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Researchers find febrile infants may not need painful tests, antibiotics, hospitalizations

New protocol can determine which infant patients with fevers are at low risk of significant bacterial infections

SACRAMENTO, Calif. - A national research team led by UC Davis Health clinicians and researchers from the University of Michigan, Nationwide Children's Hospital and Columbia University, has derived and validated a new protocol for emergency departments that can determine which infant patients with fevers, age 60 days or younger, are at low risk of significant bacterial infections.

The finding has important implications for identifying cases in which infants may not need invasive medical care such spinal taps, antibiotics or hospitalizations.

The major study, which involved nearly 2000 febrile infants who were evaluated at 26 emergency departments around the country, showed how physicians can more precisely identify babies who are at low risk of serious bacterial infections such as urinary tract infections, bacteria in the blood and bacterial meningitis, in order to avoid spinal taps (also known as lumbar punctures), antibiotic medications and hospitalizations, which also carry risks and can be costly.

The study, "A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections," is online today in *JAMA Pediatrics*.

The new protocol, which could be implemented following a larger validation study, would enhance decision-making for emergency room providers and bring relief to the parents of many of the nearly half-million febrile infants who are evaluated in U.S. emergency departments each year.

"Missing a serious bacterial infection in an infant can lead to severe complications, which is why physicians traditionally have been very cautious and included invasive procedures, medications and hospitalizations when evaluating these infants," said Nathan Kuppermann, professor and chair of emergency medicine at UC Davis School of Medicine and lead author of the study.

"We were able to derive and validate a prediction rule, essentially a mathematical tool for physicians to confidently make clinical decisions about young infants with fevers to identify those who are at low risk of serious bacterial infections."

Fewer than 10 percent of infants evaluated for fever in emergency departments in the United States typically have serious or potentially life-threatening bacterial infections. However, because of their age and the standard treatment guidelines, many must undergo invasive testing, be hospitalized and given antibiotic treatments until bacterial infection can ruled out.

Kuppermann and his research colleagues in the Pediatric Emergency Care Applied Research Network (PECARN) - a network of pediatric emergency departments throughout the country that is working to establish new, evidence-based standards for managing common and important problems in pediatric emergency care - have been working to develop better approaches to identifying febrile babies who are at low risk of serious bacterial infections.

Two years ago, the same research consortium established a proof of principle for measuring patterns of ribonucleic acid (RNA) expression in the bloodstream that could enable clinicians to distinguish bacterial infections from other causes.

Now, in this large, multi-center observational study, 1,821 infant patients with fevers who were up to two-months (60 days) old were enrolled and randomly divided into two groups. Using sophisticated statistical methods, the research team identified three easily obtainable laboratory tests - the urinalysis, absolute neutrophil count (ANC) in the blood and a serum procalcitonin - to assess and validate

the rule physicians could use to exclude serious bacterial infections with very high accuracy.

"Our data contributes important information in the decades old debate about the necessity of lumbar punctures and hospitalizations for young babies with fevers," added Prashant Mahajan, professor and vice-chair of emergency medicine at the University of Michigan Medical School and C.S. Mott Children's Hospital, and the study's senior author.

"This study adds important information that we think will decrease the variability in current protocols and minimize unnecessary tests and hospital admissions, which can carry other risks for young patients."

While encouraged by their findings, the researchers noted that further validation is important before the new rule should be fully implemented, especially among cohorts with greater numbers of invasive bacterial infections.

"Clinicians must remain particularly wary in cases where infants are younger than 28 days," noted Octavio Ramilo, division chief of Infectious Diseases at Nationwide Children's Hospital, and a principal investigator on the study with Kuppermann and Mahajan. "That is the age group in whom the risks of bacteremia and bacterial meningitis, as well as herpes encephalitis, are the greatest."

In addition to Kuppermann, Mahajan and Ramilo, researchers included Peter Dayan from Columbia University and nearly two dozen other co-authors in the pediatric research network.

This study was supported in part by grant H34MCO8509 from Health Resources and Services Administration (HRSA) Emergency Services for Children and by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R01HD062477. It was also supported in part by HRSA Maternal and Child Health Bureau, Emergency Medical Services for Children Network Development Demonstration Program under several cooperative agreements.

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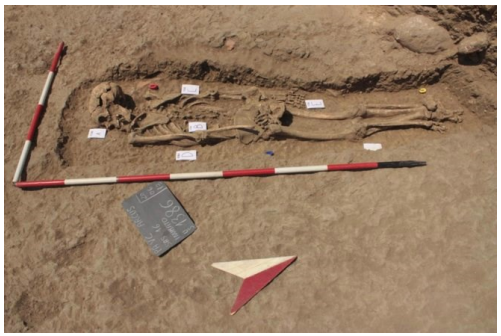
Why an Outlaw Was Stabbed to Death and Then Buried Face-Down in Medieval Sicily

By Yasemin Saplakoglu, Staff Writer

In medieval Sicily, a man was stabbed multiple times in the back, buried in a really weird way and ostensibly lost to history.

Now, hundreds of years later, archaeologists have excavated evidence of this ancient crime in the Piazza Armerina, Sicily. The researchers found the man's skeleton lying face-down in a shallow pit, empty of any funerary objects typical of ancient burials. The body was buried in a position that was unusual for that time period, they reported last month in the International Journal of Osteoarchaeology.



This medieval man's skeleton, bearing marks of stab wounds, was found facedown in a shallow pit in Sicily. **Credit: Photo courtesy of Emanuele Canzonieri; Roberto Micciche. et al. International Journal of Osteoarchaeology, 2019. Published by Wiley.**

The evidence suggests that the man, lived in the 11th century and was between 30 and 40 years old when he died. Using CT scans and 3D reconstructions, the researchers set out to determine how he died and why his burial was so unusual.

According to the report, there was evidence of six cuts on the individual's sternum (breastbone) that were indicative of stab wounds likely inflicted by a knife or dagger. On the right side of his sternum, the researchers found a chop mark where a piece of the bone had been removed, likely by a twisting motion from the weapon.

There was no evidence of other injuries on the man's vertebrae or ribs that would suggest that the man was involved in some kind of

"uncontrolled" fight, said lead author Roberto Micciché, an archaeologist at the University of Palermo in Italy.

The goal of the man's killer, it seems, was to attack the victim in a "very effective and rapid way," Micciché said; in addition, the assailant likely knew human anatomy "very well." In fact, the cuts were so clean and smooth, that the man may have been immobilized, perhaps with binding, Micciché said. The man's feet were also squished together in the burial space, which further supports the idea that his feet were bound together.

Using CT scans, the researchers were able to determine the the angle and size of the man's stab wounds, information that the investigators then used to create a 3D reconstruction of where the sharp object dug into the sternum and chest cage.

Because the blade of the knife would have entered the man's upper back at an angle, the researchers think that the man was kneeling on the ground at the time of the stabbing, Micciché said. Since the knife pierced through the thorax (the part of the body between the neck and the abdomen) and into the man's breastbone, Micciché said the weapon likely punctured the man's lung and heart repeatedly — so he probably died very quickly.

And then there's the weirdness of the burial — the first, well-documented case of a deviant burial in Sicily.

"The burial is atypical because [it] does not follow any religious prescription in the arrangement of the body," Micciché said. During this time in Sicily, three major monotheistic religions coexisted: Judaism, Christianity and Islam. Each had different traditions in burying its dead — Jews and Christians of the Middle Ages buried their dead face-up, while Muslims buried the body lying on its right side, so that the head faced southeast, toward Mecca.

This skeleton, on the other hand, was buried face-down.

Atypical burials tend to be the result of superstitious beliefs (such as if people think the dead person is a vampire or has returned from the dead) or an indication that the person was an outlaw, Micciché said. He said he thinks, in this case, that it's the latter. If in "his life, the individual was not aligned to the social order of the community, [his] burial should reflect this lack of conformity in death," Micciché said. All of this is to say that the man was likely an exile of sorts who was executed.

What's more, this was a time of "crisis and social reorganization" that occurred right after the Norman conquest of England in 1061. "As everywhere and anytime during a period of sociopolitical rearrangement, it is possible to note an increase in violent acts among people," Micciché said.

Now, Micciché and his team are looking through medieval archaeological records to find evidence of weapons that could be compatible with the marks on the skeleton and move a step closer to solving this ancient game of Clue.

http://bit.ly/2GTLff6

Neanderthals ate fresh herbivores, not rotten meat

Isotope analysis throws doubt on previous diet research.

Andrew Masterson reports.

Neanderthals were top level carnivores, even after the arrival of modern humans, chemical analysis indicates. The finding, based on measures of nitrogen and carbon isotopes in two samples of Neanderthal collagen gathered from two sites in France, confirm a carnivorous diet. It also does not support previously published suggestions that Neanderthals dined on putrid carrion left behind by other carnivores, or freshwater fish.

The latest research, led by Klervia Jaouen from the Max Planck Institute for Evolutionary Anthropology in Germany, tested carbon and nitrogen isotope ratios on single amino acids from collagen samples from Neanderthals recovered from sites at Les Cottés and Grotte du Renne. They conducted similar tests on faunal remains recovered from the same area.

The Neanderthal collagen, the scientists report in the journal *PNAS*, showed "exceptionally high [nitrogen] isotope ratios in their bulk bone or tooth collagen".

The results, Jaouen and colleagues report, were wholly consistent with "mammal meat consumption". There was no need to invoke other food sources, such as fish or mushrooms, nor food processes, such as cooking or fermentation arising from rot, to explain the readings.

The scientists acknowledge that their results do not preclude the occasional consumption of other food types and sources. However, they say, the isotope values of the Neanderthals strongly supports the contention that their main protein sources was "due to the consumption of different herbivores from different environments".

https://bbc.in/2SK1ySW

Sepsis test could show results 'in minutes'

A new rapid test for earlier diagnosis of sepsis is being developed by University of Strathclyde researchers.

The device, which has been tested in a laboratory, may be capable of producing results in two-and-a-half minutes, the Biosensors and Bioelectronics journal study suggests.

Diagnosing sepsis can be a complex process.

The UK Sepsis Trust said it welcomed the research but added that no test was perfect at spotting the condition.

It is estimated that 52,000 people in the UK die every year from sepsis, which is a serious complication of an infection.

There is a lot of research going on to attempt to find out what exactly triggers the sometimes fatal reaction involved in sepsis.

The initial problem can be quite mild and start anywhere - from a cut on the finger to a chest or urine infection - but if left untreated can set off a cascade of reactions, from shock to organ failure and in some cases, death.

Early diagnosis is key because for every hour that antibiotic treatment is delayed, the likelihood of death increases.

Diagnosis of sepsis is usually based on clinical judgement, body temperature, heart rate, breathing rate, and a series of blood tests.

As soon as sepsis is suspected, broad-acting antibiotics should be given to the patient. A blood test that aims to determine the best antibiotic to treat the infection can take up to 72 hours.

The new test uses a device to detect if one of the protein biomarkers of sepsis, interleukin-6 (IL-6), is present in the blood.

Dr Damion Corrigan, who helped develop the test, said IL-6 is one of the best markers of sepsis. "The type of test we envisage could be at the bedside and involve doctors or nurses being able to monitor levels of sepsis biomarkers for themselves."

He said the test would work well in GP surgeries and in A&E to quickly rule sepsis in or out, if it was eventually approved through clinical trials.

Dr Corrigan added that sepsis not only kills people but can also leave them with life-changing problems, such as limb loss, kidney failure and even post-traumatic stress disorder. The idea is that the device could be implanted and used on patients in intensive care.

Sepsis symptoms

Symptoms in adults:

- ***Slurred speech or confusion***
- ***Extreme shivering or muscle pain***
- ***Passing no urine in a day***
- ***Severe breathlessness***
- ***It feels like you're going to die***
- ***Skin mottled or discoloured***

Symptoms in children:

- ***Breathing very fast***
- ***Fit or convulsion***
- ***Looks mottled, bluish, or pale***

- ***Has a rash that does not fade when you press it***
- ***Is very lethargic or difficult to wake***
- ***Feels abnormally cold to touch***

With early diagnosis and the correct treatment, normally antibiotics, most people make a full recovery.

Source: UK Sepsis Trust

The project's clinical adviser and co-author, Dr David Alcorn, from Paisley's Royal Alexandra Hospital, said the tiny electrode had the potential to detect sepsis and, at the same time, diagnose the type of infection and the recommended antibiotic.

"The implications for this are massive, and the ability to give the right antibiotic at the right time to the right patient is extraordinary.

"I can definitely see this having a clear use in hospitals, not only in this country, but all round the world."

The researchers have applied for funding to develop a prototype device and hope to get commercial interest in taking it forward.

They hope the low-cost test could come into everyday use in three to five years.

Delayed diagnosis of sepsis

Ryan Sutherland, from Clackmannanshire, ended up in a coma with sepsis, which had been misdiagnosed. He had felt unwell with a sore throat that got worse, but was told by a doctor it was a viral infection.

"As the week went on, it got worse and by the Thursday it was really bad. My wife took me to the out-of-hours doctor that night and by this point I was really unwell and could barely move. But I was given an anti-sickness injection and then I was sent home."

Hours later he collapsed. He was taken to hospital and suffered two cardiac arrests. His body went into shock with the sepsis and his organs started to shut down. After eight days in a coma, Ryan woke up and made an almost complete recovery.

"No-one mentioned sepsis, although looking back I had all the symptoms," said Ryan.

"It's hard to diagnose, so if this test had been around it could have made all the difference to what happened with me."

The UK Sepsis Trust estimates that earlier diagnosis and treatment across the UK would save at least 14,000 lives a year.

Dr Ron Daniels, the trust's chief executive officer, said: "Any kind of test that enables us to identify sepsis earlier, before symptoms even present themselves, could help save even more lives and bring us closer to our goal of ending preventable deaths from sepsis.

"Systems like this are so important as, with every hour before the right antibiotics are administered, risk of death increases.

"No test is perfect in the identification of sepsis, so it's crucial we continue to educate clinicians to think sepsis in order to prompt them to use such tests."

Update 19 February 2019: This article has been amended to more accurately reflect the stage of development that this new rapid test has reached and the continuing difficulties in diagnosing sepsis.

http://bit.ly/2BFpfkH

Oral antifungal drug used to treat yeast infections linked to higher rates of miscarriage

Fluconazole linked to higher rates of miscarriage if used during pregnancy

A commonly used medication, fluconazole, used to treat vaginal yeast infections, is linked to higher rates of miscarriage if used during pregnancy, found new research published in *CMAJ (Canadian Medical Association Journal)*.

While topical treatments are first line for pregnant women with fungal infections, oral fluconazole is often used during pregnancy.

Researchers looked at data on 441 949 pregnancies from the Quebec Pregnancy Cohort between 1998 and 2015, linking to filled prescriptions listed in the Quebec Prescription Drug Insurance database. They found that taking oral fluconazole was linked to adverse outcomes.

"Our study shows that taking any dose of oral fluconazole while pregnant may be associated with a higher chance of miscarriage," says Dr. Anick Bérard, Université de Montréal, Montréal, Quebec. "Taking higher doses of fluconazole over 150 mg in early pregnancy may be linked to a higher chance of a newborn with a heart defect."

The study is consistent with other studies, although more research is needed as the study sizes are still small.

In a related commentary, Drs. Vanessa Paquette and Chelsea Elwood, British Columbia Women's Hospital and Health Centre, Vancouver, BC, write, "The study re-emphasizes safe prescribing practices in pregnancy, which include confirming the correct diagnosis and then choosing the safest medication with the largest body of data in pregnancy at the lowest appropriate doses."

"Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies" is published February 19, 2019.

http://bit.ly/2Xqwt8j

Organs of brain-dead boy under 6 to be donated, in only 10th such case for Japan

"A kind boy who would give anything to others in need"

JIJI, Kyodo

The family of a boy under 6 judged brain dead under the Organ Transplant Law has agreed to donate his organs, according to the Japan Organ Transplant Network.

This is the 10th case of organ donation by a donor under 6 announced by the network, which is the only intermediary organization for organ transplants in Japan.

The boy had been hospitalized in Gunma Prefecture. The donation of his organs was announced on Sunday.

"Because our son was a kind boy who would give anything to others in need, we believe the choice of organ transplants meets his wishes," the boy's parents said in a statement released through the network.

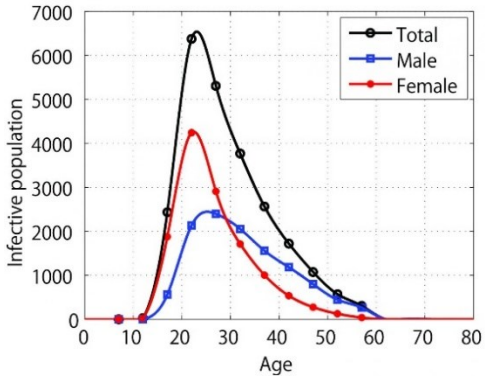
The boy's heart will be given to a girl under 10 at University of Tokyo Hospital, his lungs to a girl under 10 at Tohoku University Hospital, his liver to a girl under 10 at the National Center for Child Health and Development, and his kidneys to a teenager at Toho University's Omori Medical Center.

http://bit.ly/2Nifa1X

Epidemiological model lends insight to chlamydia outbreak in Japan

Mathematical models that quantify the dynamics of infectious diseases are crucial predictive tools for the control of ongoing and future outbreaks.

An infection's basic reproduction number (R_0) is especially important to disease modeling and epidemiology, as it determines global behavior and measures a disease's transferability within a fully-susceptible population. In short, R_0 helps public health officials discern an epidemic's intensity and the likelihood of its successful spread. If $R_0>1$, an outbreak occurs. If $R_0<1$, the infection typically dies out.



This is an interpolation of age-distributions of reported cases of chlamydia in Japan in 2015. **Toshikazu Kuniya, SIAM Journal on Applied Mathematics.**

Sometimes a disease is endemic, meaning that it is continuously present and maintained at a baseline level in a specific location. In these cases, the number of infective individuals remains nearly static and in endemic equilibrium. Chlamydia, a sexually transmitted disease in both men and women that can cause significant damage to a woman's reproductive system, has been endemic in Japan since 2012. To mathematically estimate R_0 for chlamydia's pervasiveness in Japan, one must clarify the stability of the corresponding model's endemic equilibrium.

In an article publishing on February 19th in the *SIAM Journal on Applied Mathematics*, a publication of the Society for Industrial and Applied Mathematics, Toshikazu Kuniya studies the global behavior of a multi-group SIR epidemic model with age structure and uses the model to estimate R_0 for Japan's chlamydia outbreak. Kuniya has been modeling infectious diseases since he was a master's student and is especially curious about their global behavior. "I have recently become interested in the application of epidemic models to their epidemiological considerations," he said. "I think the global behavior of epidemic models plays an important role in understanding infectious disease data in the long-time scale."

An SIR model--which stands for susceptible, infective, and recovered--is a simple compartmental model and one of the most basic mechanisms of mathematical epidemiology. It divides the total population of an affected area into the three aforementioned classes. This type of model converges to a disease-free equilibrium when $R_0<1$ and an endemic equilibrium when $R_0>1$.

While Kuniya's model is quite similar to one employed by previous researchers, Kuniya reformats it into a multi-group model with age-dependent susceptibility. "I chose a multi-group SIR epidemic model with age structure because it is useful to handle the data with the heterogeneity (sex, age, position, etc.) of each person," he said. "The age structure enables us to consider the effects of the demographic age distribution's time variation and the age-dependency of each epidemic parameter."

For the sake of simplicity, Kuniya assumes that the sum of the mortality and recovery rates is constant. He also weakens some of the prior model's restrictive assumptions that prevented successful application. "Under the previous assumption, the disease transmission coefficient was independent of the state of infective individuals," Kuniya said. "In this study, we have weakened this assumption to be able to consider the disease transmission coefficient's possible dependence on the state of infective individuals. By virtue of this, we can model the disease transmission from male individuals to female individuals and vice versa." Doing so allows him to prove that R_0 completely determines the model's global behavior. It also eliminates the possibility of an unstable endemic equilibrium if $R_0>1$.

After establishing his model, Kuniya applies it to the 2015 manifestation of chlamydia in Japan, for which there is an available heterogeneous dataset arranged by age and sex. Chlamydia's seemingly endemic state in recent years also made the disease an appropriate target. Kuniya examines four particular cases--in the form of a homogenous model, an age-independent two-sex model, an age-dependent one-sex model, and an age-dependent two-sex model--and compares the estimated results of R_0. These special cases yield an R_0 estimate between 1.0148 and 1.0535 for chlamydia in Japan. His analysis also reveals that introduction of an age structure impacts the value of R_0 more strongly than application of a two-group structure. This indicates that ordinary differential equation models lacking age structure--while typically easier to use than partial differential equation models with age structure--might ultimately underestimate R_0.

Throughout the course of his investigation, Kuniya assumes that all infective individuals are documented, when in reality some occurrences of chlamydia likely go unreported -- especially because the disease often shows no symptoms. This discrepancy may have led to underestimated R_0 values for the four individual cases. Accounting for unreported cases and improving the estimation's overall accuracy is a task for forthcoming study.

In the future, Kuniya hopes to apply his findings to more general models with more than two groups, which requires an increasingly elaborate dataset. "I think we can improve the estimation of R_0 and other epidemic parameters by using a more detailed dataset

subdivided according to the heterogeneity--for instance, sexual activity--of each individual," he said. "We can apply our theoretical results to more general cases with arbitrary numbers of groups."

Kuniya, Toshikazu. (2019). Global Behavior of a Multi-group SIR Epidemic Model with Age Structure and an Application to the Chlamydia Epidemic in Japan. SIAM J. Appl. Math. To be published.

http://bit.ly/2NileHL

Blood of the young won't spare rich old people from sadness and death, FDA says

FDA's Gottlieb: "Simply put, we're concerned that some patients are being preyed upon."

Beth Mole - 2/20/2019, 6:35 AM

Not so fast, says the FDA. **Getty | Silver Screen Collection**

The US Food and Drug Administration issued an alert Tuesday, February 19, warning older consumers against seeking infusions of blood plasma harvested from younger people. Despite being peddled as anti-aging treatments and cures for a range of conditions, the transfusions are unproven and potentially harmful.

In a statement, FDA Commissioner Scott Gottlieb and the director of FDA's Center for Biologics Evaluation and Research, Peter Marks, wrote:

Simply put, we're concerned that some patients are being preyed upon by unscrupulous actors touting treatments of plasma from young donors as cures and remedies.

Establishments in several states are now selling young blood plasma, which is the liquid portion of blood that contains proteins for clotting. The sellers suggest that doses of young plasma can treat conditions ranging from normal aging and memory loss to dementia, Parkinson's disease, multiple sclerosis, Alzheimer's disease, heart disease, or post-traumatic stress disorder, according to the FDA.

The claims are wild extrapolations from intriguing but preliminary findings in mouse studies. Over the years, rodent experiments have hinted that components of young mouse blood may invigorate older mice, potentially acting as an anti-aging treatment. However, the results are unclear, controversial, and—most importantly—not proven to have any relevance to human health.

The FDA goes on to note that such infusions are known to pose a range of health risks in humans. These risks include spreading infectious disease, triggering allergic reactions, and causing lung injuries. In some people—particularly those with heart disease—the infusions can also overload the circulatory system, causing swelling and breathing trouble, the agency explains.

Though the FDA didn't name any infusion companies specifically in its alert, one that has received a lot of media attention is a startup called Ambrosia. It has locations in Phoenix, Arizona; Los Angeles, California; Tampa, Florida; Omaha, Nebraska; and Houston, Texas, according to the company's website. Customers 30 years old and above can set up an infusion appointment for plasma harvested from healthy donors aged 16 to 25. A single liter goes for $8,000, while two liters cost $12,000. Neither is covered by insurance.

The company conducted a clinical trial of its infusions in 2016, which wrapped up last year. The trial involved 200 patients aged 35 or older and was said to assess biomarkers in the blood related to aging and certain diseases, including "anemia, neutropenia, thrombocytopenia, obesity, diabetes, high cholesterol, elevated risk of cancer, atherosclerosis, dementia, and cataracts."

It's unclear how the trial turned out or if the company had released any of the results. Ambrosia's website simply states that a trial "studied the benefits of young plasma."

Ambrosia did not respond to Ars' request for comment.

In their statement, Gottlieb and Marks added that, if they find any young-blood companies misleading consumers, they were prepared to take "regulatory and enforcement actions."

[UPDATE, 2/19/2019, 7:30ET:] *Ambrosia announced on its website that "In compliance with the FDA announcement issued February 19, 2019, we have ceased patient treatments."*

http://bit.ly/2GSZrFn

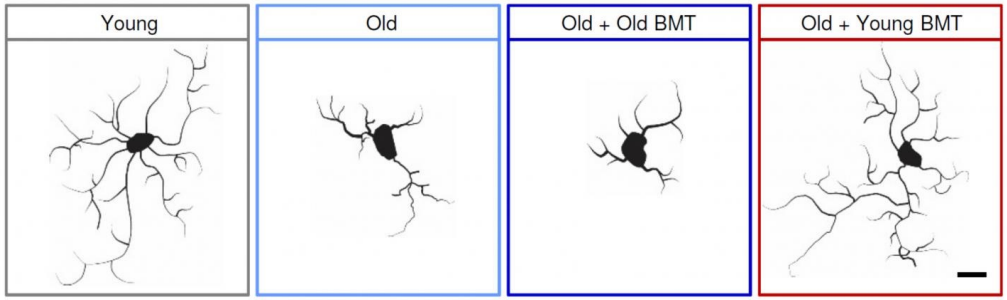
Young bone marrow rejuvenates aging mouse brains, study finds

Transplanting marrow from young lab mice to old mice preserves memory and learning skills

LOS ANGELES - A new study has found that transplanting the bone marrow of young laboratory mice into old mice prevented cognitive decline in the old mice, preserving their memory and learning abilities. The findings support an emerging model that attributes cognitive decline, in part, to aging of blood cells, which are produced in bone marrow.

"While prior studies have shown that introducing blood from young mice can reverse cognitive decline in old mice, it is not well understood how this happens," said Helen Goodridge, PhD, associate professor of Medicine and Biomedical Sciences at Cedars-Sinai and co-senior author of the study. "Our research suggests one answer lies in specific properties of youthful blood cells."

If further research confirms similar processes in people, the findings could provide a pathway for designing therapies to slow progression of neurodegenerative diseases, including Alzheimer's, that affect millions of Americans, Goodridge said.



Microglia in brains of old mice have larger cell bodies with fewer and shorter branches than those in young mice. But microglia of old mice who received bone marrow transplants (BMT) from young mice resembled those of young mice; transplants from older mice didn't have that effect. Microglia play an important role in brain health. **Cedars-Sinai / Communications Biology**

In the study, published in the journal Communications Biology, 18-month-old laboratory mice received bone marrow transplants from either 4-month-old mice or mice their own age. Six months later, both transplanted groups underwent standard laboratory tests of activity level and learning, plus spatial and working memory. Mice that received young bone marrow outperformed mice that received old bone marrow. They also outperformed a control group of old mice that did not get transplants.

The research team then examined the hippocampus, a region associated with memory, in the mice brains. Recipients of young bone marrow retained more connections, known as synapses, between neurons in the hippocampus than did recipients of old bone marrow, even though they had about the same number of neurons. Synapses are critical to brain performance.

Further tests showed a possible reason for the missing synapses. The blood cells made by the young bone marrow reduced the activation of microglia, a type of immune cell in the brain. Microglia support neuron health but can become overactive and participate in disconnection of the synapses. With fewer overactive microglia, neurons would remain healthy and more synapses would survive.

"We are entering an era in which there will be more elderly people in the population, along with an increased incidence of Alzheimer's disease, putting a huge burden on the health system," said Clive Svendsen, PhD, director of the Cedars-Sinai Board of Governors Regenerative Medicine Institute, professor of Biomedical Sciences and Medicine and co-senior author of the new study. "Our work indicates that cognitive decline in mice can be significantly reduced by simply providing young blood cells, which act on the brain to reduce the loss of synapses related to aging."

Translating the findings, if confirmed in human samples, into potential treatments may be challenging, given that bone marrow transplants are not currently feasible for this use. But for future studies in people, Svendsen is working on creating "personalized" young blood stem cells for an individual through stem cell technology. These cells possibly could be used to help replace the individual's own aging blood stem cells and help prevent cognitive decline and perhaps neurodegenerative diseases such as Alzheimer's as well.

https://wb.md/2NqqSAK

Invasive Group B Strep Rising Among Nonpregnant Adults

GBS among nonpregnant adults has risen significantly and continues to rise

Troy Brown, RN

The public health burden of invasive Group B *Streptococcus* (GBS) disease among nonpregnant adults has risen significantly and continues to rise, a large study has found. The incidence was highest among males, those aged 65 years or older, and black individuals; it also increased with age. The percentage of isolates that were resistant to clindamycin also rose.

"The incidence of invasive GBS in nonpregnant adults continues to rise, with rates now exceeding those for invasive pneumococcal disease. The rise parallels an increasing prevalence of underlying conditions, such as obesity and diabetes, and was associated with serotypes Ib, II, and IV," the researchers write. "Increasing resistance to clindamycin is also a concern given its clinical use in the management of [skin/soft tissue infections; SSTIs] a common manifestation of GBS disease."

Louise K. Francois Watkins, MD, MPH, from the Epidemic Intelligence Service Program, Centers for Disease Control and Prevention, Atlanta, Georgia, and colleagues published their findings online February 18 in *JAMA Internal Medicine*.

They conducted a population-based study that included 21,250 patients with Active Bacterial Core surveillance (ABCs) network-detected invasive GBS from 2008 through 2016. During that time, invasive GBS incidence among nonpregnant adults rose significantly from 8.1 cases per 100,000 population in 2008 to 10.9 in 2016 (P = .002 for trend).

"The focus of this study was limited to invasive GBS disease. Group B *Streptococcus* also causes a substantial burden of noninvasive disease, including urinary tract infections, noninvasive SSTIs, and pneumonia, so the overall burden in adults is likely much higher," the researchers explain.

During 2016, 3146 cases of invasive GBS were reported (59% male; median age, 64 years; age range, 18 - 103 years). When the authors projected these numbers to the US population, they estimated 27,729 cases of invasive GBS occurred in the United States in 2016, with 1541 deaths. Almost all (95%) of cases that year occurred in a patient with one or more underlying conditions, the most common of which was obesity. Rates of obesity (53.9%) and diabetes (53.4%) were high among those with invasive GBS.

Invasive GBS is often severe and can be fatal. In 2016, 94.6% of cases were hospitalized, 27.3% of cases required intensive care unit admission, and 5.6% of cases were fatal. "This rise represents a

clinical and public health concern. Incidence is rising disproportionately among certain demographic groups, particularly whites, men, and adults aged 40 to 64years," the researchers write.

The most common clinical syndromes were SSTIs (34.0%) and bacteremia without focus (32.3%), followed by osteomyelitis (13.3%), pneumonia (10.2%), septic arthritis (10.2%), and septic shock (9.4%). Other clinical syndromes were abscess, intra-abdominal infection, endocarditis, meningitis, and necrotizing fasciitis.

"Rather than a specific immune deficiency, nonpregnant adults with GBS infections share underlying conditions, such as obesity, diabetes, neurologic disease, cancer, liver disease, renal disease, heart failure, and chronic skin disorders, that may diminish blood flow and weaken barrier protection in colonized sites and allow entry of GBS into deeper tissues," Miriam Baron Barshak, MD, from the Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, writes in an invited commentary.

Resistance to clindamycin rose from 37.0% of isolates tested in 2011 to 43.2% of those tested in 2016 (P = .02). Most (86.4%) isolates tested in 2016 belonged to serotypes Ia, Ib, II, III, and V. Prevalence of serotype IV rose from 4.7% in 2008 to 11.3% in 2016 (P < .001 for trend).

"Clinician awareness of trends in antimicrobial resistance of GBS is important when susceptibility results are not available and empirical therapy is necessary. Rising clindamycin resistance is of particular clinical significance in the setting of SSTIs, where clindamycin is often considered a first-line antimicrobial agent," the authors caution.

Although the administration of intrapartum antibiotics effectively prevents neonatal GBS disease, "a time-limited duration of antibiotics" is not an appropriate strategy for nonpregnant adults, Barshak writes.

Recommendations for Clinicians

"This report alerts us that there is a large, medically complex population of nonpregnant adults at risk for GBS that is much more heterogeneous than the obstetric and neonatal populations who were the predominant hosts for these infections in the past," Barshak explains. "As internists, it is important to consider GBS as a contributor to infectious syndromes, particularly in patients with risk factors, including obesity and/or diabetes; to obtain cultures before antibiotic prescription; and to consider carefully the choice of empirical treatment in these patients."

It can be difficult to identify GBS infections before culture results are available because no unusual epidemiologic exposures are needed to develop GBS infections. "Because the clinical syndromes generally are not unique to GBS, it is critical to collect cultures that will help make the diagnosis," she continues.

The increasing resistance to clindamycin is concerning because clindamycin is a common empirical treatment for SSTIs and respiratory infections, particularly in those who are allergic to β-lactam antibiotics, she said, adding that β-lactams and vancomycin are still generally reliable antibiotics for treating GBS.

Ideally, empirical treatment in these clinical situations should include an antibiotic that is reliably effective against GBS — "specifically a β-lactam or vancomycin, because clindamycin and macrolides are not reliable agents in the current era," she adds.

Barshak cautions clinicians to recognize that GBS is likely when preliminary culture results are positive for β-hemolytic streptococci and to confirm the appropriateness of antibiotic coverage.

On the other hand, finding GBS in a sterile site culture of a patient with no known predisposing conditions can be a tip-off that the patient may have unrecognized diabetes or other underlying conditions, Barshak continues.

"Ongoing surveillance to monitor future trends in serotype distribution and antibiotic resistance is warranted. Improved physician awareness and efforts aimed at reducing risk factors, such as obesity and diabetes, along with efforts to maintain skin integrity and provide optimal wound care, may help prevent invasive GBS infections," the researchers conclude.

One study author reports receiving travel support from Sanofi Pasteur to attend a meeting on meningococcal disease and vaccines, reports receiving consulting fees from Merck to make a presentation on pneumococcal epidemiology and vaccines, and reports serving on a GlaxoSmithKline scientific advisory board on meningococcal vaccines. One author reports being a member of data safety monitoring boards for Merck and Pfizer and consulting with Dynavax, Seqirus, SutroVax, and Shionogi Inc. The remaining study authors have disclosed no relevant financial relationships. Barshak has disclosed no relevant financial relationships.

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https://wb.md/2XbUBJ7

'It's Not Every Day' This Response Rate Seen in TNBC

New Agent for Aggressive Breast Cancer in NEJM

Nick Mulcahy

A novel targeted therapy has shown activity in an aggressive type of breast cancer.

The investigational drug sacituzumab govitecan (Immunomedics) yielded a 33% response rate among patients with metastatic triple-negative breast cancer (TNBC) who were heavily pretreated.

For such patients, the current standard of treatment is chemotherapy, which historically has been associated with low response rates of 10% to 15%.

The new data come from a phase 1/2 trial published online February 21 in the *New England Journal of Medicine*.

TNBC, an aggressive disease that is associated with relatively poor prognosis, lacks three cellular targets present in more common forms of breast cancer. The lack of actionable mutations and molecular targets for drugs to act upon is part of the reason for the poorer outcomes of patients with TNBC, say the authors.

Sacituzumab govitecan may represent a change — it has a target.

Given intravenously, the experimental agent is an antibody–drug conjugate in which SN-38, an active metabolite of the chemotherapy drug irinotecan (multiple brands), is coupled to a monoclonal antibody that targets an antigen that has high expression in TNBC and induces cancer cell growth, explain the study authors.

The new study included 108 patients (median age, 56 years) who had undergone a median of three previous lines of therapy. There were 36 responses (three complete and 33 partial). The median duration of response was 7.7 months; 45.4% of patients, including those with stable disease, derived clinical benefit.

Median progression-free survival was 5.5 months, and overall survival was 13.0 months.

"It's not every day that we see this sort of clinical activity in this aggressive subtype of breast cancer," said senior study author Kevin Kalinsky, MD, in an interview with *Medscape Medical News*. He is a medical oncologist at New York–Presbyterian Hospital and Columbia University Medical Center in New York City.

Among such heavily pretreated patients, progression-free survival with standard chemotherapy is just 2 to 3 months, the study authors say.

Kalinsky added that the new data demonstrate "impressive results," despite the fact that it is an early-phase trial.

Sacitizumab represents one of the most promising new drugs for TNBC. Dr Charles Shapiro

"I think this drug has the potential to change practice, because the data look so compelling, even with the relatively small number of patients in the trial," Kalinsky said speculatively in a press statement.

Approached for comment, Charles Shapiro, MD, director of translational breast cancer research, Tisch Cancer Institute at Mount Sinai, New York City, said that on the basis of the new report,

"sacitizumab represents one of the most promising new drugs for TNBC."

If the current results are confirmed, the agent will likely be tested in the first-line metastatic setting and perhaps also in early-stage disease, Shapiro commented to *Medscape Medical News*.

He also pointed out that the drug model of a bispecific antibody drug conjugate has already been shown to be effective in breast cancer. Among such drugs is trastuzumab emtansine (TDM-1), which has shown efficacy in the treatment of HER2+ disease.

Trop-2 Target

The new drug targets humanized antitrophoblast cell-surface antigen 2 (Trop-2), which is a "transmembrane calcium signal transducer" that stimulates cancer cell growth, the authors explain. It has limited expression in normal tissue and is overexpressed in many epithelial cancers, including TNBC, they add.

"High expression of Trop-2 in triple-negative breast cancer and its association with a poor prognosis suggest that it is a rational therapeutic target in this patient population," write the study authors, citing other research.

Trop-2 expression was not measured in the current study. It will be assessed retrospectively in a confirmatory randomized, phase 3 trial (ASCENT) that is currently recruiting patients in North America and Europe. In that trial, sacituzumab govitecan will be compared with physicians' choice of chemotherapy.

New treatments are needed for all metastatic TNBC patients, inasmuch as overall survival has not changed in 20 years, the study authors point out.

Low Rate of Treatment Discontinuation

In the study, patients received sacituzumab govitecan intravenously (10 mg/kg body weight) on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity.

The 108 participants received a mean of 18.7 doses of sacituzumab govitecan, or 9.6 cycles. The median duration of exposure was 5.1 months.

Three patients discontinued treatment because of adverse events, and two patients discontinued because of drug-related events.

The most common adverse events were nausea, diarrhea, fatigue, neutropenia, and anemia, write the investigators.

The most common adverse events of grade 3 or higher included neutropenia, anemia, and a decreased white-cell count.

Diarrhea was highlighted by the investigators as the second most common adverse event, occurring in 62% of the patients overall (all grades). The incidence of grade 2 diarrhea was 14%, and the incidence of diarrhea of at least grade 3 was 8%.

No peripheral neuropathy of grade 3 or higher was reported.

"Importantly, the drug did not cause neuropathy, the numbness and tingling that can be quite painful and limiting for patients," Kalinsky said. "It is promising to have an active treatment that does not have neuropathy as a side effect," he added.

On-treatment death occurred in four patients (4%) within 30 days of the last dose. All such deaths were attributed to disease progression by the treating investigator.

Serious adverse events were reported in 35 patients (32%); the most common (>2% incidence) were febrile neutropenia (7%), vomiting (6%), nausea (4%), diarrhea (3%), and dyspnea (3%).

The study authors summarize that sacituzumab govitecan has a better side effect profile (and efficacy) than irinotecan (multiple brands), possibly because of its ability to more precisely deliver a cytotoxic drug, SN-38, to tumor cells.

In addition, the cytotoxic activity of SN-38 (delivered via sacituzumab govitecan) is much greater than that of irinotecan, add the authors, citing laboratory research.

Immunotherapy in TNBC

Sacituzumab govitecan becomes the second new agent to recently show promise in the treatment of metastatic TNBC.

In October 2018, investigators from the IMpassion130 trial reported that progression-free survival was 7.2 months for patients with metastatic disease who received the immunotherapy drug atezolizumab (*Tecentriq*, Genentech) with nab-paclitaxel vs 5.5 months for those who received placebo with nab-paclitaxel (P < .0001). Subset analyses indicated that atezolizumab may also provide an overall survival advantage.

The response rate with atezolizumab plus nab-paclitaxel was 56% in IMpassion130.

However, Kalinsky pointed out that atezolizumab plus nab-paclitaxel was used in the first-line treatment setting, whereas in the study they report, sacituzumab govitecan was tested in heavily pretreated patients.

The new drug may be a candidate to be combined with immunotherapy in the treatment of TNBC, he suggested.

In the current study, confirmed objective responses were found in patients who had received previous programmed cell death protein–1 (PD-1)–based therapy or programmed cell death–ligand-1 (PD-L1)–based therapy. This suggests a lack of cross-resistance with immune checkpoint inhibitors and the potential usefulness of combination therapy, he said.

Sacituzumab govitecan is also being studied in urothelial cancer, lung cancer, and progesterone receptor–positive breast cancer. To date, response rates have been similar to those observed in TNBC, said Kalinsky.

Immunomedics funded the study. Kalinsky reports financial ties to Immunomedics. Study authors include employees of the company. Shapiro has disclosed no relevant financial relationships.

N Engl J Med. Published online February 21, 2019. Abstract

http://bit.ly/2tybjVx

How zebra stripes disrupt flies' flight patterns

A 'costume change' for zebras and horses reveals how stripes thwart horsefly landings

Scientists learned in recent years why zebras have black and white stripes - to avoid biting flies. But a study published today in the journal *PLOS ONE* probes the question further: What is it about stripes that actually disrupts a biting fly's ability to land on a zebra and suck its blood?

Joren Bruggink of Aeres University of Applied Sciences, at left, and Jai Lake of the University of Bristol investigate how horse flies behave around horses wearing different colored coats. This was part of an experiment led by UC Davis, focused on why zebra stripes are so good at warding off biting flies.

Tim Caro/UC Davis

UC Davis Professor Tim Caro and Martin How of the University of Bristol led a series of new experiments to better understand how stripes manipulate the behavior of biting flies as they attempt to come in to land on zebras. Taking place on a horse farm in Great Britain that kept both zebras and horses, the experiments entailed:

- ***Close-up observation of zebras as flies attempted to land on them***
- ***Detailed videos to record flight trajectories as the flies cruised close to the zebras***
- ***Dressing the horses and zebras sequentially in black, white and then black-and-white striped coats.***

Stripes make lousy landing strips

In the study, flies were just as attracted to zebras as they were to horses, indicating that stripes do not deter flies at a distance.

"Once they get close to the zebras, however, they tend to fly past or bump into them," said Caro, a professor in the UC Davis Department

of Wildlife, Fish and Conservation Biology. "This indicates that stripes may disrupt the flies' abilities to have a controlled landing." Compared to rates at which flies landed on the white and the black coats, hardly any landed on the striped coats.

"Stripes may dazzle flies in some way once they are close enough to see them with their low-resolution eyes," said How.

Zebras swish and run, horses twitch

The study also noted that zebras and horses respond very differently to the presence of flies. Zebras swish their tails almost continuously during the day to keep flies off; they stop feeding if bothered by them; and if the flies are particularly persistent, the zebras will run from them. Horses, on the other hand, primarily twitch and occasionally swish to ward off flies. As a result, any flies that actually contacted zebras were soon dislodged compared to horses.

Researchers do not yet understand why zebras evolved these sophisticated defense mechanisms. A possible explanation is zebras may be highly prone to infectious diseases carried by African biting flies, although that hypothesis requires further study.

The study's co-authors include Yvette Argueta from UC Davis; Emmanuelle Sophie Briolat, Maurice Kasprowsky, Matthew Mitchell and Sarah Richardson of the University of Exeter; Joren Bruggink of the Netherlands' Aeres University of Applied Sciences; and Jai Lake from the University of Bristol.

http://bit.ly/2U6tyNu

Native California medicinal plant may hold promise for treating Alzheimer's

Salk scientists identify possible healing compound in Yerba santa

LA JOLLA - The medicinal powers of aspirin, digitalis, and the anti-malarial artemisinin all come from plants. A Salk Institute discovery of a potent neuroprotective and anti-inflammatory chemical in a native California shrub may lead to a treatment for Alzheimer's disease based on a compound found in nature. The research appears in the February 2019 issue of the journal *Redox Biology*.

"Alzheimer's disease is a leading cause of death in the United States," says Senior Staff Scientist Pamela Maher, a member of Salk's Cellular Neurobiology Laboratory, run by Professor David Schubert. "And because age is a major risk factor, researchers are looking at ways to counter aging's effects on the brain. Our identification of sterubin as a potent neuroprotective component of a native California plant called Yerba santa (*Eriodictyon californicum*) is a promising step in that direction."

Native California tribes, which dubbed the plant "holy herb" in Spanish, have long used Yerba santa for its medicinal properties. Devotees brew its leaves to treat respiratory ailments, fever and headaches; and mash it into a poultice for wounds, sore muscles and rheumatism.

To identify natural compounds that might reverse neurological disease symptoms, Maher applied a screening technique used in drug discovery to a commercial library of 400 plant extracts with known pharmacological properties. The lab had previously used this approach to identify other chemicals (called flavonoids) from plants that have anti-inflammatory and neuroprotective properties.

Through the screen, the lab identified a molecule called sterubin as Yerba santa's most active component. The researchers tested sterubin and other plant extracts for their impact on energy depletion in mouse nerve cells, as well as other age-associated neurotoxicity and survival pathways directly related to the reduced energy metabolism, accumulation of misfolded, aggregated proteins and inflammation seen in Alzheimer's. Sterubin had a potent anti-inflammatory impact on brain cells known as microglia. It was also an effective iron remover--potentially beneficial because iron can contribute to nerve cell damage in aging and neurodegenerative diseases. Overall, the compound was effective against multiple inducers of cell death in the nerve cells, according to Maher.

"This is a compound that was known but ignored," Maher says. "Not only did sterubin turn out to be much more active than the other flavonoids in Yerba santa in our assays, it appears as good as, if not better than, other flavonoids we have studied."

Next, the lab plans to test sterubin in an animal model of Alzheimer's, then determine its drug-like characteristics and toxicity levels in animals. With that data, Maher says, it might be possible to test the compound in humans, although it would be critical to use sterubin derived from plants grown under standardized, controlled conditions. She says the team will likely generate synthetic derivatives of sterubin.

Other authors on the study are senior staff scientist Wolfgang Fischer, staff scientist Antonio Currais and postdoctoral fellows Zhibin Liang and Antonio Pinto.

This work was supported by the National Institutes of Health, the Edward N. & Della Thome Memorial Foundation and the Paul F. Glenn Center for Aging Research at the Salk Institute.

http://bit.ly/2Sk4C34

Can a nerve injury trigger ALS?

Anecdotal stories raise possibility that peripheral nerve injury can be a trigger for development amyotrophic lateral sclerosis

A growing collection of anecdotal stories raises the possibility that nerve injury in an arm or a leg can act as a trigger for the development amyotrophic lateral sclerosis, or ALS -- a progressive neurodegenerative disease also known as Lou Gehrig's disease, named after the famous New York Yankee who died of it in 1941.

The connection between ALS and athletes runs deeper than a single ballplayer; people who engage in intense physical activities, such as professional athletes and people in the military, are more likely to be affected by ALS. In some, the disease seems to start after an injury -- muscle weakness at the site of the injury slowly spreads to new areas until weakness in the muscles responsible for breathing causes suffocation.

Now, researchers at the University of Illinois at Chicago are the first to demonstrate that a peripheral nerve injury can trigger the onset and spread of the disease in an animal model of ALS. Their findings, published in the journal *Neurobiology of Disease*, show that rats genetically engineered to develop ALS-like symptoms have an abnormal inflammatory response in the region of the spinal cord associated with an injured peripheral neuron. As the spinal cord inflammation and other damaging processes spread, they cause progressive muscle weakness throughout the body.

"We know that in some patients with ALS the weakness starts in a hand or leg, and the disease spreads. Coincidentally, the patient will describe a recent or remote injury to that same hand or leg that matches the location of their disease onset. We wanted to study how environmental contributions, such as a focal nerve injury, affects how the ALS starts and spreads," said Dr. Jeffery Loeb, the John S. Garvin Endowed Chair in Neurology and Rehabilitation in the UIC College of Medicine and corresponding author of the paper.

"Our results show that a single nerve injury, which is small enough that it only causes temporary weakness in normal animals, can start a cascade of inflammation in the spinal cord that initiates and causes the disease to spread in genetically-susceptible animals," said Loeb. "The ability to precipitate the disease through injury gives us a new animal model we can use to identify treatments for ALS that focus on stopping the spread of the disease after it first starts. The medical community has no therapies that significantly slow or stop the progression of the disease and we are currently putting all of our efforts on developing a drug to do this."

While a growing number of genes have been associated with the development of ALS, only about 10 percent of ALS patients have one or more of these gene mutations and none can explain why the disease presents with localized weakness or how it spreads. Ninety percent of ALS patients develop the disease for unknown reasons.

"This raises an important question of the relative contributions of environment versus genes or nature versus nurture," Loeb said.

One of the most highly-studied gene mutations in ALS is in a gene called SOD1. In their study, Loeb and colleagues used rats with mutated forms of the SOD1 gene, which causes the animals to have higher levels of the SOD1 enzyme and to develop ALS-like symptoms, including progressive muscle weakness, starting at 15 weeks of age.

The researchers surgically injured a single nerve in the leg of both SOD1 and wild-type rats at 10 weeks of age. While all rats had reduced strength in the injured leg post-surgery, the wild-type rats recovered almost completely within a few weeks. The SOD1 rats never returned to normal and also experienced weakness in their other leg.

They also found that surgically-injured rats had elevated and prolonged inflammation, and higher numbers of microglia and astrocyte cells in areas of the spinal cord associated with the injured neuron, and the inflammation and presence of these other cells spread to adjacent neurons.

"This spread of inflammation could potentially explain how the disease spreads once it first starts from the site of injury," Loeb said. "Microglia have many roles, but one role is to prune or eliminate synapses that connect one nerve cell to another. These connections are critical for normal functioning and for survival of neurons during development. Where there was increased inflammation and microglia in the spinal cord, we saw up to a two-fold reduction in the number of synapses."

Loeb explained that once a nerve loses connections with its neighbors, the neighboring cells tend to die off.

"This chain reaction of cell death could be what causes the progressive spread of muscle weakness we see in ALS," Loeb said.

Sarah Schram and Fei Song from the UIC College of Medicine department of neurology and rehabilitation and Dr. Donald Chuang, Greg Schmidt, Dr. Hristo Piponov, Cory Helder, James Kerns and Dr. Mark Gonzales from the UIC College of Medicine department of orthopedics are co-authors on the paper.

This research was supported in part by the Patrick Grange Memorial Foundation, which was founded in 2013 in honor of Patrick Grange, a former NCAA Division I soccer player at the UIC.

http://bit.ly/2VeJmxH

Nature Retracts Paper on Delivery System for CAR T Immunotherapy

The manuscript had amassed more than 50 comments about problematic figures and data on PubPeer.

Diana Kwon

Last September, a group of 27 researchers led by scientists at the Baylor College of Medicine in Texas published a paper in *Nature* reporting a new technique that would allow immune cells to cross the blood-brain barrier and home in on hard-to-reach brain tumors. After garnering more than 50 comments on the anonymous post-publication peer-review website PubPeer, the article was retracted today (February 20).

In the paper, oncologist Nabil Ahmed, Heba Samaha, a research associate at Children's Cancer Hospital Egypt 57357 who worked at Baylor for several years, and colleagues revealed a potential solution for the difficult task of getting the immune cells used in immunotherapy to brain cancers. The researchers reported that by engineering T cells with a "homing system" to bind firmly to molecules on the surface blood vessels—and adding a chimeric antigen receptor (CAR) that could identify cancer cells—they were able to successfully treat glioblastoma, an aggressive form of brain cancer, in mice.

At first, these findings were met with positive attention. The study was discussed in an associated *Nature* News & Views piece, appeared as a research highlight in an associated journal, *Nature*

Immunology, and received a press release, media coverage, and several citations. "The results were very encouraging," Samaha said in the press release. "We observed that T cells with both the homing system and CAR substantially shrunk tumors in all treated animals."

But starting last October, a few weeks after the paper was posted online, comments about potential image manipulation in the article began to appear on PubPeer, and the issue quickly caught the attention of scientists on social media.

Gaetan Burgio, a geneticist at Australian National University who posted a widely circulated Tweet about the manuscript, notes that the extent of alleged image duplication identified in this paper was "quite exceptional."

"If you look at the [PubPeer] comments, [there are] claims of duplications for pretty much every single figure . . . and raw data that did not match figures in the paper," he tells *The Scientist*.

Brian Ferguson, an immunologist at the University of Cambridge, says he was also stunned by the PubPeer posts, which, he adds, "showed suggestions of image manipulation to a degree that I hadn't seen in any paper before."

Around a week after comments started appearing on PubPeer, *Nature* added an Editor's Note to the study, alerting readers that the journal had opened an investigation into the concerns raised about the data presented in the paper.

According to the retraction notice posted today, the authors are pulling the paper "due to issues with figure presentation and underlying data." All the authors, except Samaha, the first author, agreed with the retraction.

"Unfortunately, issues were identified in the presentation of several figure panels and the underlying data [in the paper]," Ahmed writes in an email to *The Scientist*. "I promptly notified the office of research at Baylor College of Medicine, which is looking into the cause of these issues."

Samaha did not respond to *The Scientist*'s requests for comment.

According to Dana Benson, the director of communications at the Baylor College of Medicine, the institution's Committee on Scientific Integrity (COSI) reviews all allegations of scientific misconduct. In an emailed statement to *The Scientist*, she added that these evaluations "take time and these proceedings are strictly confidential."

Some commenters on both PubPeer and social media suggested that the duplicated images should have been caught by peer reviewers. But Burgio believes that the responsibility lies with the publisher, not the reviewer. "I think it's on the publisher to ensure that the paper doesn't contain any image duplication or plagiarism," he says. "It's unfair to rely solely on the reviewer to police the paper."

Nature currently conducts random spot checks of images in manuscripts prior to publication. "If concerns about a figure in a Nature paper are raised, we have software tools that enable us to evaluate images in detail," a *Nature* spokesperson writes in an emailed statement to *The Scientist*. (The spokesperson also noted that the journal could not comment on individual articles for confidentiality reasons).

Some journals, such as the *Journal of Cell Biology* and *The EMBO Journal*, have implemented procedures to screen figures in every article prior to publication. "This [practice] is absolutely admirable," Ferguson says. "How to screen really carefully for image manipulation prior to publication is something that most journals will have to address."

For now, Ferguson notes that social media and post-publication peer review websites such as PubPeer have accelerated that process of identifying and correcting issues in the scientific literature. "This is a good example where post-publication peer-review has had a clear impact," he adds. "I believe that will continue to happen—because there are individuals looking for this stuff all the time."

http://bit.ly/2SZouxR

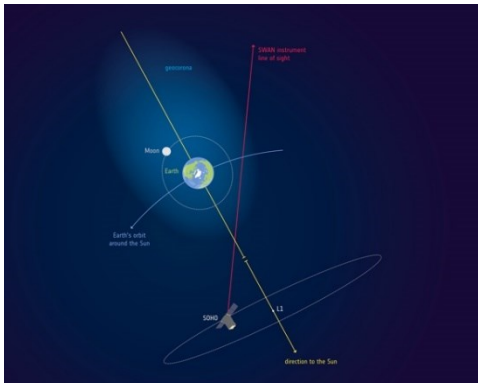
Earth's Hydrogen Geocorona Extends Well Beyond Moon

Recent observations from the NASA/ESA Solar and Heliospheric Observatory (SOHO) show that the Earth's hydrogen envelope reaches up to 391,500 miles (630,000 km) away, or 50 times the diameter of our planet.

by News Staff / Source

Where our atmosphere merges into outer space, there is a cloud of hydrogen atoms called the geocorona.

"The first telescope on the Moon, placed by Apollo 16 astronauts in 1972, captured an evocative image of the geocorona surrounding Earth and glowing brightly in ultraviolet (UV) light," said Dr. Jean-Loup Bertaux, a researcher at the Université Versailles Saint-Quentin in Guyancourt, France.



The extent of Earth's geocorona. **Image credit: ESA.**

"At that time, the astronauts on the lunar surface did not know that they were actually embedded in the outskirts of the geocorona."

The Solar Wind ANisotropies (SWAN) instrument on board SOHO used its sensitive sensors to trace the hydrogen signature and precisely detect how far the very outskirts of the geocorona are.

"The Sun interacts with hydrogen atoms through a particular wavelength of UV light called Lyman-alpha, which the atoms can both absorb and emit," Dr. Bertaux and colleagues explained.

"Since this type of light is absorbed by Earth's atmosphere, it can only be observed from space." "Thanks to its hydrogen absorption cell, the SWAN instrument could selectively measure the Lyman-alpha light from the geocorona and discard hydrogen atoms further out in interplanetary space."

The SWAN observations revealed that sunlight compresses hydrogen atoms in the geocorona on Earth's dayside, and also produces a region of enhanced density on the night side.

The denser dayside region of hydrogen is still rather sparse, with just 70 atoms per cm^3 at 37,300 miles (60,000 km) above Earth's surface, and about 0.2 atoms at the Moon's distance.

"On Earth we would call it vacuum, so this extra source of hydrogen is not significant enough to facilitate space exploration," said Dr. Igor Baliukin, from the Space Research Institute.

"There is also UV radiation associated to the geocorona, as the hydrogen atoms scatter sunlight in all directions, but the impact on astronauts in lunar orbit would be negligible compared to the main source of radiation — the Sun," Dr. Bertaux said.

"On the down side, the Earth's geocorona could interfere with future astronomical observations performed in the vicinity of the Moon."

"Space telescopes observing the sky in UV wavelengths to study the chemical composition of stars and galaxies would need to take this into account."

The findings were published in the *Journal of Geophysical Research: Space Physics*.

I.I. Baliukin et al. *SWAN/SOHO Lyman-α mapping: the Hydrogen Geocorona Extends Well beyond the Moon.* Journal of Geophysical Research: Space Physics, *published online February 15, 2019; doi: 10.1029/2018JA026136*

http://bit.ly/2NoCQBG

As pharmaceutical use continues to rise, side effects are becoming a costly health issue

The use of pharmaceuticals is on the rise and, globally, the expenses for drugs are projected to reach US$1.5 trillion by 2021.

Kevin Dew *

The ageing of populations is one of the drivers of this upward trend, but another important influence is our growing tendency to treat conditions and circumstances we didn't use to medicalise.

Proto diseases

One reason for this medicalisation is the creation of new conditions. The goal of preventing future disability and early death has fashioned new disorders – including high cholesterol and blood pressure. Such proto diseases are based on a person's risk profile at a time when disease is not present and symptoms are not felt.

Proto diseases can be identified in an ever growing proportion of the population. The belief that treating these conditions will lead to future cost savings drives up drug consumption, aimed at bringing cholesterol, blood pressure and glucose levels into line.

A simple shift towards lowering the threshold that determines when someone should be taking such drugs can lead to a substantial expansion in the number of people who are offered them by health professionals. While these medicines can indeed prevent future disease for individuals, if one takes a population health approach, it is not a given that cost savings will outweigh costs incurred.

Evidence-based medicine

Another driver is the dominance of evidence-based medicine (EBM). The idea of basing medicine on evidence would seem to be common sense. However, sitting at the top of the hierarchy of evidence-based medicine is the evaluation procedure of the double-blind, placebo-controlled trial.

This particular type of trial was designed to assess the efficacy of medications. The first such trial assessed the use of streptomycin in the treatment of pulmonary tuberculosis.

Following the fallout from the thalidomide tragedy in the 1950s and 1960s, there was an increased impetus to put in place rigorous procedures for the assessment of potentially toxic pharmaceuticals by clinical trials. This effort to prevent lethal and dangerous drugs getting on to the market was transformed from a test for new drugs to a standard that all therapeutic interventions were expected to meet. This remains the case even though many therapeutic interventions – surgery, counselling, public health advice – do not work like drugs and are not as easy to assess. As a consequence, medications are about the only form of therapeutic intervention that can successfully become evidence-based.

Since the development of the evidence-based medicine movement, there has been a trend where health professionals are required to follow evidence-based protocols and guidelines. These guidelines are an effective way of promoting the expansion of medication use. If health professionals do not follow standards and guidelines – for example don't ask you to take a cholesterol test when you reach a certain age and recommend the cholesterol-lowering drug – they are in danger of being viewed as incompetent practitioners.

For many people their sense of identity is shaped by their relationship to medications. At times they may be reliant on drugs for some quality of life, but they often have to trade off what is gained against at times debilitating side effects.

Remedies and poisons

Some pharmaceuticals work very well. They can help prolong life and ameliorate symptoms. Many people will recall situations where they were glad a drug was readily available.

But the Greek term pharmakon refers to both remedy and poison. Pharmaceuticals are well known for their toxic effects, which is one reason why access to many drugs is carefully controlled, requiring a medical doctor's prescription. But research shows that even with doctors overseeing these drugs, side effects occur on a large scale and we have woefully inadequate means of reporting side effects and adverse reactions.

The costs of responding to adverse drug reactions and the disease and premature death they can cause makes side effects an important

public health problem. Yet only around 10% of serious adverse drug reactions are reported to agencies that monitor drug safety.

To deal with this issue, we need to consider trends in drug consumption, regulation and policy. We need to understand how decisions about drug use are made in clinical consultations and in homes, and how drug monitoring agencies, drug subsidising agencies and drug trial methodologies work.

There is little resistance to the ever expanding use of pharmaceuticals. Individuals, health professionals and health care institutions, nation states and international health agencies are increasingly governed by the dominance of pharmaceutical approaches to health care.

But there are interventions that we could be putting in place to ameliorate this expansion. We need to develop more rigorous vigilance procedures so that when drugs come on the market, they are carefully monitored for adverse reactions, and both patients and health practitioners are actively encouraged to report any concerns to drug monitoring agencies.

We also need to regulate the advertising of prescription medicines more tightly, particularly in New Zealand where drug companies can advertise their products and only have to make fleeting reference to possible side effects.

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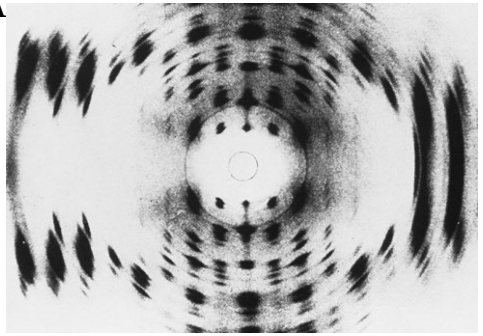
Four new DNA letters double life's alphabet

Synthetic DNA seems to behave like the natural variety, suggesting that chemicals beyond nature's four familiar bases could support life on Earth.

Matthew Warren

The DNA of life on Earth naturally stores its information in just four key chemicals — guanine, cytosine, adenine and thymine, commonly referred to as G, C, A and T, respectively.



Now scientists have doubled this number of life's building blocks, creating for the first time a synthetic, eight-letter genetic language that seems to store and transcribe information just like natural DNA.

An X-ray diffraction image of part of a molecule of DNA. The new, 8-letter version, is similarly stable. **Credit: Science Source/Science Photo Library**

In a study published on 22 February in *Science*[1], a consortium of researchers led by Steven Benner, founder of the Foundation for Applied Molecular Evolution in Alachua, Florida, suggests that an expanded genetic alphabet could, in theory, also support life.

"It's a real landmark," says Floyd Romesberg, a chemical biologist at the Scripps Research Institute in La Jolla, California. The study implies that there is nothing particularly "magic" or special about those four chemicals that evolved on Earth, says Romesberg. "That's a conceptual breakthrough," he adds.

Normally, as a pair of DNA strands twist around each other in a double helix, the chemicals on each strand pair up: A bonds to T, and C bonds with G.

For a long time, scientists have tried to add more pairs of these chemicals, also known as bases, to this genetic code. For example, Benner first created 'unnatural' bases in the 1980s.

Other groups have followed, with Romesberg's lab making headlines in 2014 after inserting a pair of unnatural bases into a living cell.

But the latest study is the first to systematically demonstrate that the complementary unnatural bases recognise and bind to each other, and that the double helix that they form holds its structure.

Benner's team, which includes researchers from various US companies and institutions, created the synthetic letters by tweaking the molecular structure of the regular bases.

The letters of DNA pair up because they form hydrogen bonds: each contains hydrogen atoms, which are attracted to nitrogen or oxygen atoms in their partner.

Benner explains that it's a bit like Lego bricks that snap together when the holes and prongs line up.

By adjusting these holes and prongs, the team has come up with several new pairs of bases, including a pair named S and B, and another called P and Z[2].

In the latest paper, they describe how they combine these four synthetic bases with the natural ones.

The researchers call the resulting eight-letter language 'hachimoji' after the Japanese words for 'eight' and 'letter'. The additional bases are each similar in shape to one of the natural four, but have variations in their bonding patterns.

The researchers then conducted a series of experiments that showed that their synthetic sequences shares properties with natural DNA that are essential for supporting life.

Data retrieval

To work as an information storage system, DNA has to follow predictable rules, so the team first demonstrated that, in a similar way to regular bases, the synthetic bases reliably formed pairs.

They created hundreds of molecules of the synthetic DNA and found that the letters bound to their partners predictably.

They then showed that the structure of the double helices remained stable no matter what order the synthetic bases were in. This is important because for life to evolve, DNA sequences need to be able to vary without the whole structure falling apart. Using X-ray diffraction, the team showed that three different sequences of the synthetic DNA retained the same structure when crystallised.

This is a substantial advance, says Philipp Holliger, a synthetic biologist at the MRC Laboratory of Molecular Biology in Cambridge, UK, because other methods of expanding the genetic alphabet are not as structurally sound.

Instead of chemicals that use hydrogen bonds to pair up, these other approaches use water-repelling molecules as their bases. These can be placed at intervals in-between the natural letters, but the structure of DNA breaks down if they are placed in a row.

Finally, the team showed that the synthetic DNA could be faithfully transcribed into RNA.

"The ability to store information is not very interesting for evolution," says Benner. "You have to be able to transfer that information into a molecule that does something."

Converting DNA into RNA is a key step for translating genetic information into proteins, the workhorses of life.

But some RNA sequences, known as aptamers, can themselves bind to specific molecules.

Benner's team created synthetic DNA that codes for a certain aptamer and then confirmed that the transcription had occurred and the RNA sequence functioned correctly.

Holliger says that the work is an exciting starting point, but there is still a substantial distance to go before reaching a true eight-letter synthetic genetic system.

One key question, for example, will be whether the synthetic DNA can be replicated by polymerases, the enzymes responsible for synthesizing DNA inside organisms during cell division.

This has been demonstrated for other methods such as Romesberg's, which uses water-repelling bases.

Variety of life

Still, Benner says that the work shows that life could potentially be supported by DNA bases with different structures from the four that we know, which could be relevant in the search for signatures of life elsewhere in the Universe.

Adding letters to DNA could also have more down-to-earth applications.

With more diversity in the genetic building blocks, scientists could potentially create RNA or DNA sequences that can do things better than the standard four letters, including functions beyond genetic storage.

For example, Benner's group previously showed that strands of DNA that included Z and P were better at binding to cancer cells than sequences with just the standard four bases[3].

And Benner has set up a company which commercialises synthetic DNA for use in medical diagnostics.

The researchers could potentially use their synthetic DNA to create novel proteins as well as RNA.

Benner's team has also developed further pairs of new bases, opening up the possibility of creating DNA structures that contain 10 or even 12 letters. But the fact that the researchers have already expanded the genetic

alphabet to eight is in itself remarkable, says Romesberg. "It's already doubling what nature has."

doi: 10.1038/d41586-019-00650-8

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http://bit.ly/2TesRV1

Foxes were domesticated by humans in the Bronze Age

Based on diet, scientists have discovered that both foxes and dogs were domesticated

In the northeast of the Iberian Peninsula, between the third and second millennium BC, a widespread funeral practice consisted in burying humans with animals. Scientists have discovered that both foxes and dogs were domesticated, as their diet was similar to that of their owners.

The discovery of four foxes and a large number of dogs at the Can Roqueta (Barcelona) and Minferri (Lleida) sites stands out among the many examples of tombs in different parts of the north-eastern peninsula. These burials reveal a generalized funeral practice that proliferated in the Early to Middle Bronze Age: that of burying humans together with domestic animals.

Artistic representation of a woman of the Bronze Age accompanied by a dog and a fox. **J. A. Peñas**

What is most striking about these sites is the way of burying the dead in large silos, along with their dogs and a few foxes. "We discovered that in some cases the dogs received a special kind of food. We believe this is linked to their function as working dogs. Besides, one of the foxes shows signs of having already been a domestic animal in those times," Aurora Grandal-d'Anglade, co-author of a study on the relationship between humans and dogs through their diet published in the journal *Archaeological and Anthropological Sciences*, has said to to Sinc.

By means of studying stable carbon and nitrogen isotopes in bone collagen, as well as archaeological, archaeobiological and

anthropological studies, researchers have been able to compare the diets of buried animals with their owners´ diet. A total of 37 dogs, 19 domestic ungulates and 64 humans were analyzed. The results indicate that the dogs' diet was similar to that of humans.

The isotopic study of the Minferri foxes shows a varied diet: in some cases it looks similar to that of the dogs at that site, and in another it looks more like that of a wild animal or one that had little contact with humans.

"The case of the Can Roqueta fox is very special, because it is an old animal, with a broken leg. The fracture is still in its healing process, and shows signs of having been immobilized (cured) by humans. The feeding of this animal is very unusual, as it is more akin to a puppy dog's. We interpret it as a domestic animal that lived for a long time with humans," explains Grandal.

Large dogs used for transporting loads

The study points out that, in some particular cases in Can Roqueta, there was a specific cereal-rich food preparation for larger dogs probably used for carrying loads, and for at least one of the foxes.

"These specimens also show signs of disorders in the spinal column linked to the transport of heavy objects. Humans were probably looking for a high-carbohydrate diet because the animals developed a more active job, which required immediate calorie expenditure. It may seem strange that dogs were basically fed with cereals, but this was already recommended by the first-century Hispano-Roman agronomist Lucius Junius Moderatus Columella , in his work De re rustica", says Silvia Albizuri Canadell, co-author of the work and archaeozoologist at the University of Barcelona.

Other animals, such as cows, sheep or goats are noted for an herbivorous diet. Their function was probably to provide milk, meat or wool rather than serve as a work force. "The horse was not yet widespread in those societies, no traces of it can be found until later times," adds the scientist.

In general, humans and dogs show somewhat higher isotopic signals than ungulates, which indicates a certain (not very high) consumption of animal protein, "not necessarily much meat; they could be, for example, derived from milk," explains Grandal. Archaeological objects included sieves that served as 'cheese making devices'.

Moreover, men seem to have included more meat than women in their diet. As for dogs, their diet may have been mainly from leftovers of what humans ate, mostly more similar to that of women and children. "That's why we thought they were more linked to these domestic environments," says the researcher. There are many ethnographic parallels that indicate this relationship between women and dogs.

Feeding and treatment of foxes and dogs

The fundamental role of dogs during the Bronze Age, when livestock, along with agriculture, constituted the basis of the economy, was that of the surveillance and guidance of herds. They were also responsible for taking care of human settlements, given the risk posed by the frequent presence of dangerous animals such as wolves or bears.

"The characteristics of dogs include their great intelligence, easy trainability and, undoubtedly, their defensive behaviour. As if that were not enough, this animal was used until the nineteenth century AD in North America, Canada and Europe for light transport on its back and for dragging carts and sleds. It also functioned as a pack animal on the Peninsula during the Bronze Age," Albizuri Canadell claims.

Some archaeological specimens from North America show bone disorders that stem from the pulling of 'travois'. There are also accounts by the first colonizers of the use of dogs in these tasks by Indian populations until the nineteenth century AD, although they had not been identified in Europe until a few years ago.

"It was the Can Roqueta specimens under study that triggered the alarm about the use of this animal for light loads since antiquity, and they're an exceptional case in Europe," says Albizuri Canadell.

Similar pathologies have also been recently identified in the vertebrae of Siberian Palaeolithic dogs, leading one to think that one of the first tasks since their early domestication was the pulling of sleds and travois, in addition to hunting.

Its role as a transport animal in the first migrations and human movements through glacial Europe could have been fundamental and much more important than believed until recently.

The reason for animal offerings

Exceptional findings, such as those of tomb #88 and #405 of the Minferri site (Lleida), show that during the Bronze Age there were already well-differentiated funeral treatments in human communities. "In the two structures mentioned above, the remains of three individuals were found together with animal offerings. In tomb #88 there was the body of an old man with the remains of a whole cow and the legs of up to seven goats. The remains of a young woman with the offering of a whole goat, two foxes and a bovine horn were also found," states Ariadna Nieto Espinet, an archaeologist from the University of Lleida and also the co-author of the study.

Structure #405 uncovered the body of an individual, possibly a woman, accompanied by the whole bodies of two bovines and two dogs. "We still don't know why only a few people would have had the right or privilege to be buried with this type of offering, unlike what happens with the vast majority of burials," the expert points out.

In Can Roqueta, clear differences have also been observed in the deposits of domestic animals within the tombs of adults, both men and women, which are even reflected in children's tombs. From this we can infer the existence of an inheritance of social status from birth. "It is tempting to think that if we understand domestic animals as a very important part of the agro- pastoral agro-shepherding economy of the Bronze Age and of the belongings of some people in life, these could be an indicator of the wealth of the deceased individual or of his clan or family," argues Nieto Espinet.

"It seems that species such as bovines and dogs, two of the most recurring animals in funeral offerings, are those that might have played a fundamental role in the economy and work as well as in the symbolic world, becoming elements of ostentation, prestige and protection," she concludes.

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http://bit.ly/2BKyq3B

New 'interspecies communication' strategy between gut bacteria and mammalian hosts uncovered

Study describes molecular language bacteria use to control host genes and development

Bacteria in the gut do far more than help digest food in the stomachs of their hosts, they can also tell the genes in their mammalian hosts what to do. A study published today in *Cell* describes a form of "interspecies communication" in which bacteria secrete a specific molecule--nitric oxide--that allows them to communicate with and control their hosts' DNA, and suggests that the conversation between the two may broadly influence human health.

The researchers out of Case Western Reserve University School of Medicine, University Hospitals Cleveland Medical Center, and Harvard Medical School tracked nitric oxide secreted by gut bacteria inside tiny worms (C. elegans, a common mammalian laboratory model). Nitric oxide secreted by gut bacteria attached to thousands of host proteins, completely changing a worm's ability to regulate its own gene expression.

The study is the first to show gut bacteria can tap into nitric oxide networks ubiquitous in mammals, including humans. Nitric oxide attaches to human proteins in a carefully regulated manner--a process known as S-nitrosylation--and disruptions are broadly implicated in diseases such as Alzheimer's, Parkinson's, asthma, diabetes, heart disease, and cancer.

The findings suggest nitric oxide is a general mechanism by which gut bacteria can communicate with mammalian hosts. Previous work to untangle communication lines to and from gut bacteria has primarily focused on rare molecules that bacteria secrete. The new findings are akin to uncovering a chemical language common across species, as opposed to single words, said senior author Jonathan Stamler, MD, director of the Institute for Transformative Molecular Medicine at Case Western Reserve University School of Medicine and president of the Harrington Discovery Institute at University Hospitals Cleveland Medical Center. "There is tremendous complexity in the gut, and many researchers are after the next unusual substance produced by a bacterium that might affect human health," he says. With trillions of bacteria in the average gut, Stamler decided to look for a common language that all bacterial species might use. "The enormity of the gut bacteria population and its relationship to the host predicts there will be general means to communicate that we humans can recognize."

The researchers demonstrated the phenomenon by feeding developing worms bacteria that produce nitric oxide. They then selected one very important protein--argonaute protein, or ALG-1--that is highly conserved from worms to humans and silences unnecessary genes, including genes critical for development. When nitric oxide secreted by the bacteria attached to ALG-1, they developed malformed reproductive organs and died. Too much nitric oxide from bacteria commanded the worms' DNA silencing proteins and impaired healthy development.

"Practically, animals will not let this happen," Stamler said. Instead, the authors speculate a mammalian host outside of a laboratory setting will adjust to accommodate changing nitric oxide levels. Said Stamler, "The worm is going to be able to stop eating the bacteria that make the nitric oxide, or it will begin to eat different bacteria that makes less nitric oxide, or change its environment, or countless other adaptations. But by the same token, too much nitric oxide produced by our microbiome may cause disease or developmental problems in the fetus."

The study adds to a growing body of evidence that bacteria living in the gut, determined by diet and environment, have a tremendous influence on mammalian health. Stamler imagines nitric oxide may represent an opportunity to manipulate this symbiotic relationship. Just as probiotics are designed to improve digestion, inoculating a person's gut with bacteria to improve nitric oxide signaling is conceivable. "I now think of this therapeutically, as a drug. There are tremendous opportunities to manipulate nitric oxide to improve human health."

While nitric oxide and S-nitrosylation may be a general mode of interspecies communication with broad health implications, it will require additional future research. Will nitric oxide be the only chemical communication channel? "We're basically seeing a new field opening for general strategies of communication," says Stamler. "There will be others."

Stamler collaborated with several researchers from Case Western Reserve University School of Medicine on the new study, including first authors Puneet Seth, MD and Paishiun (Nelson) Hsieh, MD, PhD; Suhib Jamal; Liwen Wang, PhD; Mukesh Jain, MD; and Jeff Coller, PhD.

This research was supported in part by grants from the National Institutes of Health (R01-GM099921 to J.S.S., T32GM007250 and F30AG054237 to P.N.H, and R35HL135789 to M.J.).

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http://bit.ly/2Tc4DLa

Could saffron be as effective as stimulant medicines in treating ADHD?

Saffron shown to be as effective at controlling symptoms as Ritalin

New Rochelle, NY - A new short-term pilot study in children and teens 6-17 years old with attention-deficit hyperactivity disorder (ADHD) has shown saffron to be as effective at controlling symptoms as methylphenidate, the commonly prescribed drug Ritalin. Saffron may be a promising herbal alternative for treating ADHD, particularly for the 30% of patients who do not respond to or cannot tolerate stimulants like methylphenidate, as reported in an article published in the *Journal of Child and Adolescent Psychopharmacology*, a peer-reviewed journal from Mary Ann Liebert, Inc., publishers. Click here to read the full-text article free on the *Journal of Child and Adolescent Psychopharmacology* website through March 21, 2019.

The article entitled "*Crocus sativus L.* Versus Methylphenidate in Treatment of Children with Attention-Deficit/Hyperactivity Disorder: A Randomized, Double-Blind Pilot Study" was coauthored by Sara Baziar, MD, Ali Aqamolaei, MD and colleagues from Tehran University of Medical Sciences, Iran. The researchers note that saffron also has anti-depressant and memory-enhancing properties. They compared the effects of *Crocus sativus L.* to methylphenidate in 54 patients over a 6-week period and showed no significant difference in effectiveness as well as similar frequency of adverse effects.

"This is a very interesting study and an intriguing finding. It is worthy of replication and further study to understand the mechanism of action," says Harold S. Koplewicz, MD, Editor-in-Chief of the *Journal of Child and Adolescent Psychopharmacology* and President of the Child Mind Institute in New York.

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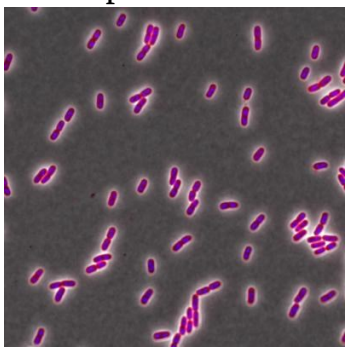
Chemical added to consumer products impairs response to antibiotic treatment

Triclosan added to toothpaste, mouthwash to kill bacteria inadvertently makes such cells stronger

Grocery store aisles are stocked with products that promise to kill bacteria. People snap up those items to protect themselves from the germs that make them sick. However, new research from Washington University in St. Louis finds that a chemical that is supposed to kill bacteria is actually making them stronger and more capable of surviving antibiotic treatment.



This is E. coli from the strain used in this study. The cell wall is shown in red and DNA is shown in blue. **Petra Levin laboratory, Washington University in St. Louis**

The study, available online Feb. 19 in the journal Antimicrobial Agents & Chemotherapy, suggests that triclosan exposure may inadvertently drive bacteria into a state in which they are able to tolerate normally lethal concentrations of antibiotics -- including those antibiotics that are commonly used to treat urinary tract infections (UTIs).

Triclosan is the active ingredient responsible for the "antibacterial" property marketed on many consumer products. It is added to toothpaste, mouthwash, cosmetics and even to clothing, baby toys and credit cards with the intention of reducing or preventing bacterial growth.

"In order to effectively kill bacterial cells, triclosan is added to products at high concentrations," said Petra Levin, professor of biology in Arts & Sciences.

In 2017, the U.S. Food and Drug Administration cited both safety concerns and lack of efficacy when it recommended against adding triclosan to consumer soaps, but these guidelines have not discouraged companies from adding it to other products. What's more, Levin said, "Triclosan is very stable. It lingers in the body and in the environment for a long time."

The new study in mice uncovers the extent to which triclosan exposure limits the body's ability to respond to antibiotic treatment for urinary tract infection. It also sheds new light on the cellular mechanism that allows triclosan to interfere with antibiotic treatment.

Escaping death

Some antibiotics kill bacterial cells, while others keep them from growing.

Levin and her colleagues were particularly interested in bactericidal antibiotics -- those that can kill bacterial cells and are typically prescribed by doctors to treat bacterial infections. They wanted to know whether triclosan could protect bacteria from death in the presence of killing antibiotics.

Corey Westfall, postdoctoral scholar in the Levin lab, treated bacterial cells with bactericidal antibiotics and tracked their ability to survive over time. In one group, the bacteria were exposed to triclosan prior to being given the bactericidal antibiotic. In the other group, they were not.

"Triclosan increased the number of surviving bacterial cells substantially," Levin said. "Normally, one in a million cells survive antibiotics, and a functioning immune system can control them. But triclosan was shifting the number of cells. Instead of only one in a million bacteria surviving, one in 10 organisms survived after 20 hours. Now, the immune system is overwhelmed."

Triclosan exposure allowed the bacteria to escape death by antibiotics. And the protective property was not limited to any single family of antibiotics. In fact, multiple antibiotics that are considered unique in how they kill cells were less effective at killing bacteria exposed to triclosan.

"Triclosan increased tolerance to a wide breadth of antibiotics," Westfall said. "Ciprofloxacin (also known as Cipro) was the most interesting one to us because it is a fluoroquinolone that interferes with DNA replication and is the most common antibiotic used to treat UTIs."

Antibiotics can't do their job with triclosan around

UTIs occur when bacteria, primarily Escherichia coli (E. coli), enter and infect the urinary tract. Antibiotics such as Cipro are commonly used to kill the bacteria and treat the infection.

UTIs are common; so is exposure to triclosan. A shocking percentage -- about 75 percent -- of adults in the United States have detectable levels of triclosan in their urine. About 10 percent of adults have levels high enough to prevent E. coli from growing. Could triclosan's presence in the body interfere with treating UTIs?

Westfall and Levin worked with collaborators at Washington University School of Medicine in St. Louis to answer this question.

Ana Flores-Mireles, an assistant professor at the University of Notre Dame, worked on this study as a postdoctoral scholar in the lab of Scott Hultgren, the Helen L. Stoever Professor of Molecular Microbiology at the School of Medicine. With the help of Jeffrey Henderson, associate professor of medicine and molecular biology, she figured out that mice which drink triclosan-spiked water have urine triclosan levels similar to those reported in humans.

"This result meant we could actually test the impact that human urine levels of triclosan have during antibiotic treatment of UTIs in mice," Levin said.

All of the mice with the infection received Cipro to treat the UTI. Only some of the mice drank triclosan-spiked water. After antibiotic treatment, mice with triclosan exposure had a large number of

bacteria in their urine and stuck to the bladder; mice without exposure had significantly lower bacterial counts.

"The magnitude of the difference in bacterial load between the mice that drank triclosan-spiked water and those that didn't is striking," Levin said.

"If the difference in the number of bacteria between the groups was less than tenfold, it would be difficult to make a strong case that the triclosan was the culprit," Levin added. "We found 100 times more bacteria in the urine of triclosan-treated mice -- that is a lot."

This striking result has an equally striking message -- antibiotics are less effective at treating UTIs when triclosan is around, at least in mice.

Triclosan's dirty weapon: ppGpp

Triclosan is interfering with antibiotic treatment, but how?

Levin and her colleagues found that triclosan works with a cell growth inhibitor, a small molecule nicknamed ppGpp, to render cells less sensitive to antibiotics.

During times of stress, ppGpp responds by shutting down the biosynthetic pathways that make the building blocks -- DNA, RNA, protein and fat -- that ultimately become new cells. This response helps divert resources away from growth and towards survival.

"There is a rule in medicine that you don't give drugs that slow cell growth before drugs that kill cells," Levin said.

Bactericidal antibiotics kill by targeting specific biosynthetic pathways. Ampicillin targets the enzymes that make the bacterial cell wall, for example, while Cipro targets DNA synthesis. When these pathways are shut down, bactericidal antibiotics have trouble doing their job.

If triclosan triggers ppGpp, biosynthesis is curtailed and bactericidal antibiotics would become ineffective at killing cells. Biosynthesis continues in bacteria lacking ppGpp, however, and these cells would be expected to die.

Levin and colleagues tested their hypothesis by engineering E. coli mutants unable to make ppGpp and compared them to E. coli able to make ppGpp. The absence of ppGpp in the mutant E. coli removed triclosan's ability to protect the cells from bactericidal antibiotics.

While clinical studies would be required to definitely prove that triclosan is interfering with antibiotic treatments in humans, Levin said, "My hope is that this study will serve as a warning that will help us rethink the importance of antimicrobials in consumer products."

http://bit.ly/2H0EsjO

'It eats everything'—the new breed of wildfire that's impossible to predict

We're fighting a different kind of wildfire whose behaviour experts are struggling to predict.

Climate change and negligent forest management are causing higher-intensity, faster-moving fires that can generate enough energy to evolve into erratic firestorms, known as pyroCbs, in the face of which first responders can do little.

"Traditionally we could predict the fire behaviour and the direction of the fire but under those conditions and those moments it's not possible," said Marc Castellnou, president of the Spanish independent wildfire prevention group Pau Costa Foundation.

As a wildland fire analyst with the Catalan fire services, Castellnou reconstructs wildfires using simulations, satellite, on-the-ground and other data.

This wildfire shows a different behaviour than those of the past, he says. "It eats everything."

While these fires are rare, when one strikes it can generate 100,000 kilowatts of energy per metre. In firefighting terms, this is 10 times what a firefighter can handle, but even at 4,000 kilowatts, firefighters cannot go near the flames and require aerial support. "The old way of fighting fires by sending firefighters – that's gone," Castellnou said.

New normal

There have been signs of trouble since the 1990s, according to Castellnou.

"This change has been cooking for a long time, but the first time we realised something wrong was happening were the years 2009 and 2012," he said, referring to the Black Saturday bushfires in the Australian state of Victoria that killed 173 people and wildfires in Spain, Portugal, Chile and California, US. Many in the fire community initially thought these were just abnormal events, he says. But then wildfires in Chile and Portugal in 2017 indicated that those weren't simply extreme years. "That was the new normal arriving. 2018 has confirmed that," he said, referring to the deadly wildfires in Greece and in California.

On October 15, 2017, Castellnou was in central Portugal to conduct analysis then support the local services as the wildfires became firestorms.

"What I saw was the pace of the fires ... You think: "Well that cannot be real." When you go there (and see the damage) you understand that that is the reality," he said.

Castellnou, who spoke about the future of fighting wildfires at the EU's security research event in December 2018, first joined the Catalan fire and rescue services as a seasonal firefighter when he was a teenager. In the past, he says, a fire that destroyed 25,000 hectares a day was considered extreme. According to his figures, the October fires in Portugal consumed 220,000 hectares of forest, an area 22 times the size of Lisbon and killed more than 40 people. Castellnou says that at their peak, wildfires burned at a rate of 10,000 hectares per hour over seven hours.

"This is something that blew my mind and I cannot use technology to simulate that because models can't predict it," he said. The challenge is now predicting how they will behave, he says. "We're still not there. We're struggling."

Flammable

Wildfire experts say that climate change, causing a long-term rise in temperature and less rainfall, is creating unprecedented flammable conditions that are making forests burn with more intensity. Wildfires now occur in the wintertime and affect regions in latitudes beyond the fire season-prone countries of Spain, Greece, Italy, Portugal and France. Castellnou says that wildfires are expected to affect highly populated areas like central Europe.

"Last summer, it was the first time in history we were having wildfires in (nearly) every single country in Europe," he said.

"It's not that climate change will create these new scenarios. No, no. The new scenario is already here, and it has come a lot faster than expected."

According to experts, urbanisation and poor forest management for reducing fuel – the grasses and shrubs that fires feed on – are also to blame.

David Caballero, who also spoke at the security research event, assesses the wildfire risks in populated areas, focusing on the wildland-urban interface, where infrastructure and urban development intermingle with forests and other wildlands. He is contributing to a project called Clarity that is working to join up different IT systems to protect cities and infrastructures from the effects of climate change.

He says we're seeing more fast-growing, high-energy fires affecting populated areas.

"We have to be prepared. Whenever we have forest in Europe, we eventually will have forest fires," he said.

He travelled to the seaside village of Mati, Greece, in the immediate aftermath of Europe's deadliest wildfires last year which killed 99 people in the region of Attica. Speaking to firefighters and survivors, he learnt that many people did not expect the fires to cross the

highway that runs parallel to the coast. In the past the fires had halted at this point, but this time they leapt across, burning through Mati.

"There was an enormous amount of fuel due to the lack of management for 40 years," he said. The fires tore through the village and reached the coast in just 20 minutes.

Caballero says that all along the Mediterranean coast, unregulated construction with little regard for safety and evacuation routes and lax vegetation management mean that more places are at risk. He says local and regional authorities can no longer afford to be negligent. "We are living surrounded by fuel," he said.

Culture of risk

Pau Costa Foundation, established to speed up the sharing of information and know-how between fire services and society, works on a number of prevention campaigns. For a project called Heimdall, set up to contribute to an EU-wide information system about fires and other emergencies, the foundation is ensuring that the general public has a voice in shaping it.

One of the foundation's aims is to change the social perception of wildfires. A tendency to fight every fire, small or large, has let landscapes thrive artificially, Castellnou says. "Not all fire is bad," he said. By clearing old trees, fires can make way for the growth of new forests that are adapted to climate change.

Smaller fires, through activities such as prescribed burning, also have a role to play in creating scars in the land which break up a bigger fire's path. "A mosaic of landscape of different ages and low-intensity fires is the best protection against the big fires," he said.

Oriol Vilalta, director of the foundation and a volunteer firefighter, says with wildfires killing more people in Europe, causing more than 200 deaths in the past three years, it's time we learnt how to coexist with them.

"We need to create a culture of risk. The Japanese know very well what to do in case of an earthquake, but we don't know what to do in Europe with fires," Vilalta said.

In the past, the tendency was to evacuate people, but the general public must become part of the solution through self-protection, he says. '(That's) what to do and what not to do, where to stay and where not to stay in case of a fire."

http://bit.ly/2BQqLaN

Revealed: the carrot of youth

A Japanese salad vegetable is a natural source of a compound with anti-ageing properties.

Natalie Parletta reports.

A Japanese relative of the carrot might hold the key to longevity, scientists have discovered. The flowering ashitaba (*Angelica keiskei*) plant, traditionally used in Asian medicine, contains a flavonoid called *4,4'-dimethoxychalcone*, or DMC.

European researchers discovered the substance's superior health benefits when testing 180 subclasses of flavonoids for their anti-ageing properties.

Ashitaba, a staple in Japan. **bungoume/ Getty Images**

DMC was their "top hit", as reported in the journal *Nature Communications* – even outperforming other known protective compounds, including resveratrol, a chemical found in red wine .

The large research team was led by Frank Madeo and Guido Kroemer from the University of Graz in Austria and the Centre de Recherche des Cordeliers in Paris, France. "Our rationale was that there is a million years of coevolution between animals (humans) and plants, which is probably the reason why many of the blockbusters in medical treatment are plant-based substances," says Madeo.

In a series of experiments, DMC prolonged the lifespan of yeasts, fruit flies, worms and human cells. It also showed protective benefits for heart and liver in mice.

Further experiments using "genetic tricks" revealed that, in most cases, DMC switches on the fasting response of cells.

This process is called autophagy: "a cellular cleansing and recycling program", explains Madeo, that sweeps damaged protein and mitochondria out of cells – both causes of age-related diseases such as Parkinson's and dementia. Other ways to induce autophagy include fasting and calorie restriction.

The results support previous suggestions that the antioxidant properties of flavonoids, the most abundant phytonutrients found in edible plants, may not be their only health-promoting virtues.

Whether the findings are transferable to humans remains to be seen. But the researchers could detect DMC in the blood of mice fed with chow enriched with the compoud, suggesting that mammals can absorb it from food.

And Asians have long used ashitaba – the only natural source of DMC that the researchers could find – for its longevity and health-promoting properties. The plant grows in many Japanese gardens.

http://bit.ly/2XmtB9O

The Real Dino Killer: A One–Two Punch

An asteroid impact and volcanoes acting together could have done in the beasts, new rock dates indicate

By Howard Lee

What killed the dinosaurs? Scientists have long debated whether it was an asteroid that crashed into Earth 66 million years ago or a powerful wave of volcanic eruptions at that time.

Two papers published today in *Science* say the real answer is— both, in a catastrophic coincidence. But the two teams of researchers disagree on a key point: whether the impact from space came first and boosted the eruptions into a climate-altering, dinosaur-killing frenzy, or whether they were two unrelated disasters with remarkably bad timing for the beasts that once stalked our planet and still stomp through our minds.

After decades of arguments between asteroid advocates and volcano boosters, in 2015 some scientists suggested both might be right, because an asteroid impact in Mexico—marked by a crater named Chicxulub—may have created seismic waves that shook the planet so violently that it sped up ongoing volcanic activity under India. That magma, in a region called the Deccan Traps, exploded in sunlight-dimming eruptions that chilled the climate, and then their release of carbon dioxide would have warmed it—a whiplash few creatures could survive.

The idea was eruptions and impact together may have wiped-out the dinosaurs along with nearly 70 percent of species in a mass extinction at the end of the Cretaceous period.

The papers published today, revealing newly refined dates for both the lava flows from the eruptions and traces of the asteroid impact in other rocks, were supposed to reinforce this notion. But the sets of dates—one from scientists at the University of California, Berkeley, and the other from a group at Princeton University—come from different ways of dating rocks, and they disagree.

The Berkeley team, led by Courtney Sprain (a geochronologist now at the University of Liverpool), used a method called argon–argon dating on samples from lava flows in India that occurred near the end of the Cretaceous, and compared them with dates for the asteroid impact drawn from other rocks. They were able to put the date for the asteroid impact at 66.052 million years ago, give or take 8,000 years, and timed the lava dates just after that point in time. The sequence convinced them there was indeed a boost to the eruptions right after the impact, validating the asteroid-to-eruptions idea.

But the Princeton team, led by geochronologist Blair Schoene and using another method called uranium–lead dating, concluded the

opposite. The techniques are equally accurate, but the uranium-lead method can identify more details.

The Princeton scientists used it to compare the age of volcanic ash from the Deccan Traps lava flows to rocks found in Colorado that bore the mineral signatures of the asteroid impact. The researchers found the Deccan Traps erupted in four huge pulses, separated by quiet periods lasting 100,000 years or more.

But the key finding was that the impact date fell in one of those peaceful moments of geologic time, not right before any of the pulses. That timing, they say, makes it hard to argue the impact preceded and thus caused the eruptions. “It is highly unlikely that there is a relationship between eruption rates of the Deccan Traps and the Chicxulub impact, and that the coincidence…is one of the most remarkable coincidences in Earth history,” they wrote.

Despite their differences about the primary cause, the dates are still close enough for both teams to blame a combination of the eruptions and the asteroid for the demise of the dinosaurs. “Deccan volcanism probably made the mass extinction worse and made ecosystems more susceptible to the abrupt climate changes that came with the Chicxulub impact,” Sprain says. And Schoene agrees that “the evidence for coincidence between the impact and the big pulse of extinctions is pretty strong.”

If the impact did boost the eruptions, as the Berkeley researchers conclude, then their simultaneous effect would have been calamitous and hard to disentangle in the rock record. If the impact instead happened in between eruption pulses, as the Princeton team found, then the repeated and extreme environmental changes would have been devastating, but the main extinction event was caused by the impact.

So whereas attempts to single out a dino killer may have failed, for now, they do point to a conspiracy of culprits.

http://bit.ly/2IAO4EF

Pharmaceutical residues in fresh water pose a growing environmental risk

First research examining risks of two particular medicines in global freshwater sources

Over the past 20 years, concentrations of pharmaceuticals have increased in freshwater sources all over the world, as research by environmental experts at Radboud University has revealed. Levels of the antibiotic ciprofloxacin have reached the point of potentially causing damaging ecological effects. The research is the first to examine the risks of two particular medicines in global freshwater sources, and is being published in *Environmental Research Letters* on February 22nd. "The study calls for more widespread data gathering to measure the problem around the world."

"Getting an accurate picture of the environmental risks of pharmaceuticals around the world depends on the availability of data, which is limited," says Rik Oldenkamp, lead author of the article. "It's true that there are models, such as the ePiE model, which can give detailed predictions of pharmaceutical concentrations in the environment, but these are often only applicable to places where we already have a lot of information, such as rivers in Europe." The new model developed by the researchers, which builds on an existing model with a lower resolution, makes it possible to come up with worldwide predictions for individual ecoregions.

Damaging concentrations

For the two pharmaceuticals investigated in the study - carbamazepine, an anti-epileptic drug, and ciprofloxacin, an antibiotic - the environmental risks were found to be 10 to 20 times higher in 2015 than in 1995. The increased human use of ciprofloxacin was found to have a particularly high impact globally. "The concentrations of this antibiotic can be harmful for bacteria in the water, and these bacteria in turn play an important role in various

nutrient cycles," says Oldenkamp. "Antibiotics can also have a negative impact on the effectiveness of bacteria colonies used in wastewater treatment."

Antibiotic resistance as an environmental issue

Antibiotic resistance has been on the agenda of the World Health Organization (WHO) and United Nations General Assembly for a few years now. "Generally, it's seen as a problem for the health sector, as resistant bacteria can be spread within hospitals or through livestock," says Oldenkamp. "But there's little awareness of the role of the environment in this problem, even though it becomes increasingly clear that the environment functions as a source of resistance for various pathogens."

More data in high-risk areas

"Our model predicts a relatively high environmental risk for ecoregions in densely populated and dry areas such as the Middle East, yet those are precisely the areas where there is little data on pharmaceutical use and concentrations in surface waters," says Oldenkamp. The researchers predicted human pharmaceutical consumption in these areas using regression models based on consumption in other countries, along with socio-economic and demographic information, and linked this to information related to other factors such as water sources and the number of people with access to wastewater treatment.

"Our model shows a particular need for new data in these types of areas," says Oldenkamp. "The model is really a starting point for creating an insight into the environmental risks posed by pharmaceuticals all over the world."

http://bit.ly/2NrsL7h

Fungus from the intestinal mucosa can affect lung health

Our microbiome can impair our immune system through the harmless fungus Candida albicans

The composition of the microbiome - the countless bacteria, fungi and viruses that colonize our body surface, skin, intestines or lungs - makes a decisive contribution to human health or disease. However, biological mechanisms that cause inflammations in the microbiome are still largely unknown. Together with a group of researchers from the University of Kiel and the University Hospital of Schleswig-Holstein, Professer Dr. Oliver Cornely (head of the Center of Excellence for Invasive Fungal Diseases at Cologne University Hospital) has deciphered a mechanism by which specific intestinal microbiota amplify inflammatory reactions in the lungs. The results of the study, published in Cell, could accelerate the development of new therapies for common diseases.

'The fungus *Candida albicans*, which colonizes the intestines, skin and mucous membranes, is actually harmless', Cornely said. 'However, our study has shown that *Candida albicans* affects the balance of our immune system.'

Candida albicans stimulates the immune system to produce specific defence cells, so-called Th17 cells. However, some of these Th17 cells then attack other fungi, such as Aspergillus fumigatus. This phenomenon is called cross-reactivity. The research showed that immune-compromised individuals have an increased level of cross-reactive Th17 cells in their lung tissue. This concentration is associated with a deterioration of these patients' health. The protective Th17 reaction in the intestine seems to amplify pathogenic immune processes in the lungs.

'With this observation, we were able to show for the first time how a single member of the microbiome, *Candida albicans*, influences the specific immune response to a large group of other microbes. Immune cross-reactivity is probably a common mechanism by which the microbiome manipulates the immune system - with both protective and harmful effects', Cornely remarked.

Deciphering such specific effects of individual microbes will in future contribute to the development of targeted therapies.

https://bbc.in/2BSFN92

Flu vaccine 'working better for children'

The flu vaccine is so far proving more effective in children than in adults in the UK, mid-season figures suggest.

The nasal spray flu vaccine is 87% effective in children aged two to 17 against the main circulating flu strain, influenza A(H1N1)pmd09, Public Health England data indicates.

Meanwhile, the flu vaccine is 39% effective against the same strain in adults aged 18 to 64.

No data is yet available for the over-65s or for other flu strains.

The data shows that more children than ever are being vaccinated, although take-up is lower in younger age groups.

The figures are preliminary and are subject to being revised by the end of the flu season in May, when more data is available.

Some 43% of two-year-olds have been vaccinated, compared with 45% of three-year-olds.

Among school-aged children, 56% to 64% have been vaccinated, depending on the year group.

Last year's final figures for the whole flu season of 2017-18 showed that the vaccine was only 15% effective among all age groups.

This included effectiveness of about 27% in children aged two to 17, 12% among people in at-risk groups aged 18 to 64, and 10% in those aged 65 and over.

For this latest flu season, a new "booster" vaccine has been brought in to improve effectiveness among the over-65s.

'Super-spreaders'

Dr Mary Ramsay, head of immunisation at PHE, said: "It is encouraging to see that this year's vaccines are offering a high level of protection against the main circulating strain of flu - particularly for children.

"Children tend to be 'super-spreaders' of flu and so protecting them is crucial for protecting the rest of the population.

"We're pleased that more parents have been taking up the offer of vaccination for their children and encourage anyone who is eligible to do so every winter.

"It's the best defence we have against this unpredictable virus."

Health Secretary Matt Hancock said: "The most basic instinct for any parent is to do whatever they can to protect their child. Vaccinations save countless lives and are absolutely vital.

"More children have been vaccinated this year to protect against flu and it is a positive sign that the vaccine itself appears to be more effective than in previous years.

"Our world-leading vaccination programme saves lives and I urge all parents of young children to make sure their child is vaccinated against flu and other childhood diseases."

http://bit.ly/2H1qaiU

If You Don't Have This Gene, You May Recover Better from a Stroke

People without a certain gene may recover better from strokes and other traumatic brain injuries than people with the gene, a new study suggests.

By Yasemin Saplakoglu, Staff Writer

The gene — called CCR5 — is the same gene at the center of the recent CRISPR babies controversy, in which a Chinese scientist edited the gene out of two embryos to make babies who were resistant to HIV.

People who don't have the CCR5 gene do show resistance to HIV — and indeed, an HIV drug called Maraviroc works by blocking the CCR5 receptor. (The CCR5 gene tells cells to create the CCR5 protein, and this protein binds to the CCR5 receptor.)

In the new study, published Feb. 21 in the journal Cell, researchers found that when they gave Maraviroc to mice to block their CCR5

receptors, the mice had increased control of their gait and their limbs. Even though the mice didn't experience stroke, the findings could shed light on the disease because people who've had a stroke may experience difficulty moving and controlling parts of their body.

But just because something has an effect in animals doesn't mean it will have the exact same effect in humans. So, to see how the CCR5 gene might play a role in humans and stroke recovery, the researchers collaborated with Israeli scientists at Tel Aviv University who were already tracking the recoveries of nearly 450 patients who had experienced a mild or moderate stroke.

Many of these patients didn't have the CCR5 gene, said senior author Dr. Thomas Carmichael, a professor and chair of neurology at the University of California, Los Angeles. (The gene is often absent in Ashkenazi Jews, and many of the patients in the study were Ashkenazi, Carmichael added.)

As suspected, the researchers found that patients who lacked the gene seemed to be recovering from strokes better, both physically — in terms of controlling their movement — and mentally, with improvements in memory, verbal function and attention, compared with patients with the gene.

Carmichael said that one possible explanation for the findings is that a lack of the CCR5 gene prevents the loss of brain cell connections located close to the site of the stroke, and also stimulates new connections in more distant areas of the brain. Conversely, the brains of patients that have the gene may have a reduced ability to change and reorganize.

Dr. Heidi Schambra, the director of neuro-epidemiology at NYU Langone Health who was not a part of the study, said that "the results suggest a novel approach for promoting recovery after stroke and [traumatic brain injury]." But for Maraviroc to be used as a treatment for recovering stroke patients, it has to first go through a clinical trial that directly tests how well it works for this particular purpose, she told Live Science.

Indeed, the researchers are now starting a stage 2 clinical trial to answer this question.

And though an absence of CCR5 may seem like a good thing, the gene could confer some benefits, Carmichael said. Past research, for example, has suggested that it plays an important role in stopping the formation of memories.

Memories form when groups of brain cells link up following a stimulus. To stop memory formation, CCR5 tells that group of cells not to link up with a certain stimulus. If you walk into your kitchen and crack an egg in a frying pan, "you want to remember that you've done that," Carmichael said. But you don't want that memory to also link up with the loud noise that just came from the backyard. That's where CCR5 is thought to come in.

Still, Carmichael noted that if the reports about the gene-edited babies are true and that scientist did edit out the CCR5 gene, the effects — whether beneficial or not — could affect far more than the immune system. "The brain and the immune systems are so complex, [so] it's hard to know," he said.