with AF may be completely asymptomatic, opportunistic screening for silent AF can be easily performed at low cost and little burden for the patient, and is therefore recommended in patients aged > 65 years by guidelines from the European Society of Cardiology (ESC)[2] and the American Heart Association Stroke Council.[3] There has been increasing interest in the development of smartphone-connected wearable devices that collect the carrier's ECG (usually using a single lead) and issue a warning notice when a suspected pathologic finding is detected. However, none of these devices is currently approved by the US Food and Drug Administration, and patients can be unsettled by false-positive results.

AF is usually not life-threatening, but it can elicit serious complications. Several studies have shown a robust association between AF and thromboembolic events.[4] AF results in a state of hypercoagulation due to stasis and turbulence in the atrial auricles and may trigger the development of clots causing thromboembolic events. However, the link between the timing of stroke and the presence of AF is complex

and not well understood. In a study of patients with pacemakers and defibrillators, no temporal relationship between the episodes of AF was identified.[3] Likewise, maintaining sinus rhythm by using electric cardioversion and/or antiarrhythmic drugs does not reduce the risk for stroke. On the contrary, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial suggested a mortality benefit in rate-controlled patients compared with rhythm control.[5]

Furthermore, AF is associated with an increased risk for heart failure, ventricular arrhythmias, and death, and it worsens the prognosis of concomitant cardiovascular diseases. However, it remains uncertain whether AF is causally linked to these conditions.

Calculating Risk

The benefit of anticoagulation for stroke prophylaxis in patients with AF is well established.[6] Several studies also proved that the efficacy of anticoagulation is superior to that of antiplatelet agents alone.[7,8]

However, clinicians often face a much more challenging dilemma in identifying the optimum anticoagulation method and determining the patient's risk benefit between the risk for stroke or bleeding. In this regard, the CHA_2DS_2VASc score—a seven-variable score consisting of age, sex, history of heart failure, hypertension, stroke, vascular disease, and diabetes—has replaced and expanded the previously used $CHADS_2$ score.[9]

The risk for stroke or systemic embolic events grows with increasing scores, and therefore oral anticoagulation should be considered in all patients with a score ≥ 2; patients with a score of 0 are at low risk. The European guidelines[2] also recommend oral anticoagulation in males with a score of 1, whereas the ACC/AHA/HRS guidelines[1] consider a point score of 1 as intermediate risk and antithrombotic or anticoagulant therapy may be withheld, acknowledging uncertainty in the level of evidence. Supporting the US guidelines, a recent systematic review[10] concluded that stroke rates differ substantially among tested cohorts, and indicated that annual stroke rates were < 2% in most patients with CHA_2DS_2VASc scores of 0-2—the presumed threshold to expect a clinical benefit from anticoagulation therapy.

The trade-off between the risks and the benefits of anticoagulation is often summarized as the net clinical outcome.[11] However, weighting these risks may be difficult, because some elderly patients may perceive suffering from stroke as a larger threat than death from bleeding.

Risk assessment of bleeding is challenging because many bleeding scores share the same variables that are used to estimate the risk for stroke or systemic embolic events. In addition, the presently available bleeding scores exhibit low discrimination, with an area under the curve < 0.70. The HAS-BLED score[4] (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol use concomitantly) is one of the most established scores, with scores of ≥ 3 indicating a high risk for bleeding.

Alternative scores are the $HEMORR_2HAGES$[12] and ATRIA[13] scores. Of note, the mentioned bleeding scores should not be primarily used as a decision-making tool regarding in which patients to avoid anticoagulation, but to assist in the identification of modifiable risk factors to reduce the risk for major bleeding.

There is growing evidence that biomarkers may become helpful tools in the risk stratification of bleeding events. A multimarker approach using cardiac troponin I, *N*-terminal pro-B–type natriuretic peptide, and D-dimer levels improved risk stratification when added to the CHA_2DS_2VASc score.[14] In addition, the ABC bleeding score, a combined clinical and biomarker score that was derived and validated in two modern AF trials, had a higher c-statistic than the HAS-BLED score.[15]

Choosing Anticoagulation Therapy

Four non-vitamin K antagonist oral anticoagulants (NOACs) were shown to be noninferior to warfarin in reducing stroke and systemic embolic events and are now available as an alternative to warfarin in patients with AF.[16-18] A meta-analysis of the NOAC versus warfarin

trials[19] found significant reductions in stroke or systemic embolic events, intracranial hemorrhage, and mortality, but increased risk for gastrointestinal bleeding compared with warfarin. Another meta-analysis examined the risks and benefits of NOACs versus warfarin in patients concomitantly taking aspirin found that NOACs also significantly reduced major bleeding compared with warfarin in these patients.[20]

Other benefits of NOACs, including the rapid onset of therapeutic effect, the lack of food interactions and substantially less frequent drug/drug interactions, and the lack of a monitoring requirement with repeated blood sampling, are appealing to patients despite the higher cost compared with warfarin. NOACs should be used with caution in patients with severe obesity or severely impaired renal function because dosing may be unclear or, in the latter case, pharmacokinetics are affected.[21] In addition, NOACs are contraindicated in patients with mechanical valves or mitral stenosis, those who are pregnant or lactating, and children.[22,23]

Patients on oral anticoagulation may have to stop oral anticoagulation before surgical interventions. The American College of Cardiology provides an electronic BridgeAnticoag app that can be used online or with a smartphone to support clinical decisions regarding interrupting, bridging, and restarting patients on oral anticoagulation.

Gaps in Knowledge

Besides the unanswered questions about low- to intermediate-risk patients with a CHA_2DS_2-VASc score of 0 or 1 as discussed above, data on the clinical significance of short-term episodes of AF are scarce. Although brief episodes were considered to be associated with an increased risk for thromboembolic events, a recent study showed that episodes of less than 20 seconds did not increase the risk for thromboembolic events, and it may therefore be safe to omit oral anticoagulation in younger patients with short-term AF and a low risk for cardiovascular disease.[24]

Furthermore, the optimum management of patients with AF and concomitant antiplatelet therapy (especially dual-antiplatelet therapy) is not well established, and recommendations regarding the management of patients diverge. Contrary to the ACC/AHA/HRS guidelines, the ESC discourages concomitant antiplatelet therapy in patients with stable coronary artery disease (without recent ACS or revascularization) who are on an anticoagulant.

Even more challenging, the optimum duration and intensity of antithrombotic therapy in concomitant AF after coronary revascularization or acute coronary syndrome remain unclear.

Summary

AF is the most common cardiac arrhythmia and all patients with diagnosed AF should be carefully evaluated for an indication for anticoagulation. The CHA_2DS_2VASc score is the most established risk score and is recommended by both American and European guidelines. Oral anticoagulation should be begun in all patients with a CHA_2DS_2VASc score of 2 or greater. The majority of these patients should preferentially receive a NOAC, owing to the superior efficacy and safety profile of these agents compared with vitamin K antagonists. Patients with a CHA_2DS_2VASc score of 1 should be evaluated individually, but female sex alone is not an indication for anticoagulation. Risk stratification for bleeding is challenging and risk scores should be applied to identify modifiable risk factors to reduce the risk for bleeding events, but not as decision tools regarding in which patients to avoid anticoagulation.

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http://bit.ly/2JeDIqe

Is there life adrift in the clouds of Venus?

Scientists are dusting off an old idea that promises a new vista in the hunt for life beyond Earth: the clouds of Venus

MADISON, Wis. -- In the search for extraterrestrial life, scientists have turned over all sorts of rocks.

Mars, for example, has geological features that suggest it once had -- and still has -- subsurface liquid water, an almost sure prerequisite for life. Scientists have also eyed Saturn's moons Titan and Enceladus as well as Jupiter's moons Europa, Ganymede and Callisto as possible havens for life in the oceans under their icy crusts.

This is a Venus Atmospheric Maneuverable Platform, or VAMP. The aircraft, which would fly like a plane and float like a blimp, could help explore the atmosphere of Venus, which has temperature and pressure conditions that do not preclude the possibility of microbial life. **Northrop Grumman Corp.**

Now, however, scientists are dusting off an old idea that promises a new vista in the hunt for life beyond Earth: the clouds of Venus.

In a paper published online today (March 30, 2018) in the journal Astrobiology, an international team of researchers led by planetary scientist Sanjay Limaye of the University of Wisconsin-Madison's Space Science and Engineering Center lays out a case for the atmosphere of Venus as a possible niche for extraterrestrial microbial life.

"Venus has had plenty of time to evolve life on its own," explains Limaye, noting that some models suggest Venus once had a habitable climate with liquid water on its surface for as long as 2 billion years. "That's much longer than is believed to have occurred on Mars."

On Earth, terrestrial microorganisms -- mostly bacteria -- are capable of being swept into the atmosphere, where they have been found alive

at altitudes as high as 41 kilometers (25 miles) by scientists using specially equipped balloons, according to study co-author David J. Smith of NASA's Ames Research Center.

There is also a growing catalog of microbes known to inhabit incredibly harsh environments on our planet, including the hot springs of Yellowstone, deep ocean hydrothermal vents, the toxic sludge of polluted areas, and in acidic lakes worldwide.

"On Earth, we know that life can thrive in very acidic conditions, can feed on carbon dioxide, and produce sulfuric acid," says Rakesh Mogul, a professor of biological chemistry at California State Polytechnic University, Pomona, and a co-author on the new paper. He notes that the cloudy, highly reflective and acidic atmosphere of Venus is composed mostly of carbon dioxide and water droplets containing sulfuric acid.

The habitability of Venus' clouds was first raised in 1967 by noted biophysicist Harold Morowitz and famed astronomer Carl Sagan. Decades later, the planetary scientists David Grinspoon, Mark Bullock and their colleagues expanded on the idea.

Supporting the notion that Venus' atmosphere could be a plausible niche for life, a series of space probes to the planet launched between 1962 and 1978 showed that the temperature and pressure conditions in the lower and middle portions of the Venusian atmosphere -- altitudes between 40 and 60 kilometers (25-27 miles) -- would not preclude microbial life. The surface conditions on the planet, however, are known to be inhospitable, with temperatures soaring above 450 degrees Celsius (860 degrees Fahrenheit).

Limaye, who conducts his research as a NASA participating scientist in the Japan Aerospace Exploration Agency's Akatsuki mission to Venus, was eager to revisit the idea of exploring the planet's atmosphere after a chance meeting at a teachers' workshop with paper co-author Grzegorz Słowik of Poland's University of Zielona Góra. Słowik made him aware of bacteria on Earth with light-absorbing properties similar to those of unidentified particles that make up unexplained dark patches observed in the clouds of Venus. Spectroscopic observations, particularly in the ultraviolet, show that the dark patches are composed of concentrated sulfuric acid and other unknown light-absorbing particles.

Those dark patches have been a mystery since they were first observed by ground-based telescopes nearly a century ago, says Limaye. They were studied in more detail by subsequent probes to the planet.

"Venus shows some episodic dark, sulfuric rich patches, with contrasts up to 30-40 percent in the ultraviolet, and muted in longer wavelengths. These patches persist for days, changing their shape and contrasts continuously and appear to be scale dependent," says Limaye.

The particles that make up the dark patches have almost the same dimensions as some bacteria on Earth, although the instruments that have sampled Venus' atmosphere to date are incapable of distinguishing between materials of an organic or inorganic nature.

The patches could be something akin to the algae blooms that occur routinely in the lakes and oceans of Earth, according to Limaye and Mogul -- only these would need to be sustained in the Venusian atmosphere.

Limaye, who has spent his career studying planetary atmospheres, was further inspired to revisit the idea of microbial life in the clouds of Venus by a visit to Tso Kar, a high-altitude salt lake in northern India where he observed the powdery residue of sulfur-fixing bacteria concentrated on decaying grass at the edge of the lake being wafted into the atmosphere.

Limaye notes, however, that a part of the equation that isn't known is when Venus' liquid water evaporated -- extensive lava flows in the last billion years likely have either destroyed or covered up the planet's earlier terrestrial history.

In the hunt for extraterrestrial life, planetary atmospheres other than Earth's remain largely unexplored.

One possibility for sampling the clouds of Venus, says Limaye, is on the drawing board: VAMP, or Venus Atmospheric Maneuverable

Platform, a craft that flies like a plane but floats like a blimp and could stay aloft in the planet's cloud layer for up to a year gathering data and samples.

Such a platform could include instruments like Raman Lidar, meteorological and chemical sensors, and spectrometers, says Limaye. It could also carry a type of microscope capable of identifying living microorganisms. "To really know, we need to go there and sample the clouds," says Mogul. "Venus could be an exciting new chapter in astrobiology exploration."

The Wisconsin scientist and his colleagues remain hopeful that such a chapter can be opened as there are ongoing discussions about possible NASA participation in Russia's Roscosmos Venera-D mission, now slated for the late 2020s. Current plans for Venera-D might include an orbiter, a lander and a NASA-contributed surface station and maneuverable aerial platform.

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http://bit.ly/2pYbMOt

CRISPR paper that sent stocks tumbling is retracted

A scientific paper that purported to lay bare serious flaws in the gene-editing tool known as CRISPR and briefly tanked shares of genome-editing companies has been retracted by its publisher.

***By* Meghana Keshavan @megkesh**

The paper, published last year in Nature Methods, claimed that CRISPR wreaked havoc on the genome, causing hundreds of unintended mutations in mice — and that the algorithms typically used to detect these changes were routinely missing them.

Such “off-target effects” had been on scientists’ radars for months, and many said they had begun to develop workarounds to help detect and even mitigate any effects. The news still sent the stock for CRISPR companies like Editas Medicine and Intellia Therapeutics tumbling.

The paper, led by Stanford scientists, also immediately stirred up controversy, with critics — particularly those at the affected companies — taking exception with their methodology.

Specifically, they said the paper lacked the appropriate controls and sample size to be taken seriously — and that the Stanford scientists’ use of CRISPR was not necessarily representative of how it’s wielded by others.

Two months after publication of the paper, Nature Methods published an “an expression of concern” about the paper in July.

The retraction notice, appended Friday, goes further, saying the authors did not use mice that had been bred in their own laboratory — so they could not know if any genetic mutations were the result of their intervention with CRISPR editing, or if it stemmed from variations in the mice’s own genomes.

The lead author, Vinit Mahajan, and some co-authors objected to the retraction.

In an editorial, Nature Methods said the central claim of the paper was not sufficiently supported by the data. The publication said the paper had been peer reviewed but should have been subject to more scrutiny.

“On the question of whether CRISPR can be safely used in vivo, the stakes are high for many. But for none are they higher than for the people in whom this technology may be used in the future,” the editorial said. “They are owed a careful and rigorous answer.”

http://bit.ly/2GsSv2E

Elevated blood pressure before pregnancy may increase chance of pregnancy loss

NIH researchers suggest lifestyle changes may reduce hypertension risk

Elevated blood pressure before conception may increase the chances for pregnancy loss, according to an analysis by researchers at the National Institutes of Health. The authors conclude that lifestyle changes to keep blood pressure under control could potentially reduce the risk of loss. The study appears in Hypertension.

The analysis found that for every 10 mmHg increase in diastolic blood pressure (pressure when the heart is resting between beats), there was an 18-percent-higher risk for pregnancy loss among the study population. Millimeter of mercury, or mmHg, is the unit of measure used for blood pressure. The researchers also found a 17 percent increase in pregnancy loss for every 10 mmHg increase in mean arterial pressure, a measure of the average pressure in the arteries during full heart beat cycles. The study was conducted by researchers at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

"Elevated blood pressure is linked to heart disease, stroke, and kidney disease" said the study's senior author, Enrique Schisterman, Ph.D., chief of the Epidemiology Branch at NICHD. "Our findings suggest that attaining a healthy blood pressure before pregnancy could not only have benefits later in life, but also reduce the chances for pregnancy loss."

NICHD researchers analyzed data collected as part of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, which sought to determine if daily low-dose aspirin (81 milligrams) could prevent miscarriage in women who had a history of pregnancy loss.

The EAGeR trial enrolled more than 1,200 women ages 18 to 40 years and took blood pressure readings before the women were pregnant and again in the fourth week of pregnancy. Average diastolic blood pressure for the women in the study was 72.5 mmHg; normal blood pressure in adults is a diastolic reading of below 80 mmHg. The authors began to see an increase in pregnancy loss among women who had a diastolic reading above 80 mmHg (approximately 25 percent of the participants). None of the women in the study had stage II high blood pressure (above 90 mmHg in systolic high blood pressure or above 140 mmHg in systolic blood pressure).

The researchers note that the study does not prove that elevated blood pressure causes pregnancy loss. It is possible that another, yet-to-be identified factor could account for the findings. They added, however, that the relationship between preconception blood pressure and pregnancy loss remained the same when they statistically accounted for other factors that could increase pregnancy loss, such as increasing maternal age, higher body mass index or smoking.

"Our results suggest that further research could help determine if treating elevated blood pressure and other health risks before conception improves pregnancy outcomes," said the study's first author, Carrie Nobles, Ph.D., a postdoctoral fellow in the NICHD Epidemiology Branch.

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